WC●P

World Conference on Pharmacometrics

September 5 - 7, 2012
Grand Hilton Seoul, Korea

| Organized by |
WCoP Organizing Committee

| Supported by |
Population Approach Group in Korea
Korean Society for Clinical Pharmacology and Therapeutics

WCoP

World Conference on Pharmacometrics

CONTENTS

Dear all,

On behalf of the organizing committee, it is my great pleasure to announce the first World Conference on Pharmacometrics (WCoP) to be held in Seoul, Korea, 5-7 September, 2012.

With the rapid progress of pharmacometrics and increasing interest in regional meetings such as PAGE, there has been on-going discussion about holding a global pharmacometrics meeting to accommodate the growing needs world-wide. Meanwhile, the establishment of ACoP has brought a great success with continued dramatic increases in the number of attendants.

Encouraged and motivated by these discussion and success, the WCoP has been created (i) to give a local stimulus by holding it outside Europe and the US as well, thereby enhancing global development & networking opportunities in pharmacometrics and (ii) to provide opportunities of discussing the future of pharmacometrics from a strategic perspective. WCoP will be held every 4 years. It will not replace the existing meetings (e.g., PAGE, ACoP, PAGANZ, etc) which will continue to be scheduled in the same year.

Considering 60% of world population living in Asia, it is meaningful that the first WCoP will be held in Asia. It is hoped that WCoP 2012 will contribute to increasing Asian countries' interest in pharmacometrics as well as discussing future directions of the pharmacometrics in the world.

Seoul, the conference venue, has been very active in hosting international PKPD symposia in recent years. As the capital city for more than 600 years since the Chosun Dynasty, the last dynasty of Korea, it will present you a cultural experience with a mixture of old tradition and hi-technology during the stay.

Thank you in advance for your participation and support.

Kyungsoo Park, PhD, MD
Local host, WCoP 2012
Population Approach Group in Korea

COMMITTEES

Global Organizing Committe

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Mats Karlsson, Uppsala University, Sweden

Holly Kimko, Janssen Research & Development, USA

France Mentré, Université Paris Diderot, France

Kyungsoo Park, Yonsei University, Korea
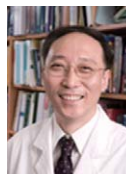
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Ramalingam Sankaran, Institute of Medical Sciences and Research, India

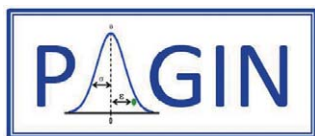Chun-Jung Lin, National Taiwan University, Taiwan

Lai-San Tham, Eli Lilly and Company, Singapore

🔴 Supporting Organizations

PAGE (Population Approach Group Europe)
ACoP (American Conference on Pharmacometrics)
PAGANZ (Population Approach Group in Australia and New Zealand)
PAGK (Population Approach Group in Korea)
PAGJA (Population Approach Group in Japan)
JCoP (Japanese Conference on Pharmacometrics)
PAGIN (Population Approach Group of India)
ISoP (International Society of Pharmacometrics)

🟥 CONFERENCE INFORMATION

Title : World Conference on Pharmacometrics 2012 (WCoP 2012)

Date : September 05~ 07, 2012

Venue : Grand Hilton Seoul, Seoul, Korea

Organized by : WCoP Organizing Committee

Supported by : Population Approach Group in Korea
Korean Society for Clinical Pharmacology and Therapeutics

Official Language : English

Website: http://www.go-wcop.org

Secretariat : Before & after the conference
Tel. +82-2-2269-4381 / Fax. +82-2-2269-4380 / Email. wcop2012@conventionpm.com
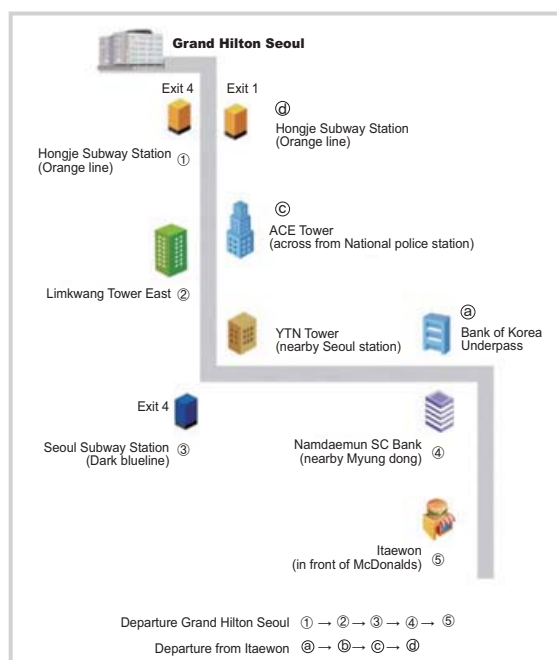
On-site Secretariat_Peacock Room
- Operating dates & hours
September 5-6 (Wed-Thu) 07:30-19:00 / September 7 (Fri) 07:30-12:30

Hotel Shuttle Schedule

• **Monday to Sunday**

To Itaewon		From Itaewon	
09:00	16:00	09:30	16:30
10:00	17:00	10:30	17:30
11:00	18:00	11:30	18:30
12:00	19:00	12:30	19:30
13:00	20:00	13:30	20:30
14:00	21:00	14:30	21:30
15:00	22:00	15:30	22:30

Departure from Grand Hilton Seoul	Departure from Itaewon
1. Hongje Subway Station, Exit 4(Orange line)	1. Bank of Korea Underpass
1. Limkwang Tower East	2. YTN Tower(nearby Seoul station)
3. Seoul Subway Station, Exit 4(Dark blue line)	3. ACE Tower (across from National police station)
4. Namdaemun SC Bank (nearby Myung dong)	4. Hongje Subway Station, Exit 1(Orange line)
5. Itaewon(in front of McDonald's)	5. Hotel arrival

Grand Hilton Seoul

Exit 4　Exit 1

ⓓ Hongje Subway Station (Orange line)

Hongje Subway Station (Orange line) ①

ⓒ ACE Tower (across from National police station)

Limkwang Tower East ②

YTN Tower (nearby Seoul station)

ⓐ Bank of Korea Underpass

Exit 4

Seoul Subway Station (Dark blueline) ③

Namdaemun SC Bank (nearby Myung dong) ④

Itaewon (in front of McDonalds) ⑤

Departure Grand Hilton Seoul ① → ② → ③ → ④ → ⑤
Departure from Itaewon ⓐ → ⓑ → ⓒ → ⓓ

🔴 CONFERENCE INFORMATION

Registration Desk

Date	Time	Place
September 5-6 (Wed-Thu)	07:30-18:00	2F, Grand Ballroom Lobby
September 7 (Fri)	07:30-12:00	

You are kindly requested to wear your name badge throughout the conference. Please note that admission to the scientific session rooms will be restricted to registered participants wearing their badges.

■ On-site Registration Fee (unit: USD)

Category	On-site Registration
Industry	USD 900
Academia & Government	USD 600
Student	USD 300

■ Full payment registration includes;

Admission to all scientific sessions
Opening ceremony and social evening
Admission to Poster and technical exhibition
Conference materials (bag & name tag, abstract book, etc)
Coffee breaks and lunches (except Sep. 7)

Secretariat_Peacock Room

Secretariat is operated during the conference period. For any help or request, please come to the secretariat.

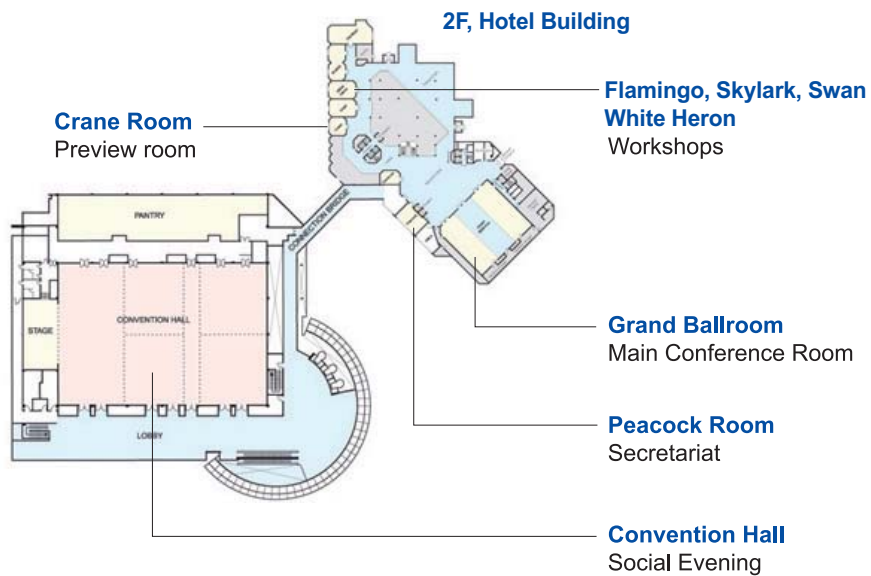## Social Evening

Date & Time: 18:30, September 6, 2012
Place: Convention Hall, 4F Convention Center
Open to all registered participants. It will be great opportunity for the participants to enjoy a pleasant evening and excellent dinner, and make new friends!
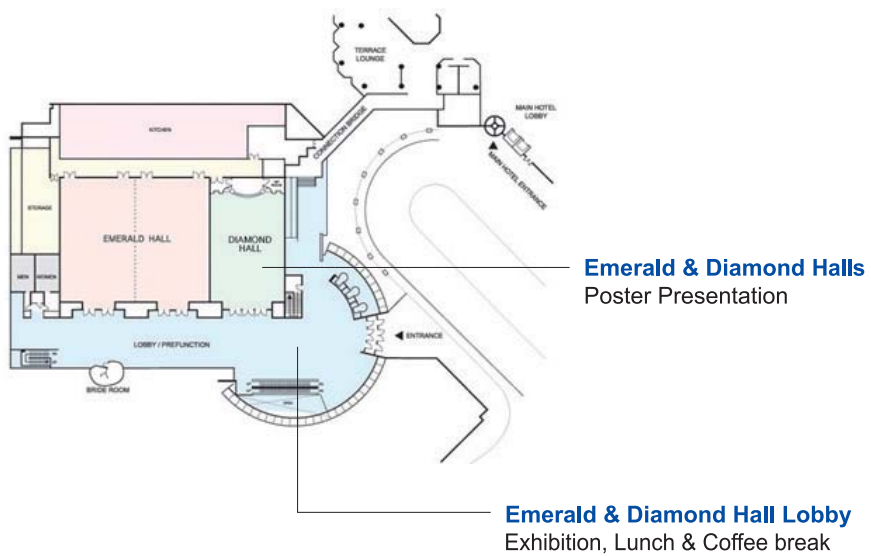
FLOOR PLAN

4F ➡ Convention Hall

2F, Hotel Building

Crane Room
Preview room

**Flamingo, Skylark, Swan
White Heron**
Workshops

Grand Ballroom
Main Conference Room

Peacock Room
Secretariat

Convention Hall
Social Evening

3F ➡ Emerald Hall / Diamond Hall

Emerald & Diamond Halls
Poster Presentation

Emerald & Diamond Hall Lobby
Exhibition, Lunch & Coffee break

🟥 SPONSORS & EXHIBITION

Sponsors

The organizing committee of the World Conference on Pharmacometrics (WCoP) would like to express our sincere appreciation all companies and organizations for their contribution to make this conference a great success.

▪ Gold Sponsors

▪ Silver Sponsors

▪ Organizations

Exhibition

All participants will have opportunity throughout the conference to visit the industrial exhibition.
The exhibition booth will be located at the Lobby of Emerald & Diamond Halls. (3F, Convention Center)

■ **Exhibition Date & Time**

September 5-6, 09:00-18:00   -September 5, 09:00-17:00
                                 -September 6, 09:00-18:00

■ **Exhibition Floor Plan**

No. of Booth	Company
1-2	Korea National Enterprise for Clinical Trials
3	Lixoft
4	GVK Biosciences PVT. Ltd
5	Mango Business Solutions Ltd
6	Bayer Technology Services, GmbH
7	Pharsight Consulting Services, part of Certara™
8	Pirana Software & Consulting / Uppsala University

GENERAL INFORMATION

Useful Website

Grand Hilton Seoul Hotel	http://www.grandhiltonseoul.com
Incheon International Airport	http://www.airport.kr
Gimpo International Airport	http://www.airport.co.kr/doc/gimpo
About Seoul	http://english.seoul.go.kr
About Korea	http://www.tour2korea.com
Ministry of Foreign Affairs and Trades	http://www.mofat.go.kr

Currency

The unit of currency is Korean Won (KRW), expressed as   .
Coin denominations are   10,   50,   100 and   500. Bank notes are   1,000,   5,000,   10,000 and   50,000.
As of August, 2012, the exchange rate is approximately   1,150 for USD1.

Credit Card

Visa, and MasterCard are accepted at almost all retail outlets, but Diners Club and American Express may only be accepted at major hotels, shops and restaurants in the larger cities. Check with your credit card company for details on merchant acceptance and other available services.

Electricity

Outlets for 220 Volts/60Hz are mostly used in Korea. In order to convert the power into 110 volts, please contact the hotel housekeeping and current transformer will be available.

Business Hours

Government office hours are usually from 9am to 6pm on weekdays and closed on Saturdays and Sundays. Banks are open from 9:00am to 4:00pm on weekdays and closed on Saturdays and Sundays. Major department stores are open every day from 10:30am to 8pm including Sundays.

Tax & Tip

Value-added Tax (VAT) is levied on most goods and services at a standard rate of 10% and is included the retail price. Tipping is not regularly practiced in Korea. Service charges are often included in the bill for rooms, meals, and other services at hotels and upscale restaurants.

Emergency Dial Numbers

Police: 112 / Fire & Ambulance: 119 / Medical emergency: 1339
※ These services are available 24 hours.

🔴 GUIDELINES FOR PRESENTATION

For Oral Presentation

■ **Language: English**

- Please check the time allocated to each presentation. We strongly encourage a presentation of no more than alloted time for discussion and to entertain questions from those in the audience.
  Please note the chair is under strict instructions to follow the limited time allotment per presenter for smooth running of the session.
- Arrive at your session room at least 20 minutes before the session begins.
- You will be responsible for controlling/advancing the slides during your presentation.

■ **Presentation Material Format**

- Use a PowerPoint (PPT) file for your presentation.
- Use a standard font such as Times New Roman, Arial or Tahoma. If you use any special or unique fonts for your presentation it may not appear correctly using the session room computers.

■ **A/V Equipment**

- The session room will be equipped with the following items: A computer running Windows with MS Office 2007 or 2010, Acrobat Reader 8.0 and Windows Media Players, and a microphone.
  A podium with monitor will be provided for speakers as well.
- There will also be an AV technician in the session room to assist with any technical issues.
- We DO NOT recommend using your own laptop computer for your presentation to avoid problems with computer-projector compatibility and to save the time that would otherwise be needed for changing connections.
- Please let us know in advance if you would like to use your own computer.

■ **Preview Room : Crane Room, 2F, Grand Hilton Hotel**

- A preview room for you to practice your presentation or review prior to uploading will be available in Crane Room.
- When reviewing your presentation file, please make sure all fonts and images appear as expected. The computers in the session rooms will be identical to those in the Preview Room.
- Final presentation file(s) must be uploaded at 30 minutes before the start of their sessions.

■ **Preview Room Schedule**

Date	Available Hours
September 5 (Wed)	07:30 ~ 17:00
September 6 (Thu)	08:00 ~ 17:00
September 7 (Fri)	08:00 ~ 11:00

GUIDELINES FOR PRESENTATION

For Poster Presentation

Poster Board Size: 95cm (width) x 200cm (height)
Poster Size: within 90cm (width) x 180cm (height)
Place: Emerald Hall & Diamond Hall, 3F, Convention Center
Poster Display Dates & Times: -Septembers 5, 09:00-17:00
-Septembers 6, 09:00-18:00
Poster Mounting: 07:30-08:30, September 5
Poster Demounting: by 19:00, September 6

Poster should be attached on the board **by 08:30 on September 5, 2012.** Each poster should be displayed on the numbered board assigned to each presenter. Please see page (18-30) for your board number. Materials to attach the poster on the board will be provided at the entrance of each room. All posters should be removed **by 19:00 on September 6** and those which are not removed will be discarded by the secretariat.

Each poster must include text in a large enough font to be read easily by attendees from a distance of 1 m. Lettering on illustrations should be large and legible.

PROGRAM

08:45 - 10:05   **Oral session 1:Methodology I**   *chair: France Mentré*

08:45 - 09:05   Red blood cell survival and its influence on clinical biomarkers   32
Julia Korell

09:05 - 09:25   Optimal design for discrete data and BQL   33
Andrew Hooker

09:25 - 09:45   Prediction of human pharmacokinetic profile using data under drug development   34
Yoshitaka Yano

09:45 - 10:05   PBPK joined with IVIVE: A marriage under the arch of systems pharmacology   35
Amin Rostami-Hodjegan

10:05-11:35   **Poster 1 / Exhibit 1 / Break**
Emerald & Diamond Halls, 3F Convention Center   37

11:35 - 12:35   **Oral session 2: Regulatory**   *chair: Holly Kimko*

11:35 - 11:55   Ethnic differences in pharmacokinetics and pharmacodynamics   37
Rujia Xie

11:55 - 12:15   Model-based pivotal decisions   38
Didier Renard

12:15 - 12:35   Exposure-response in oncology   39
Yaning Wang

12:35 - 12:40   **The International Society of Pharmacometrics (ISoP)**   *speaker: Nick Holford*

12:40 - 14:05   **Lunch**,   Emerald Hall Lobby, 3F Convention Center

14:05 - 14:45   **Plenary lecture 1: ISoP lecture**   *chair: Steve Kern*
Pharmacometrics within drug development   41
Peter Milligan

14:45 - 15:15   **Coffee Break,** Grand Ballroom Lobby

15:15 - 16:30   **Workshop 1 & Tutorial**
Grand Ballroom, Flamingo, Skylark, Swan, White Heron

Workshop1: Group discussion on plenary lecture 1
Tutorial: Principles of pharmacokinetic and pharmacodynamic modeling   43
Nick Holford

16:30 - 17:00   **Round-up session 1**

🔴 PROGRAM

08:30 - 09:50 **Oral session 3: Therapeutics**   *chair: Goonaseelan C. Pillai*

08:30 - 08:50	Challenges in Infectious diseases *Gerry Davies*	45
08:50 - 09:10	M&S based development of antibiotic dose calculator for burn patients *Dong-Seok Yim*	46
09:10 - 09:30	Diabetes *Vikram Sinha*	47
09:30 - 09:50	Experience with pharmacogenetics and clinical research in Africa *Collen Masimirembwa*	48

09:50 - 11:20 **Poster 2 / Exhibit 2 / Break**
Emerald & Diamond Halls, 3F Convention Center

11:20 - 12:50 **Oral session 4: MBDD & Bridging in Asia**   *chair: Yusuke Tanigawara*
Sponsored by K-NECT

11:20 - 11:35	Modeling & simulation through research and development processes *Ryosei Leo Kawai*	50
11:35 - 11:50	Outcome of a quantitative analysis comparing treated Chinese/Asian and Western patients with pain due to knee osteoarthritis patients *Guangli Ma*	51
11:50 - 12:05	MBDD & Bridging in Asia - Korean perspective *In-Jin Jang*	52
12:05 - 12:20	MBDD & Bridging in Asia - Taiwanese perspective *Oliver Yoa-Pu Hu*	53
12:20 - 12:35	MBDD Bridging in Asia - Japanese regulatory perspective *Naomi Nagai*	54
12:35 - 12:50	Panel discussion	

12:50 - 14:10 **Lunch**
Emerald Hall Lobby, 3F Convention Center

World Conference on Pharmacometrics

🟥 PROGRAM

Thursday, September 6 — Grand Ballroom

14:10 - 14:50   **Plenary lecture 2**   *chair: Peter Milligan*

Pharmacometrics beyond drug development   56
Steve Kern

14:50 - 15:50   **Oral session 5: Oral presentation of selected abstracts**   *chair: Mats Karlsson*

14:50 - 15:05   Flexible description of delayed events in modeling of alzheimer's disease by Inclusion of dispersion term   58
Akihiro Hisaka

15:05 - 15:20   Identification of a dual mechanism of action for Danoprevir, a protease inhibitor currently in phase 2, using a mechanistic viral kinetic model   59
Nicolas Frey

15:20 - 15:35   Quantitative analysis of reflux episodes in gastroesophageal reflux disease (GERD)   60
Donghwan Lee

15:35 - 15:50   Applications of modeling and simulation in treatment of tuberculosis in South Africa   61
Emmanuel Chigutsa

15:50 - 16:20   **Coffee Break,** Grand Ballroom Lobby

16:20 - 17:30   **Workshop 2 & Software Demo**
Grand Ballroom, Flamingo, Skylark, Swan, White Heron

Workshop 2 Group discussion on plenary lecture 2
Software Demo: Mango, Bayer, Lixoft, Pirana, Pharsight, Uppsala

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17:30 - 18:00   **Round-up session 2**

18:30 -   **Social Evening**
Convention Hall, 4F Convention Center

PROGRAM

09:00 - 10:00	**Oral session 6: Methodology II**	*chair: Nick Holford*
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09:20 - 09:40	DDMoRe *Mats Karlsson*	64
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10:00 - 10:10	**Preview of WCoP 2016**

10:00 - 10:15	**CPT: Pharmacometrics & Systems Pharmacology**	*speaker: France Mentré*

10:15 - 10:50	**Coffee Break,** Grand Ballroom Lobby

10:50 - 12:10	**Oral session 7: Application**	*chair: Stephen Duffull*
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11:10 - 11:30	M&S in pharmacogentics /personalised medicine *Julie Bertrand*	68
11:30 - 11:50	Mechanistic PK/PD modeling *Wei Lu*	69
11:50 - 12:10	Modeling and simulation in pediatrics *Bernd Meibohm*	70

12:10 - 12:20	**Closing**

12:20 - 12:35	**Audience Input**

🔻 POSTER PRESENTATION

Presentation Time & Date: 10:05-11:35, September 5

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PA2-1	A Population Pharmacokinetic / Pharmacodynamic Approach to Fluconazole Use in Burn Patients with Candida Infection *Seunghoon Han, Jongtae Lee, Sangil Jeon, Taegon Hong, Heungjeong Woo, Dong-seok Yim*	73
PA2-2	Evaluation of Colistin Dosing Protocols by Simulations: Flat-Fixed Dose versus Weight-based Loading Dose and Creatinine Clearance (CRCL)-based Maintenance Dose *Ami Mohamed, Otto Cars, Lena Friberg*	74
PA2-3	Population Pharmacokinetic Analysis of Colistin in Burn Patients *Jongtae Lee, Taegon Hong, Sangil Jeon, Seunghoon Han, Dong-seok Yim, Heungjeong Woo*	75
PA2-4	Establishment and Utilization of an *in vivo* Concentration-Effect Relationship for Piperaquine in Preventive Treatment of Malaria *Martin Bergstrand, François Nosten, Khin Maung Lwin, Mats O Karlsson, Nicholas White, Joel Tarning*	76
PA2-5	Population Pharmacokinetic and Pharmacodynamic Modeling of Amodiaquine and Desethylamodiaquine in Women with Plasmodium Vivax Malaria during and after Pregnancy *Joel Tarning, Palang Chotsiri, Vincent Jullien, Marcus J Rijken, Martin Bergstrand, Mireille Cammas, Rose Mcgready, Pratap Singhasivanon, Nicholas Day, Nicholas J White, Francois Nosten, Niklas Lindegardh*	77
PA2-6	An *in vivo* Pharmacokinetic/Pharmacodynamic Model of Fecal Bacterial Resistance to Ciprofloxacin in Piglets Treated with Ciprofloxacin - Application to Design a New Study of Antibiotic Resistance *Thu Thuy Nguyen, Elisabeth Chachaty, Jean De Gunzburg, Antoine Andremont, France Mentré*	78
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PA2-9	Pharmacokinetic Modeling of Cefepime Concentration Data in Human Lung and Target-organ-specific Pharmacodynamic Simulation *Kazuro Ikawa, Satofumi Iida, Norifumi Morikawa*	81

PA9-2	Population Pharmacokinetic (PPK) Analysis for 5-FU, Tegafur (FT), Gimeracil (CDHP) and Oteracil Potassium (Oxo) in the Eight Clinical Studies of S-1 in Western Patients with Solid Cancer _Ken-ichiro Yoshida, Kazumasa Ikeda, Kunihiro Yoshisue, Wuilbert Rodriguez, György Bodoky, Vladimir Moiseyenko, Mikhail Abramov, Mikhail Lichinitser, Kaku Saito, Fabio Benedetti, Jaffer Ajani, Yusuke Tanigawara_	120
PA9-3	PKPD-Modeling of Standard Uptake Value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) Patients Treated with Sunitinib _Emilie Schindler, Paul Westwood, Michael Amantea, Emma K Hansson, Peter A Milligan, Mats O Karlsson, Lena E Friberg_	121
PA9-4	PKPD Modeling of Predictors for Side Effects and Overall Survival in Patients with Gastro Intestinal Stromal Tumor Treated with Sunitinib _Emma K Hansson, Guang Li Ma, Michael Amantea, Jonathan French, Peter A Milligan, Lena E Friberg, Mats O Karlsson_	122
PA9-5	Evaluation of Tumor-Size Response Metrics to Predict Survival and Progression Free Survival in in Western and Chinese Patients With First-Line Metastatic Colorectal Cancer _Laurent Claret, Manish Gupta, Amita Joshi, Nenad Sarapa, Jing He, Bob Powell, Rene Bruno_	123
PA9-6	Pharmacokinetics and its Relation to Toxicity of Pegylated-liposomal Doxorubicin in Chinese Patients with Breast Tumors _Ling Xu, Wei Wang, Yucheng Sheng, Qingshan Zheng_	124
PA9-7	Pharmacokinetics and Tissue Distribution Study of the Nanoporous Octanuclear Cu(II) Wheel Complexes in Rats by High-performance Liquid Chromatography _Man Yuan, Binglin Cui, Lina Xu, Xia Xu_	126
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PA9-9	Population Pharmacokinetics and Pharmacogenomic Analysis of Methotrexate in Patients after Hematopoietic Stem Cell Transplantation _In-wha Kim, Hwi-yeol Yun, Boyoon Choi, Nayoung Han, Myeong Gyu Kim, Seonyang Park, Hye Suk Lee, Jung Mi Oh_	128
PA9-10	Population Pharmacokinetic and Pharmacodynamic Analysis of Docetaxel; Hematologic Side Effects in Japanese Lung Cancer Patients _Masato Fukae, Yoshimasa Shiraishi, Mika Yamahashi, Koichi Takayama, Yoichi Nakanishi, Ichiro Ieiri_	129
PA9-11	Use of Modeling and Simulation in the Early Clinical Development of a Novel Oral Paclitaxel, DHP107 _Hyeong-seok Lim, Kyun-seop Bae, Jin-ah Jung, Seok-joon Jin, Ae-kyung Hwang, Hyeyoun Kim, Yong Sang Hong, Kyu Pyo Kim, Jae-lyun Lee, Min Hee Ryu, Heung Moon Chang, Yoon-koo Kang, Tae Won Kim_	130
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Presentation Time & Date: 09:50-11:20, September 6

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PD-3	Population Pharmacokinetics of Alcohol in Korean Healthy Volunteers with ADH/ALDH Genotypes *Hyekyung Han, Kwang-hee Shin, Hyungmi An, Kyungsang Yu, Seong Ho Yoo, Jae-yong Chung*	157
PD-4	Population Pharmacokinetics of Oxcarbazepine after Oral Loading in Patients with Epilepsy *Namyi Gu, Dong Wook Kim, Hyeong-seok Lim, Kyoung Soo Lim, Joo-youn Cho, Seo Hyun Yoon, Kyung-sang Yu, Kon Chu, Sang-kun Lee, In-jin Jang*	158
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PD-8	Population Pharmacokinetics Analysis of Two Different Formulations of Megestrol Acetate in Healthy Volunteers *Seonghae Yoon, Donghoon Shin, Kwang-hee Shin, Sung Eun Kim, Kyung-sang Yu, Joo-youn Cho, Jae-yong Chung*	162
PD-9	Race Difference: Model-based the Pharmacodynamics of Rosuvastatin in Western and Asian Hypercholesterolemia Patients *Juan Yang, Lujin Li, Kun Wang, Yingchun He, Yucheng Sheng, Ling Xu, Xiaohui Huang, Feng Guo, Qingshan Zheng*	163
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Abstracts

Oral session 1

Methodology I

Chair: France Mentré

Red blood Cell Survival and its Influence on Clinical Biomarkers

S1-1

Julia Korell, Stephen B. Duffull

School of Pharmacy, University of Otago, Dunedin, New Zealand

Red blood cells (RBCs) are highly specialised cells with a unique physiology. They lack the ability of self-renewal and circulate in the body for a finite time, defined as their lifespan. In healthy individuals this lifespan is thought to be in the order of several months, but it can be significantly reduced in pathological conditions such as chronic kidney disease (CKD).

The most commonly used clinical biomarker that is derived based on RBC data is glycated haemoglobin (HbA1c), which is used to assess glycaemic control indiabetic patients. Glycation of haemoglobin occurs throughout the lifespan of RBCs. Hence HbA1c is a measure of cumulative exposure to glucose and is a useful marker of diabetic control. However, a reduced RBC survival results in lower HbA1c concentrations, which can lead to a false assumption of adequate glycaemic control. Thus, understanding RBC survival and how it is affected by pathological conditions is important when dealing with RBC derived clinical biomarkers.

However, all methods available to determine the lifespan of RBCs are inherently flawed and the reported values for the mean RBC lifespan vary considerably when using different methods (100 – 125 days) [1,2]. In addition, there is no reliable information available on the actual distribution of RBC lifespans in humans. Plausible physiological mechanisms involved in RBC destruction include senescence, age independent random destruction as well as cell death due to early or delayed failure. We propose a novel statistical model for RBC survival which is based on a probability density function that accounts for these destruction mechanisms [3]. Furthermore, flaws associated with the most commonly used methods to determine RBC survival *in vivo* have been incorporated into the survival model [4]. The model has been applied to RBC survival data obtained in healthy individuals as well as CKD patients [5]. We propose that this mechanism based model will prove useful in the future to obtain a better insight into RBC destruction mechanisms and how they are affected by pathological conditions, thus providing a better understanding of RBC survival.

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Optimal Design for Discrete Data and Limit of Quantification Data

S1-2

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Several developments have facilitated the practical application and increased the general use of optimal design for nonlinear mixed effects models. These developments include new methodology for utilizing advanced pharmacometric models, faster optimizationalgorithms and user friendly software tools.   However, the methodology is still lacking in some aspects commonly encountered in population modeling problems. In this presentation, methods are presented to incorporate discrete data models and limits of quantification levels in optimal design calculations.

For nonlinear mixed effect models describing discrete data measurements, analytic approximations of the Fisher Information Matrix (FIM), used to optimize experiments, have been derived using generalized linear mixed models (GLMM). However, to use the GLMM approach the link function which relates the responses to a linear model has to be known. Here a general simulation based method is presented and compared to the GLMM approach. This general method [1] computes the FIM derived from the marginal likelihood calculated using either an analytic expression using a Laplace integral approximation or a Monte Carlo integration approach. The general method is shown to be more flexible, with the ability to use it on nearly any imaginable model, but time consuming, while the GLMM approach is faster but limited in model scope.

For handling LOQ levels in optimal design calculations, seven different methods were compared, ranging from ignoring the existence of LOQ levels to calculation of the FIMby integrating over simulated data with a joint likelihood for regular type data (not LOQ) and LOQ data (M3 method) using the Laplace approximation [2]. In this case the simulation based/Laplace method is shown to be a good approximation of the parameter uncertainty seen in stochastic simulation and re-estimation experiments (SSE), but other more approximate methods have faster runtimes and are just as general in model scope. The use of OD methods anticipating LOQ data in planned designs are shown to allow for better parameter estimation than simply ignoring LOQ limits.

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Prediction of Human Pharmacokinetic Profiles Using Data under Drug Development

S1-3

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Estimation of a first-time-in-human (FTIH) dose is an essential element during drug development, and several strategies for predicting pharmacokinetics of drugs in human have been proposed[1,2]. The prediction strategy consists of two steps; the first step is to predict pharmacokinetic parameters such as clearance (CL) and distribution volume (Vd) in human. The second step is to simulate drug concentration profiles in plasma or tissues using appropriate models. Under drug development, available data of a new drug candidate for the prediction are often limited, and therefore a simple and practical method is expected for speedy decision making. Considering these, we have proposed a simple and practical method for predicting drug concentration-time profile in human using 'normalized curves', which is often called Css-MRT method or Wajima Approach[3]. As we mentioned[3], this method is independent of the ways to predict pharmacokinetic parameters such as Vss and CL and is flexible to be combined with any other approaches. Of course, as criticized[2], prediction accuracy is an important factor for choosing an appropriate prediction method and also for using prediction results for decision making. However, I believe that Css-MRT method has potential to be used widely during drug development.

Prediction of time courseprofile is a kind of wave analysis, and a concept of system control can be applicable. In this concept, the Css-MRT method is a 'module'to obtain a weighting function (or a transfer function in Laplace domain) after intravenous drug input. If we have other 'modules'to explain drug absorption process, tissue distribution process etc., we can construct a full prediction system by combining these modules. In this presentation, some advanced approaches using the Css-MRT method, i.e. simulations of oral plasma concentration profiles, simulations of tissue concentration profiles with Fast Inverse Laplace Transform (FILT) algorithm[4,5], and simulations of pediatric pharmacokinetic profiles using adults' data in clinical phase 1 studies[6], will be discussed.

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PBPK Joined with IVIVE: A Marriage under the Arch of Systems Pharmacology

S1-4

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Classical pharmacokinetics rarely takes into account the full knowledge of physiology and biology of the human body. However, physiologically-based pharmacokinetics (PBPK) is mainly built from drug-independent 'system' information (see Figure). PBPK is nota new concept, though it has shown a very rapid rise in recent years. This has been attributed to a greater connectivity to in vitro - in vivo extrapolation (IVIVE) techniques for predicting drug absorption, distribution, metabolism and excretion (ADME) and their variability in humans. The marriage between PBPK and IVIVE under the overarching umbrella of 'Systems Biology'has removed many confinements related to cut-off approaches on prediction of ADME [1]. PBPK-IVIVE linked modes have repeatedly shown their value in guiding decisions when predicting the effects of intrinsic and extrinsic factors on pharmacokinetics. The models might be extended to pharmacodynamics and drug safety faster if the necessary structure for holding the system information is created.

Applications of IVIVE-PBPK linked models have provided guidance in dealing with dosage changes under different scenarios such as co-morbid disease, variations due to age, sex, ethnicity, genotypes, environmental factor such as food and smoking [1] and they have been of particular interest for regulatory agencies [2]. The availability of common platforms can reduce the reliance on specialized modeling experts to carry out the initial step of "creating generic models" (precompetitive level by all pharmaceutical companies) but it shifts the focus to wider "applications of specific models" for the drugs developed by industry [3].

Figure - The essence of the separation between "drug data" and "systems data" is captured in the diagram [1]. De-assembling the information and separating the elements enables a re-assembling at a later stage for populations that have never been exposed to the drug. This approach is used for assessing the likelihood of differences in PK (/PD) in that population before conducting any clinical studies (see the text for case examples). IVIVE, in vitro–in vivo extrapolation; PBPK, physiologically based pharmacokinetics; PD, pharmacodynamics.
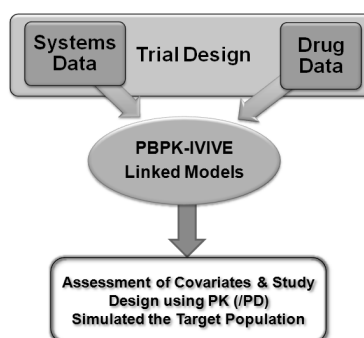
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Oral session 2

Regulatory

Chair: Holly Kimko

Ethnic Differences in Pharmacokinetics and Pharmacodynamics

S2-1

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Objective: Unmet medical needs in China are growing rapidly and pharmaceutical companies are interested in global drug development (GDD). Understanding ethnic difference in pharmacokinetics (PK), pharmacodynamics (PD) and safety is critical for the GDD strategy.

Methods: Preliminary literature search was conducted to identify main potential sources of ethnic PK and PD differences. Genotype and body weight (potential intrinsic factors) were reviewed and summarised. Approved dosage of 59 compounds in China was compared with that in other countries (US, EU and Japan) [1]. The reasons for the different dosages among the countries were explored in the PK, PD and safety aspects.

Results: The difference of average body weight (BW) between Chinese and American is about 10-20% [2,3]. With such difference in BW, it expected for most drugs that BW could only account for a relatively small percentage of inter-individual PK variability. BW/body size based dosage adjustment is often considered for narrow therapeutic window (eg. Prasugerl) and cytotoxic anticancer agents. The effect of genetic polymorphism on PK was well studied for CYP2C9 (Warfarin), CYP2C19 (Plavix), CYP2D6 (Propanolol), UGT1A1 (Irinotecan), and BCRP (rosuvastatin). Genetic polymorphism on PD was reported for vitamin K–epoxide reductase protein (VKORC1) (Warfarin) and epidermal growth factor receptor (EGFR). The prevalence of EGFR-mutant NSCLC is appreciably higher in East Asian than in Caucasian populations. Based on Malinowski et al work[1], the comparison of the dosage regiment in China to other regions showed that 46 out of 59 drugs were recommended same doses as the original approved regions and total of 13 drugs have different doses including anti-hypertension, anti-coagulant, HMG CoA inhibitor, diabetics and depressant compounds. These were due to PK, PD or safety concerns.

Conclusions: Ethnic difference in PK and PD can be evaluated from different aspects of intrinsic and extrinsic factors. Genetic polymorphism plays an important rolein ethnic difference in PK, PD and safety. Dose adjustment should be based on clinical outcomes and consideration of risk/benefit balance, not only PK difference. A comprehensive systematic review is required for further understanding the intrinsic and extrinsic factors accounted for ethnic differences.

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Model-based Analyses for Pivotal Decisions

S2-2

D. Renard[1], B. Bieth[1], G. Heimann[1], I. Demin[1], B. Hamren[2], S. Balser[3], F. Mentre[4]

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[2]Clinical Pharmacology, AstraZeneca R&D Mölndal, Sweden
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Objectives: Modeling and simulation principles are frequently used in an exploratory manner in drug development and non-linear mixed effects (NLME) models are rarely, if ever, specified for primary analysis purposes in protocols of pivotal clinical trials. Our objective in the present work was to prospectively specify an NLME analysis that is sufficiently robust from a statistical viewpoint to satisfy stricter regulatory standards as those routinely applied in Phase 3 studies.

Methods: The principle of our approach is illustrated in the context of biosimilar equivalence in rheumatoid arthritis, using the American College of Rheumatology 20% (ACR20) response criterion as primary study outcome. Since it is difficult to qualify all aspects of NLME analyses, we opted for pre-specification of several candidate models to describe the expected time course of ACR20 response, using different types of Markov models [1]. This approach was used primarily as a means to minimize risks of model misspecification in the planned analysis. Since the study aims to demonstrate equivalence between the originator product and the biosimilar, a key modeling outcome is the mean response rate difference between the two groups at primary end-point. We envisioned to rely on model averaging [2] to combine the individual model estimates. A confidence interval for the model average estimate can be derived using bootstrap and this confidence interval can serve for formal equivalence testing. The traditional approach to equivalence testing would be to estimate the mean difference in ACR20 response rates solely relying on end-point data. The proposed model-based test was compared to the classical equivalence test through extensive simulations. Operational characteristics, such as type 1 error and power, were of particular interest. This investigation was performed under a range of simulation models and scenarios

Results: Type 1 error appeared to be controlled under the simulation scenarios investigated.
The gain in power with the model-based test was substantial compared to the classical equivalence test.

Conclusion: While those simulation results appeared promising, initial feedback from European health authorities suggested that further work should be undertaken to more thoroughly evaluate the performances of the proposed approach. In particular, the absence of theoretical results to justify type 1 error control appears to be a critical concern deserving careful consideration.

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Exposure-Response in Oncology

S2-3
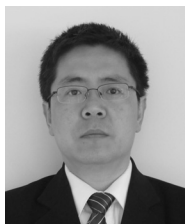
Yaning Wang

US Food and Drug Administration, USA

The success rate of new molecules in oncology is 5%, lowest compared to other therapeutic areas. The success rate for oncology phase 3 trials declined from 67% during 97-2002 to 46% during 2002 to 2007. The top driver for oncology phase 3 failure is lack of superior efficacy for a new regimen compared to an active treatment. The second driver is failure to show the efficacy of a new regimen against placebo or best supportive care. Combining the top two drivers, almost 80% of the failure is related to efficacy. The high failure rate related to efficacy in phase 3 trials should be due to a poor estimation or overestimation of the efficacy based on the earlier clinical trials. Poor selection of dose and dosing schedule is one of the multiple reasons that could be related to the poor estimation of effect size. Dose-ranging trial to optimize dose selection for efficacy is rarely conducted for oncology program. Exposure-response analysis based on one dose level in a randomized phase 3 trial was conducted to assess whether the proposed dosing regimen was supported by the exposure-response relationship. Due to the non-randomized nature of this analysis, potential confounding factors could lead to biased estimation of exposure-response relationship. Even though a multivariate regression method can be used to analyze such data, false conclusions can arise due to inappropriate assumption about the structure model. A case-control analysis was combined with the exposure-response analysis to minimize the bias in the estimation of the treatment effect at a certain exposure level. Valuable exposure-response information can be extracted even from a single dose trial with the appropriate analysis method. Such information can serve as the basis for designing a new trial to optimize the dose. Similar analysis should be conducted earlier during the drug development to not only improve the success rate of oncology phase 3 trials but also optimize the dose for each patient.

Plenary lecture 1

Chair: Steve Kern

Pharmacometrics within Drug Development: Advancing the Intellectual Health of Clinical Drug Evaluation?

PL-1

Peter A Milligan

Pharmacometrics, Global Clinical Pharmacology, Pfizer

In 1997 Lewis Sheiner published his seminal work on *learn-confirm cycles* (7) which has become his most cited, and arguably his most influential, article on both the theory and application of quantitative approaches within a drug development context.

Fifteen years on however, late stage development failure is the greatest obstacle to Pharmaceutical Industry productivity with insufficient, or a complete lack of efficacy, being the most common factor associated with study/compound failure. Clearly the ability (or capacity) of existing early stage information to provide sufficient and adequate "learning" still has to be appropriately addressed if the high failure rate in late stage development is to be reduced.

Over the years, the learn-confirm paper has transcended the "narrow" Clinical Pharmacology and Pharmacometrics communities to enter the common parlance of the broader Drug Development and Regulatory environments in both "words and deeds". It can be argued that for this broader constituency (and perhaps even the narrower Clinical Pharmacology and Pharmacometrics community) this paper has become so synonymous with Sheiners' thinking on Drug Development that it has come to define his views and characterise the extent of his publication/presentation output.

Listed below, in chronological order, are 10 manuscripts that I believe provide a more complete and comprehensive illustration of his views and the majority of this presentation will actually consider a much earlier, but in my opinion, equally important and visionary paper (3). I will aim to determine what has been resolved in the intervening 20 years since that paper was published, what continues to be problematic and what appear to be opportunities for quantitative approaches (specifically Pharmacometrics) to advance the intellectual health of drug evaluation.

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5) Intention-to-treat analysis and the goals of clinical trials, Lewis B. Sheiner and Donald B. Rubin, Clinical Pharmacology & Therapeutics (1995) 57: 6–15
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Tutorial

Nick Holford

Principles of Pharmacokinetic and Pharmacodynamic Modelling

Tutorial

Nick Holford

Pharmacology & Clinical Pharmacology, University of Auckland, New Zealand

Objectives

To describe the principles of pharmacokinetic and pharmacodynamic (PKPD) modelling

Methods

Clinical pharmacology is based on understanding the dose-effect relationship. The link between dose and effect is controlled by drug concentration. Pharmacokinetics links drug doses to concentration. Pharmacodynamics links concentration to effect.

Results

Pharmacokinetic models are used to provide the initial driving force for pharmacodynamics. A linking model is almost always needed to account for the delay between drug concentration in the circulating blood and the drug concentration at the site of action.

Linking models reflect a combination of processes which determine the delay in drug effect (distribution, binding, physiological changes).

Pharmacodynamic models are based on receptor binding theory but are often empirically modified to account for a limited range of experimental concentrations (linear model) or complex drug-receptor actions (sigmoid Emax model).

Conclusions

PKPD models are only part of theprocess of understanding clinical pharmacology (1). Effects of drugs on disease progression are frequently needed to describe the time course of response (2). Clinical outcomes such as increased survival or reduction of risk of a medical event can be understand by linking PKPD models to disease progress and then using disease progress to describe the hazard of death or other medical event (3).

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Oral session 3

Therapeutics

Chair: Goonaseelan C. Pillai

Challenges in Infectious Diseases

S3-1

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Infectious diseases remain a huge public health problem worldwide and pose unique challenges in drug development and deployment. Since such diseases target the poor, overcoming these challenges has typically relied on effective public-private partnerships between academia, NGOs and the pharmaceutical industry. Among them are the routine use of drug combinations, the relationship between measures of infectious burden and clinical outcome, the influence of factors such as host immunity and the need to maintain durability of population response in the face of inducible resistance. Only a better understanding the PK-PD relationships that drive clinical response can result in a fully rational approach to optimizing therapy in this area.

The role of pharmacometrics as an effective tool for drug development in infectious disease is illustrated using tuberculosis (TB) as a case study. TB remains a leading global killer of young adults. Current first-line therapy requires six months of a four-drug regimen for stablecure and is critically dependent on rifampicin, with those resistant to this drug requiring at least 24 months of treatment to achieve cure rates of only 60%. No new class of TB drugs has been licensed for more than thirty years.

Phase II development in TB has recently begun to adopt quantitative measures of bacterial load amenable to PK-PD analysis as a means to identify and to prioritise the best treatments but there are limited data to assess the predictive power of these measures for long term stable cure of the disease. However, use of adaptive or selection designs based on these endpoints appears to be the only means of optimising regimens for Phase III trials. New technologies may contribute new information regarding the evolving biology of organisms during treatment but raise questions as to how best to incorporate this data into pharmacodynamic models.

A more comprehensive disease model-based approach which formally incorporates the most useful preclinical PK-PD information from in vitro and in vivo systems has the potential to address some of these problems and to reduce the uncertainty in predictions of efficacy. The multidisciplinary PreDiCT-TB consortium will develop such a framework over the coming five years.

A Web-based Prediction System for Therapeutic Outcome of Antimicrobials Used in Burn Patients

S3-2

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Background: The PK parameters of antimicrobial drugs in burn patients are known to be significantly different from those of unburned patients. For successful antimicrobial therapy in severely burned patients, finding the optimal dosage regimen based upon the PK and PD chracteristics i.e., the susceptibility of the microbes (e.g. minimum inhibitory concentration, MIC), is a critical issue. We recently developed a web-based dosing recommendation system for clinicians who prescribe antibiotics to burn patients using the population PK-PD study results performed in the patients for the past several years.

Methods: For easy access by clinicians, we aimed to develop a web-based interactive system where doctors can provide the patient information affecting PK property (e.g. age, weight, sepsis status), the MIC of the microbe, and the dosing regimen. For this purpose, mixed-effect population PK models which have been developed for meropenem, fluconazole, and colistin in burn patients were applied. The efficacy of drugs in each individual was characterized by fAUC/MIC or T>MIC at steady-state as previously reported. The final PK models including inter and intra-subject variability and the fAUC/MIC or T>MIC as PD parameters were reproduced using R (ver. 2.11.1) scripts in order to simulate the PK/PD in the web page.

Results: With PK-PD simulation including random MIC sampling in 10,000 virtual patients, therapeutic outcomes were predicted as the percentage of patients who achieved a certain target value of efficacy parameters in the web page. Once the information is entered, the system returns the value of "probability of target attainment (PTA)" for the dosing regimen entered.

Conclusion: The PK models were successfully implemented in the web-based system to predict the PTA. The web-based therapeutic outcome prediction system presented herein is expected to help the prescribing clinicians to choose the optimal antibiotic dosage regimen for their burn patients.

The Application of Drug-Disease Models in the Development of Anti-Hyperglycemic Agents

S3-3

Vikram Sinha PhD

Lilly Research Laboratories, Eli Lilly & Company

Diabetes is a chronic disease characterized by hyperglycemia resulting from defects in the regulation of glucose and insulin homeostasis. Hyperglycemia, if not well controlled, will progress to more serious complications. Therefore, all available treatments aim to lower blood glucose by various mechanisms of action. Glucose and glycosylated hemoglobin (HbA1c) are well established and readily measurable biomarkers of the disease.

As the need for new medicines to treat diabetes and associated complications increases, pharmaceutical companies are faced with three key challenges:(1) identifying targets and developing medicines that differentiate from existing standards of care in an efficient manner; (2) convincing regulators of the added benefit of such treatments and (3) providing useful guidance to prescribers and payers (including patients) on using these medicines effectively.

The traditional pharmacokinetic/pharmacodynamic models are evolving to include integrated predictive models that can be utilized in quantitative decision making. These predictive models are now being applied in the following areas:

1. *Target prioritization*: using physiological models to assess effects of target modulation and test possible combinations.
2. *Clinical trial simulations*: using models to simulate the exposure–response relationships of investigational drugs that form the basis of exploring aspects of variability using clinical trial simulations.
3. *Assessing clinical outcomes*: using outcome models to project from randomized controlled trial data to long-term clinical outcomes, costs or commercial viability of a new investigational drug.
4. *Dosing calculators and guidance tools*: using models that form the basis for interactive computer program that can predict an individual patient's response and identifies the optimal therapeutic regimen for the patient.
5. *Disease progression*: using model to predict long-term improvements to glycemic control and b-cell function and potential to delay or modify progression of the disease.

In this presentation, a brief overview of the disease and the types of drug-disease models that may be applied in various stages of drug development will be provided. Through simulations, these models are the essential tools to aid the optimization of clinical trials and to learn about the safety and efficacy of new drugs relative to the standards of care and to face the increasing challenges of drug development for the treatment of diabetes.

Experience with Pharmacogenetics and Clinical Research in Africa

S3-4

Collen Masimirembwa[1], Eleni Aklillu[2]

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[2]Clinical Pharmacology, Karolinska Institute, Sweden

Objectives Genetic variability is a major contributor to variable response to medicines with respect to efficacy and safety. Most studies have been done in Caucasian and Asian populations with little work on African populations. Studies with various genetic markers have however shown that African populations exhibit more genetic variation than that observed within Caucasian and Asian populations. We therefore embarked on population pharmacogenetics and clinical studies in African populations based on the postulation that these populations could exhibit genetic variability of clinical importance.

Methods We studied the genetic polymorphism of major drug metabolising enzymes (DMEs): CYP21A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6,3A5; NAT-2, GST, UGT, and FMO in over 10 African populations (Yoruba, Ibo, Hausa, Luo, Maasai, Kikuyu, Amhara, Tigrei, San, Shona, Venda) using standard PCR-RFLP, RT-PCR and DNA sequencing methods. The data was analysed using principal component analysis (PCA) and genotype-phenotype correlations. Clinical pharmacogenetics studies were conducted on the anti-retroviral drug, efavirenz, in Zimbabwean, Ethiopian and Tanzanian patients.

Results PCA analysis of the allele frequency of the DMEs SNPs showed significant population clustering which separated the African, Caucasian and Oriental populations. Re-sequencing studies led to the discovery of novel SNPs in African populations. Given that the DMEs evaluated are major determinants of the pharmacokinetics ofmany drugs in clinical use, these observations allude to the likely clinical importance of the observed polymorphisms. The variants of CYP2B6, *6 and *18 showed significant correlation with efavirenz exposure. In Zimbabweans, over 50% of the patients had levels above the minimum safe concentration. Further analysis using partial least square analysis (PLS) modelling led to the derivation of a pharmacogenetics guided dosing algorithm where patients homozygous for the CYP2B6*6 required 200 mg instead of 600mg efavirenz a day to achieve safe and efficacious concentrations.

Conclusions Our population pharmacogenetics data support the postulation that genomic variation of African populations could have clinical implications. Pharmacogenetics guided dosing of efavirenz based on the algorithm developed in this study could have a major clinical impact in African populations where up to 20% of the patients are homozygous for the CYP2B6*6 variant.

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Oral session 4

MBDD & Bridging in Asia

Chair: Yusuke Tanigawara

Modeling and Simulation through Drug Development Processes

S4-1

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Variety of models are applied to broad scope of drug development starting from lead optimization through confirmatory clinical study or even post-approval, life-cycle management efforts in pharmaceutical industries. This presentation will highlight our experience and strategy in model-based drug development in Japan during preclinical to clinical stages.

Mechanism based PKPD is a tool to extrapolate quantitative drug responses (efficacy and safety) from animal models to those in patients,which are translated from biomarker readout. For oncology (anticancer drugs), tumor size in tumor-bearing mice is a common biomarker of efficacy[1]. For anti-diabetic drugs, multiple biomarkers, such as plasma glucose and insulin, are commonly quantified[2]. In either example, in vitro data related to PK and PD, using animal and human materials, are the key source to increase accuracy of cross-species bridging. Often missing information is drug response (PD) parameters in man or their comparison to those in animals before conducting a clinical study. Reference compound data (if in vitro and in vivo available) are often used to mitigate such uncertainty. Otherwise, the model approach allows a range of human PKPD projections which can be logically defined based on common data- and/or knowledge-bases.

Physiologically-based PK (PBPK) model further explores mechanism-based PKPD by adding even more data-/knowledge-bases. A PBPK model structure is a robust tool to bridge PKPD systems across species, as well as diversity of human/patient populations, e.g., pediatric, obese, elderly, various disease conditions, etc. PBPK modeling is performed with different tools/approaches depending on the compound's characteristics or issues to be addressed. In addition to commerciallyavailable generic software, GastroPlus and SimCYP, which employ state-of-the-art model building packages (rich database with in silico tools), specifically-tailored models are developed if needed; e.g., for drugs showing unique nonlinearity, target-dependent distribution[3], etc. PBPK modeling supports virtual patients'PKPD simulation before entering human testing, including variability across populations, thus, effectively supports designing first-in-human studies.

Population PKPD (Pop PKPD or NLME; nonlinear mixed effect) modeling is the main modeling tool during clinical development phases, characterizing dose − exposure (PK) − response (efficacy and safety) relationships in a given population. The model, once developed with initial (typically phase I study) data, evolves by adapting it to different populations of data sets (healthy to patients in various disease states and geographic regions). Bridging clinical data between diverse global regions (North America, Europe, Asia, and emerging market) is one of the key tasks effectively achieved by this modeling approach. Difference in body size and genetics of drug metabolizing enzymes (such as 2C19、2D6) are well known "intrinsic" ethnic factors accounting for the PK differences observed between populations, which may or may not be reflected by adjustment of recommended (standard) dose/regimen among the regions, depending on their clinical relevance (particularly for safety). Genetic difference is also a consideration for pharmacologic sensitivity. Increasing use of biomarkers for both PK and PD helps translate such racial/regional differences into individual factors. In addition, medical environment, patients'/regulators' preference, or others identified as "extrinsic" factors may potentially have a significant impact on the drug's clinical responses[4]. It is thus prudent to quantify these ethic factors carefully by full use of PopPK modeling in order to accumulate clinical lessons learnt and to achieve eventually a successful global drug development.

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Outcome of a Quantitative Analysis Comparing Treated Chinese/Asian and Western Patients with Pain due to Knee Osteoarthritis Patients

S4-2

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BACKGROUND: In order to determine if there were any difference in the perception of pain in Chinese/Asian patients with knee osteoarthritis (OA) compared to those in the West, a model based meta-analysis was conducted on clinical studies performed in both regions. The information obtained from this analysis should be very valuable for informing future study designs for the treatment of knee OA pain in Chinese/Asian patients.

AIM: To identify and determine potential key factors, which may impact the treatment effects, when designing a study to evaluate pain relief due to Knee OA in Chinese/Asian cohorts.

METHODS: Study level data (n=21) of OA pain for Treatment A and B were pooled from Pfizer internal database. Graphical exploration was used to identify the potential differences between China/Asia and western countries. After identification of potential factors, external literature data (n=5) were collected by predefined search criteria. Internal data and external data were combined (n=8) for building a pain intensity progression model to assist the study design of OA pain treatment in Chinese patients.
NONMEM, PsN, and Xpose were employed in modeling and simulation. The model was evaluated using graphical and numerical diagnostic tools.

RESULTS: The following potential differences in OA pain between China/ Asia and western countries were identified:

1. The baselines of pain intensity in the patients of eastern countries are lower than those in western countries. The difference might be largely due to the flare design in the western countries verses non-flare design in the eastern countries i.e treatment was adjunctiveto standard of care In western patients (flare design), the pain relief generally reached plateau at 2 to 6 weeks, while the OA pain intensity in Chinese patients continued to decrease during the 12 week study, despite the lower baseline at entry.
2. Study design difference: active-controlled and non-flare design were commonly used in Chinese/Asian patients while placebo-controlled and flare design were used in western countries.

An OA pain intensity progression model was built based on 8 non-flare design studies.
EMAX = EMAXplacebo+EMAXtreatment
ET50   = ET50placebo+ET50treatment
EMAX = EMAX*EXP(ETA1)
ET50   = ET50*EXP(ETA2)
RESP=-EMAX*TIME/(ET50+TIME)

Where RESP is response of OA pain, pain intensity; EMAX is max effect (CFB); ET50 is time to achieve 50% of max effect; ETA is intra-individual/arm variability (IIV).
Estimated EMAXplacebo and ET50placebo were 43.4 and 2.76 years, respectively. EMAXtreatment and ET50treatment were 16.9 and -0.228 years, respectively. IIV was 40% and 72% for EMAX and ET50, respectively.

CONCLUSIONS: Graphical explorations were helpful in understanding the differences in the key factors which may determine the baseline of pain intensity and treatment effect in OA patients coming from different countries/regions. Quantification of OA pain intensity and its progression in non-flare design studies is very useful in a clinical study design to determine the effect and duration of the treatment (as an adjunctive therapy) for OA pain in Chinese/Asian patient population However it will be important to compare the placebo response in Chinese\Asian cohorts with those in Western studies to determine if there are true differences in responsiveness.

MBDD & Bridging in Asia - Korean Perspective

S4-3

In-Jin Jang, MD, PhD

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Korean regulatory agency adopted ICH E5 guideline for marketing approval of medicine developed in foreign countries. Therefore, any type of data from Korean subjects can be used for bridging purpose. The data can be pharmacokinetic (PK), pharmacokinetic/pharmacodynamic (PK/PD), dose-response, clinical outcome and so on. Recently, trials of bridging purpose are less than before as data from global multi-national trials are used for bridging purpose in Korea. Sometimes interpretation of those multi-national trial data is challenging as numbers of Korean subjects are limited or outcomes are not identical. PK or PK/PD data from bridging purpose trials frequently demonstrated difference from other ethnic groups. The assessment of clinicalsignificance of the difference is also challenging issue. We have more knowledge of the ethnic difference in PK or PD from pharmacogenetic background but other unknown factors are still significant. For more confident assessment of similarity or planning for the bridging data generation, model based approach is essential to overcome the limitation of data generated in Korean population.

MBDD & Bridging in Asia
- Taiwanese Perspective

S4-4

Oliver Yoa-Pu Hu, Ph.D., FAAPS.

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To eliminate redundant or unnecessary clinical trials and to better understand the possible ethnic sensitivities of a new drug, the International Conference on Harmonization (ICH) E5 guidance: Ethnic Factors in the Acceptability of Foreign Clinical Data (1) was adopted by the Taiwanese Department of Health (DOH) on December 12, 2000 (the Double-Twelve Announcement). It clearly stated the scope and principles for implementing the bridging study beginning January 1, 2001.The bridging study evaluation(BSE) assessment process proceeded in Taiwan, entirely following to the principles described in the ICH-E5 document.

According to the ICH-E5 guideline, there are two steps in the assessment of foreign data for extrapolation. First, the product's pharmacokinetic and pharmacodynamic(PK/PD) characteristics as well as its clinical properties are analyzed to assess the product's potential sensitivity to ethnic factors.

For cases with ethnic concerns, Taiwan FDA requests clinical trials conducted in Asian populations. Data generated from these trials were then compared with those conducted and derived from foreign, mostly Caucasian trials. Some other Asian countries chose a quite narrow definition of what should be counted as "Asian clinical data," based on subjects from other Asian states, failed to be recognized as a substitution for those based on their own countries.

In Taiwan, if the results of these trials were comparable (eg, similar PK or/and PD profiles, clinical efficacy, and safety profiles between Asian and non-Asian populations) or they provided appropriate information for dosage adjustment for Taiwanese patients, the bridging study will be waived.

In this report, 11 years of BSE cases were collected and analyzed to determine the rate and the reasons at which clinical trial waivers were not granted. Taiwan FDA , from years 2001 till 2012, have evaluated possible intrinsic ethnic and extrinsic differences, several steps have been adapted. First, PK and PD comparison between Asian and nonAsian, then, dose response curve fitness in Asian, now, population Pharmacokinetics (popPK) analysis was used to identify PK and non PK factors. Between 2007 and 2011, 97 cases were evaluated, among them, popPK gave less ambiguity and low percentages of ethnicity difference(popPK v.s PK：8.7% v.s 24.32％, in ambiguity; none v.s 6.76％ in ethnicity).

In the evaluation of ethnic differences, drug characteristics and target population were the two major elements be considered. Genetic polymorphism, hepatotoxicity and tuberculosis (TB) were two major safety concerns in the bridging assessment in Taiwan. Difference in the disease epidemiology and disease manifestation were another important issues. Furthermore, medical practice usually is one of the greatest variations and the most difficult to harmonize and possible drug–drug interactions are all essential considerations in the evaluation for the need of BS.

Model Building Drug Development (MBDD) and Bridging in Asia - Japanese Regulatory Perspective

S4-5

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Pharmacokinetics (PK) and Pharmacodynamics (PD) provide scientific backgrounds not only for optimizing drug therapy in the medical practice but also for planning and conducting clinical trials in the drug development. After issuing the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5, E15 and E16 guidelines as well as regional regulatory documents on clinical PK studies and global clinical trials by the Ministry of Health, Labour and Welfare (MHLW)[1-5], drug development strategy for the regulatory approval in Japan has remarkably changed by making use of new concept and methodology, for example, biomarkers, pharmacogenomics, population PK(PPK) approach, PK-PD modeling and simulation (M&S) and multinational/multiregional clinical trials. As a result, effects of various factors such as genetic variants and ethnic differences on PK, efficacy and safety of an investigational drug have currently been evaluated using the same clinical data sets among different regions including Asian countries. Therefore, the role and contribution of clinical pharmacology on recent clinical development management and decision-making have steadily become more important, and the new drug applications (NDAs) in Japan including PPK approach, pharmacogenetic information and global clinical trial data have been increasing. Based on these trends, the concept of model based drug development (MBDD), in which preclinical and available clinical data are integrated for appropriately designing subsequent clinical trials as well as for describing relationship between drug exposure and efficacy/safety, has come to be recognized as a powerful methodology, because accelerating speed and success rate of new drug development is still difficult.

Further discussion and collaboration among industry, academia and regulatory agencies as well as collecting and sharing successful experiences of MBDD are expected.

In my presentation, I'll talk the following three things,
1) Summary of current situation on PPK approach in the NDAs in Japan
2) PPK and M&S information for some drugs recently approved using results of the multinational clinical trials conducted in Asia
3) Brief outline of the project team regarding MBDD, which has been organized across multi-offices in the PMDA

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Plenary lecture 2

Chair: Peter Milligan

Pharmacometrics beyond Drug Development

PL-2

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Pharmacometrics as a field was born from efforts to improve drug therapy for individual patients - to "personalize" their medicine, a term that has recently regained emphasis but in actuality has been the driving force of the field for a long time. Recognition of the concept of a therapeutic window, where one needs to give a person the right dose at the right schedule to maximize benefit and minimize risk of unwanted effect catalyzed the use of quantitative methods to understand the "system behavior" of a patient taking a medicine in order to achieve this therapeutic goal. Pharmacometrics within drug development essentially arose as a consequence of realizing that if quantitative methods could be used to provide therapy to individual patients, it should also play a role in informing decisions about the drug as it moves through its pre-clinical and clinical development.

While much energy is devoted to improving pharmacometrics as a methodological field within drug development, it's important to recognize that the primary motivation is still to bring the right dose to the right patient at the right time. To do this requires using pharmacometric methods to address questions regarding the best way to treat patients with our compounds and to assess whether our new agents truly offer an incremental benefit over the existing standard of care. This may require finding pharmacometric solutions that are motivated by different questions than producing the lowest model objective function and can be understood by non-quantitative "partners" who need to endorse our solutions because they conceptually understand the insight we are deriving from our analysis. These "partners" include drug development project team members, regulators, payors, physicians and perhaps ultimately, the patients who will benefit from our efforts. When thought of in this context, pharmacometrics beyond drug development challenges us to bring our knowledge and insight beyond WCoP, ACoP, and PAGE to the world at large. In doing so, we create new opportunities to advance the science of drug development and pharmacotherapy around the world.

Oral session 5

Oral presentation of selected abstracts

Chair: Mats Karlsson

Flexible Description of Delayed Events in Modeling of Alzheimer's Disease by Inclusion of Dispersion Term

S5-1

Akihiro Hisaka[1], Masashi Honma[2], Takashi Moritoyo[3], Yoshihiro Arakawa[4], Takeshi Iwatsubo[5], Hiroshi Suzuki[2]

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Objectives In order to analyze efficacy of long-term pharmacotherapy, time-dependent progress of the disease needs to be considered quantitatively in an appropriate disease model. Alzheimer's disease (AD) is characterized by cognitive impairment and progressive neurodegeneration triggered by accumulation of amyloid-beta containing plaques in the brain. Delays from the accumulation of plaques to the cognitive impairment are more than several years and extremely variable between patients. However, current mathematical techniques used in the disease modeling lack ability in describing delays flexibly. In the present study, a dispersion term is included in disease modeling for the first time to overcome this situation.

Methods Mathematically, dispersion term is described with a partial differential equation, and special calculation technique, such as the finite difference method (FDM), is required to solve them under nonlinear conditions (1). In the present study, the equations of FDM including appropriate boundary conditions were converted into a series of ordinary differential equations, and solved with Runge-Kutta-Fehlberg algorithm widely implemented in conventional computer applications. Preciseness of the calculation was compared with those by analytical solutions or FILT method for special cases, and by FDM for general cases.

Results In conventional disease modeling, a state in the disease is expressed with a distinct compartment, and hence, delays cannot be considered within a compartment because of its well-stirred property. In several modeling analyses, delays have been successfully implemented by assuming multiple compartments connected in series. However, it should be noted that, in these models, relationships between extent and variance of the delays are mathematically fixed by number of compartments used. For this reason, it is difficult to examine inter-situation and/or inter-individual variability of the delays. In contrast, models with a dispersion term allowed description of various events with a naturalgradient of delays. The extent and variance of the delay were able to defined arbitrarily. Preciseness of the calculation was confirmed successfully by comparing results with the other algorithms. Usefulness of dispersion terms in modeling of AD was demonstrated.

Conclusions It was revealed that dispersion terms were useful to characterize delays of various events and responses in modeling of long-term diseases such as AD.

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Identification of a Dual Mechanism of Action for Danoprevir, a Protease Inhibitor Currently in Phase 2, Using a Mechanistic Viral Kinetic Model

S5-2

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Objectives The goal of this analysis was to describe the effect of Danoprevir (DNV) ±Ritonavir (RTV), which is used to enhance DNV exposures, and ± PEG-IFN/Ribavirin (P/R) on HCV RNA viral loads using a mechanistic viral kinetic (VK) model addressing the host-virus-drug interactions with system and drug effect parameters and then to use the model to support the Phase 3 clinical development of DNV.

Methods The structure of the VKmodel used in this analysis was previously characterized on a large viral load database of CHC patients treated with P/R [1]. The effect of DNV has been incorporated in the VK model using available PK and viral load data from treatment-naive, non-cirrhotic patients with HCV genotype 1 infection in phase 1 and 2 clinical studies and was externally validated using another phase 1 study. The system and PEG-IFN effect parameters estimated in the previous model were re-estimated to take advantage of the rich early viral kinetic information from the phase 1 studies. DNV treatment effect was investigated by including an exposure-dependent inhibition and/or induction on various model parameters, estimating parameters using MONOLIX [2].

Results Re-estimating the free virion clearance, virion production rate, and PEG-IFN effect allowed a better description of the rapid early viral load decline. Free virion clearance was higher compared to previous estimates, in agreement with literature reports [3]. Two MoA were identified: inhibition of virion production and increase of the infected hepatocytes clearance. Good agreement was demonstrated between the observed and predicted time courses of response rate in phase 2 and viral load in phase 1.

Conclusions A mechanistic VK model was developed to describe the effect of DNV ± RTV, and ±P/R on HCV viral load. Phase 1 data contributed to a better estimation of parameters related to the early viral decline. The additional effect on clearance of infected cells in addition tothe inhibition of virion production is in agreement with earlier reports [4,5] suggesting that protease inhibitors have dual MoA; Inhibiting the virion production and restoring the immune response. Enhancement of the infected cells clearance as a second MoA was suggested for another protease inhibitor [6].

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Quantitative Analysis of Reflux Episodes in Gastroesophageal Reflux Disease (GERD)

S5-3

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Objectives The purposes of this study was to develop a time-to-event model to characterize the reflux patterns in Proton Pump Inhibitor (PPI)-resistant and PPI-reactive groups among GERD patients and examine the associated influencing factors, to assess the feasibility of applying the model-based drug treatment approach in GERD, and to find diagnosis criteria for PPI-resistant versus PPI-reactive GERD patients.

Methods A repeated time to events model was developed using a dataset composed of reflux events through a24hr combined pH/impedance monitoring device. [1] The likelihood at each event time L(t) was formulated as $L(t)=S(s,t) \cdot h(t)$ where $S(s,t)$ and $h(t)$ denote the survival and the hazard function (s and t are the previous and current event time). Constant, Gompertz and Weibull hazard functions were tested. [2,3] The covariate effects were tested with stepwise covariate modeling. The differences between the two groups in the number of acidic and nonacidic refluxes and the ratio of non-acidic to acidic refluxes were exploratively examined.

Results The reflux events were best explained by the constant hazard model. The log hazard for acidic and non-acidic refluxes were 1.36 and 0.534 in responders and 1.03 and 0.645 in non-responders for treatment patients, and 1.30 and 0.748 in responders and 1.64 and 0.736 in non-responders for non-treatment patients, indicating the hazard of non-acid refluxes lower than that of acid refluxes. The disease duration had a significant effect for the non-responder group with PPI, resulting in a decrease in the log hazard by 0.2 per 56 months of disease duration. No other covariate was found significant. While the data in on-PPI group showed that in the responder group the number of acidic refluxes and the ratio of acidic to non-acidic refluxes were significantly suppressed compared to the non-responder group as a result of the treatment effect (p=0.045 and 0.027, respectively), the data in off-PPI group didn't.

Conclusions This work represented the feasibility of applying a model-based approach in characterizing reflux patterns in GERD which can be used as a supportive tool for diagnosis and an optimal treatment. This preliminary modeling result showed that the hazard rate is lower in non-acidic refluxes.

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Applications of Modeling and Simulation In Treatment of Tuberculosis In South Africa

S5-4

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Objectives To develop a method to analzye data comprising of days to a positive test result for tuberculosis in automated liquid culture.To describe the pharmacokinetics of first line drugs in a South African population of patients on treatment for tuberculosis.To describe the pharmacokinetics and pharmacodynamics of ofloxacin in patients on treatment for multi-drug resistant tuberculosis.To assess the adequacy of antitubercular drug concentrations in paediatric patients.

Methods Pharmacokinetic, pharmacodynamic and pharmacogenetic data from South African adults and children with drug susceptible and drug resistant tuberculosis in routine clinical settings were included in the analyses. A time to event modeling approach was used for the days to positivity pharmacodynamic data. In patients with drug resistant tuberculosis, ofloxacin exposure was adjusted for the individual minimum inhibitory concentration to investigate the probability of target (AUC/MIC≥100) attainment. Children receiving treatment for drug sensitive tuberculosis were investigated and their drug plasma concentrations were compared to those in adults. Monte Carlo simulations were performed using the final pharmacokinetic models for dose adjustment and probability of target attainment.

Results We report a novel time to event pharmacodynamic model to analyze data comprising of days to positivity in liquid culture. The model describes the biexponential decline of mycobacteria in patients during treatment and the growth kinetics of the bacteria upon introduction to liquid culture until the day a positive (or negative) result is recorded. This model can be used to investigate patient demographics and drug exposure when testing new drug regimens. The pharmacokinetics of several first line antitubercular drugs were adequately described. We found that an African-specific drug transporter polymorphism that exists at a frequency of 70% significantly reduced rifampicin absorption by up to 30%, perhaps explaining low cure rates. The ofloxacin probability of target attainment expectation based on the current 800mg daily dose was only 45%, suggesting that ofloxacin should be replaced by more potent fluoroquinolones. Drug concentrations in children were low compared to adults and we have used Monte Carlo simulation to evaluate recently revised recommendations for dosing.

Conclusions Modeling and simulation has been a powerful tool in analyzing complex datasets and making recommendations for clinical practice in South Africa

Oral session 6

Methodology II

Chair: Nick Holford

Data Sharing in Children

S6-1

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Pooling data from different paediatric studies can provide a single robust pharmacokinetic analysis that allows covariate analysis and hypothesis testing. Data sharing should be driven by the altruistic purpose of improving drug understanding to the clinical benefit of children. Electronic communications have rendered the sharing of data relatively easy and data sharing within the wider scientific community has become commonplace. Data sharing allows verification of results, saves costs and time, allows new interpretation of old data and can fulfill teaching benefits. It may stimulate cooperative competition between researchers and allow individual researchers to concentrate on unique aspect of the scientific puzzle. However, there is occasionally a reluctance to share, in part because of fear of others stealing the hard work of a research group, which may not be recognized in subsequent publications that reuse data. Providing data may require additional effort for presentation in a suitable format. Data may be abused or used for purposes other than those for which they were collected. Propriety claims may limit access to industry sponsored research of drugs. The question of who has ownership of data is contentious. Investigators often consider data they have collected to be theirown property. Reputations and grants may be hinge on ownership of a data set. However, other team members, institutions, funding agencies and the public also have a stake. The difficulties identified in the general scientific community also apply to data sharing for paediatric PK studies. There are few clearly established rules at present, and consideration of the issues hinges on ethical and philosophical arguments. Some data bases, set up by enthusiastic altruistic participants, are freely available to all e.g., e.g. that set up by anesthesiologists for propofol (http://www.opentci.org). The development of further data bases will depend on collaboration and cooperation and greater clarity and consensus over appropriate processes and procedures (1-8).

Some Perspectives

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DDMoRe - Drug Disease Model Resources

S6-2

W.M. Aartsen, J. Chard, L. Cochard, L. Harnisch, M.O. Karlsson and I. Matthews on behalf of DDMoRe

The DDMoRe consortium was founded in 2011 by a group of enthusiastic EFPIA partners, academics and SMEs across Europe to address concerns to those who want to bring new medicines to patients in a safe, but also efficient manner. The conis developing a public drug and dismodel library supported by an open source interoperability framework providing access to existing modelling tools and those of the future (www.ddmore.eu). This may be ambitious; however we wish the standards and tools developed to become the reference for future collaborative drug and disease M&S work, serving internal and external stakeholders, regulators, academics, and the pharmaceutical industry in better adthe current bottlenecks in the drug development process.

The first year of this unique 5-year partnerwas fruitful, with efforts focused on coland harmonizing requirements for the consortium deliverables. Major achievements were as follows:

• A collection of models, both existing and requiring development, were selected for their value in drug development in diabetes, oncology and other therapeuareas;

• Amodel description language has been drafted bringing together the features of various model coding languages and is intended to be flexible, extensible, easy to code, understand and use;

• Specifications for a task execution lanhave been drafted connecting the users modelling aims, the immediate task of execution of a modelling related task and the overarching workflow withthe framework;

• A prototype interoperability software platform was scoped to lay out an early implementation of the framework;

• Relevant markup languages were identiand evaluated to determine wheththey could form part of the DDMoRe markup languages;

• Collaborations with CDISC and others have been esto ensure consistency with existing standards;

• Knowledge gaps in model selection, diand the implementation of complex models were identified leading to a methodological development prowith some early results;

• A prototype of a clinical trial simulaengine was developed;

• Surveys on optimal/adaptive design, and technical and conceptual requirein Drug/Disease Modelling and Simulation (DD M&S), were conducted to highlight areas for improvements in trial design and related statistical methodologies and to identify opportunities for training and education purposes re

Longitudinal Model-Based Meta-Analysis with NONMEM

S6-3

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Integrated analyses of publicly available data play an important role in quantitative decision making in the context of model-based drug development. Meta-analyses employing parametric models are particularly useful as they allow a better description of dose-response and understanding of time course of clinical response, with associated uncertainty in response and time course. However, one of the challenges with quantifying longitudinal aggregated literature data is to adequately account for within-study and within-treatment arm correlations over time. Observations within a study are correlated because the patients come from a common population. Additionally, the mean observations over time within a treatment arm are also correlated because they are based on the same set of patients. In this presentation, approaches handling both within study and within treatment arm correlations in NONMEM will be presented. Evaluation of each method based on simulated data and the implications will also be discussed.

Oral session 7

Application

Chair: Stephen Duffull

Allometry, Geometry, and Errantry...Exploration of PK Relationships by Size and Race

S7-1

Bruce Green

Model Answers Pty Ltd, Australia

Understanding the relationship between PK parameters, body size, and race is important to help optimize dosing guidelines across differing populations. Scaling PK parameters using allometry is a common method to facilitate this goal and is based upon some innovative work in the field of fractal geometry. Many purport scaling clearance and volume of distribution by total body weight with fixed exponents derived from between-species scaling. This has provedpartially successful when scaling from adult to paediatric subjects, or scaling between subjects of normal body weight, although fixing the exponents to literature defined values remain contentious when scaling between subjects of differing body compositions.

This session will describe a semi-mechanistic approach to scale PK parameters between subjects of differing body compositions. It will discuss some of the theoretical background and assumptions behind the use of fixed allometric exponents when scaling between subjects of differing body sizes and races, and the appropriateness of the approach to human subjects. The presentation will also include results of a meta-analysis conducted on published works by pharmacometricians, demonstrating that fixing exponents may be supported by results of our own population analyses. The presentation will close with a discussion on the role of functional liver volume as an alternate metric to consider in place of simple allometry, and a method to predict this metric from demographic data.

M&S in Pharmacogenetics /Personalised Medicine

S7-2

Julie Bertrand

MRC research fellow at University College London Genetics Institute

Studies of the influence of single nucleotide polymorphisms (SNPs) on drugpharmacokinetics have usually been limited to the analysis of a single quantity, such as the observed drug concentration at one time point, or the area under the concentration versus time curve. Nonlinear mixed effects models enable analysis of the full concentration versus time profile, even for sparse data, but until recently there has been no systematic way to examine the effects of multiple SNPs on the model parameters. Lehr et al.[1] proposed a simple but computationally-intensive stepwise regression approach to PGPK analysis using NLMEM, which they applied to 198 SNPs in a study of nevirapine in HIV patients. More recently, Wu et al.[2] have proposed a modelling-based approach that pools the observations from all subjects within each genotype. Several recent statistical genetics studies have found that penalized (or "shrinkage") regression methods can give superior performance in selecting parsimonious sets of predictors that tag most or all causal variants[3].

Using realistic genetic simulations, we assessed different penalized regression methods for including SNPs in pharmacokinetic analyses, and compared their performance with a classical stepwise approach through simulations under the null and an alternative hypothesis. Our simulated PK model is based on the study of efavirenz in ambulatory HIV-1-infected patients by Kappelhoff et al.[4] but with a design selected to ensure reasonable precision of parameter estimates for the basic model and including 300 subjects with 6 sampling times. The SNP simulation is based on the DMET Chip[5], which includes 1227 genetic variants in 171 genes involved in drug metabolism, distributed over the 22 autosomes and chromosome X. The median (range) interval spanned by the SNPs is 29 Kb (0 – 804) per gene, and the median (range) number of SNPs per gene is 6 (1 -- 56). Under the alternative, we randomly picked 6 SNPs per simulated data set with minor allele frequency above 5% and which together explain 30% of the variance in the logarithm of the apparent clearance of elimination.

We found that all approaches showed similar power but penalized regression was less computationally-demanding and tended to select fewer false positives. We therefore conclude that it should be preferred over stepwise procedures for PK analyses with a large panel of genetic covariates.

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Mechanism-Based Pharmacokinetic/ Pharmacodynamic Model of Exenatide Long-Acting Microspheres in Diabetic Rats

S7-3

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The aim of this study was to establish an integral model to characterize exenatide loaded double-walled microspheres (DWMS) *in vivo* release, pharmacokinetics, pharmacodynamics, and *in vitro* and *in vivo* correlation (IVIVC). Exenatide loaded DWMS was prepared using O/O/W method[1], and its physicochemical characteristics, *in vitro* release and degradation were investigated. Male Harlan-Sprague-Dawley rats were treated with high-fat diet/streptozotocin to induce type II diabetes[2]. The pharmacokinetics and pharmacodynamics (PK/PD) of exenatide solution and exenatide DWMS were investigated after subcutaneous administration to diabetic rats. A two-compartment model with a series of transit-compartment[3] was applied to describe the long-term *in vivo* release of exenatide from DWMS, and the distribution and clearance of exenatide. On the basis of exenatide's insulinotropic effects and the relationship between insulin and blood glucose, a precursor independent indirect response PK/PD model was constructed to characterize the insulin concentration-time profiles. Consideredthe sites of action and the hypoglycemic effects of insulin, the turnover of blood glucose was described by an effect compartment/indirect response combined PK/PD model. The model parameters were estimated by NONMEM, and the constructed PK and PK/PD models were evaluated via visual predictive check. Moreover, on the basis of the transit-compartment model, model simulation was conducted to predict the *in vivo* release and absorption of exenatide from DWMS, and the IVIVC of exenatide was established. In conclusion, DWMS was a promising vehicle for a 50-day long-term delivery of exenatide after sc administration, and the proposed PK/PD model allowed a better understanding of the pharmacological properties of exenatide loaded DWMS. The integral PK/PD model with a series of transit-compartment developed in the current studies provided a good option for the description and prediction of *in vivo* release, as well as the profiles of PK and PK/PD for drug in a sustained released preparation.

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Modeling and Simulation in Pediatrics

S7-4

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Pediatrics is one of the last frontiers in clinical pharmacology. The evaluation of medications in pediatric populations, especially newborns, infants and preschool children, has long been neglected. Three quarters of all FDA-approved drugs lack labeling for pediatric the pharmacokinetics and pharmacodynamics between adults and pediatric subpopulations of various age.

Pharmacokinetics (PK) is especially in early childhood frequently different from adults due to the gradual maturation of physiologic processes relevant to drug disposition, such as renal and hepatic elimination mechanisms (e.g. drug metabolizing enzymes and drug transporters). Pharmacodynamics has also shown to deviate in some cases between children and adults due to differences in disease etiology and developmental changes in molecular response mechanisms. Nevertheless, the study of medications in children is still frequently limited to PK assessments, especially in cases where the disease etiology is comparable to adults, based on the assumption that exposure-response relationships established in adults are similar to those in pediatric populations and that safety and efficacy can be conferred from adult to pediatric populations if comparable drug exposure is achieved. In recent years, pediatric drug development has received several boosts by legislative action and regulatory incentives and/or requirements, predominantly in the United States, but more recently also in the European Community. Nevertheless, pediatric populations remain one of the most difficult groups of patients to study due to the ethical, legal and logistic constraints in study design and performance. Children are considered a vulnerable population protected by legislation and ethics committees,thereby largely excluding non-therapeutic studies in children. In addition, the number and size of specimens, which can be collected in pediatric studies, is usually very limited, especially if invasive sampling such as venipunctures for blood collection are performed. Pediatric clinical studies are further hampered by the fact that pediatric research subjects can usually not be confined to a clinical study unit for a prolonged time period. These issues become even more relevant the younger the studied subpopulations are, particularly with studying drug disposition in full-term and premature neonates.

Modeling and simulation approaches have increasingly been used to facilitate pediatric drug development research and improve applied pharmacotherapy. The application of PK and PKPD modeling and simulation (*M&S*) techniques in pediatrics has been strongly promoted by various groups in academia, industry, and regulatory agencies. Two basic areas of M&S application have emerged in recent years in pediatric clinical pharmacology research: 1.) *A priori*application of M&S techniques to optimize trial designs, select dose levels and dosing regimens to be studied, develop sampling schemes, and select outcome measures, and 2.) *A posteriori* application of M&S techniques toanalyze PK and PKPD data from pediatric studies, especially using population based approaches to derive maximum information content from the limited data collected in pediatric studies and to establish a consistent framework that allows the exploration of model-based dosing recommendations.

The presentation will provide example for these applications and will highlight future opportunities, but also current limitations with regard to M&S in pediatrics.

Poster

Applications- Biologicals/vaccines

PA1-1

Pharmacodynamic Model of Hepcidin Regulation of Iron Homeostasis in Cynomolgus Monkeys

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Objectives

Hepcidin (H_{25}) is a hormone peptide synthesized by the liver that binds to ferroportin, resulting in reduced iron export [1]. In this study H_{25} was inhibited by administration of single and multiple doses of an anti-H_{25} monoclonal antibody Ab 12B9m in cynomolgus monkeys. Pharmacokinetics of Ab 12B9 and H_{25} have been reported elsewhere [2]. This project objective was to develop a pharmacodynamic model describing the mechanism of the H_{25} control of the iron homeostasis.

Methods

Data available from pharmacokinetic and toxicokinetic studies in cynomolgus monkeys were used in this analysis. Total serum H_{25} and Ab 12B9m were determined in each animal. Corresponding measurements of serum iron and hemoglobin (Hb) were obtained. The PD model consisted of iron pools in serum (Fe_S), reticulo-endothelial macrophages (Fe_M), hemoglobin (Fe_{Hb}), and liver (Fe_L). The iron was transported between the Fe_S, Fe_{Hb}, and Fe_M unidirectionally at first-order rates k_S, k_{Hb}, and k_M. Fe_L was modeled as a peripheral compartment. H_{25} inhibited the distribution of iron from Fe_M and Fe_L pools by means of the sigmoidal E_{max} function. H_{25} serum concentrations were described by the PK model with the parameter fixed at their estimates obtained elsewhere [2]. The naive pooled serum iron and Hb data were fitted simultaneously using ADAPT 5 [3].

Results

The loss of iron due to blood drawing in toxicokinetic studies was found to be significant and was modeled as a short negative infusion. The first-order constant k_S was better described by a zero-order process. The corresponding estimates of the rate constants were k_S=0.165 µg/dl/h, k_M=0.00134 h^{-1}, and k_{Hb}=0.00330 h^{-1}. The EC_{50} value for the H_{25} inhibitory effect was 9.55 nM. The PD model predicted negligible effect of Ab 12B9m on Hb for analyzed doses. The simulated time courses of Fe_L and Fe_M relative to the baselines for 300 mg/kg q.w. IV for four weeks resulted in decreases of 20.0% and 42.9%, respectively.

Conclusions

The presented PD model adequately described the serum iron time courses. The Ab 12B9m induced inhibition of H_{25} resulted in a temporal increase in serum iron, and a decrease in the stored iron amounts. Ab 12B9m exhibited a negligible effect on Hb.

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Applications- Infection

PA2-1 **A Population Pharmacokinetic / Pharmacodynamic Approach to Fluconazole Use in Burn Patients with Candida Infection**

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Objectives

Because of the intensive interventions and physiological changes, the pharmacokinetic property of fluconazole might be significantly altered in major burn patients. In this study, fluconazole pharmacokinetics in burn patients was investigated using a population approach. In addition, the optimal fluconazole regimen in burn patients was recommended based upon the predicted therapeutic outcome of the current dosing regimen.

Methods

Patients were given daily 100 ~ 400 mg of intravenous fluconazole. At steady-state, blood samples for pharmacokinetic analysis were obtained at 0 (just before dosing), 3, 5, 9, 24, 27, 48 and 51 hours after the initiation of infusion. Non-linear mixed effect modeling was performed using NONMEM. Steady-state 24-hr area under the free drug concentration curves (fAUC) were simulated from 10,000 virtual patients receiving daily 400mg fluconazole using the final model and minimum inhibitory concentration (MIC) values were sampled from the MIC distribution at the study site. fAUC/MIC > 100-hrs was used as the criterion for the therapeutic success.

Results

The pharmacokinetic parameter estimates (Clearance, Volume of Distribution) were larger in burn patients as compared to those of the non-burn population, particularly when the hypermetabolism was significant.

Continuous renal replacement therapy (CRRT) also raised the probability of therapeutic failure by increasing fluconazole clearance.

Conclusions

A standard fluconazole regimen might not guarantee a successful treatment against Candida spp. in burn patients even against a susceptible strain. From our findings, it is recommended that 800 mg/day fluconazole should be given to major burn patients to obtain an almost 100% therapeutic successes; especially for those experiencing overt hypermetabolism or receiving CRRT.

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Applications- Infection

PA2-2

Evaluation of Colistin Dosing Protocols by Simulations: Flat-Fixed Dose versus Weight-based Loading Dose and Creatinine Clearance (CRCL)-based Maintenance Dose

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Objectives

Colistin is increasingly being used clinically due to escalating antibiotic resistance, but its optimal dosing regimen is still under debate. Recently a loading dose of the prodrug, colistin methanesulphonate (CMS), was demonstrated to be needed to quickly achieve therapeutic colistin concentrations (1,2). In this study, simulations were performed from a combined PK and PKPD model to compare drug concentrations and bactericidal effects following different dose algorithms.

Methods

In the simulations the PK model (2 compartments for CMS and 1 compartment for colistin) (2) was combined with a semi-mechanistic PKPD model describing the time course of colistin's bactericidal activity against Pseudomonas aeruginosa (2,3). A flat-fixed dosing (9MU loading dose; 4.5MU q12h maintenance dose) was compared to a suggested dosing algorithm with a weight-based loading dose and CrCL-based maintenance dose (2). CrCL as a covariate on CMS clearance was evaluated for reducing between-subject variability (BSV) in bacteria kill. Percentiles of CMS and colistin concentrations, and of bacteria kill, were computed for each simulated scenario. The influence of infusion duration and the start time of maintenance dosing (12 vs. 24h) were also investigated.

Results

Weight as a covariate on V1 had limited impact on the CMS peak concentration, and importantly, a weight-based loading dose resulted in 1.7 less log-bacteria kill at 24h for a 50 kg compared with a 90 kg patient. For the model with CrCL-CMS relationship, the log-bacteria kill was clearly higher for CrCL of 30 compared with 120 ml/min (3.6 vs. 2.7). The CMS peak concentration reduced with infusion duration (14, 12 and 8 mg/L for a 15, 30 and 120 min infusion of 4.5MU) but resulted in similar colistin concentration and bacterial kill profiles. A 24h interval between the loading and initiation of maintenance dosing resulted in regrowth of bacteria at 20h. The limited BSV reduction in PK parameters with CrCL inclusion as a covariate translated to a negligible reduction in BSV of bacterial kill.

Conclusions

Based on the simulations, we recommend a flat-fixed loading dose with an infusion duration of up to 2h. To avoid regrowth of bacteria, the maintenance dose should preferably be initiated at 12h after the loading dose.

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Applications- Infection

PA2-3

Population Pharmacokinetic Analysis of Colistin in Burn Patients

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Objectives

Colistin is increasingly used as salvage therapy of nosocomial infections caused by multidrug-resistant gram-negative bacteria such as Psuedomonas aeruginosaand Acinetobacter baumannii. However, the available pharmacokinetic (PK) data of colistin are limited to guide dosing. The aim of this study was to develop a population PK model for colistin in burn patients.

Methods

Fifty patients with burns ranging from 4% to 85% of total body surface area treated with Colistimethate sodium (CMS) were studied. CMS which is hydrolyzed in vivo to the active metabolite was intravenously administered at a dose of 150 mg every 12 h. Blood samples were collected right before and at 1, 2, 4, 6 and 8 h after more than five infusions. The population PK model was developed using a mixed effect method (NONMEM, ver. 6.2).

Results

A one-compartment linear PK model for colistin best described the data. Covariates included in the final model were creatinine clearance on the fraction of CMS converted into colistin and body weight on the central volume of colistin. The mean population pharmacokinetic parameters were clearance (5.79 L/h), volume of distribution (53.7 L), the turnover rate of CMS converted into colistin ($0.766 - EDEMA \times 0.429$), the fraction of CMS converted into colistin ($1 - 0.203 \times EXP(CLcr/120)$) with interindividual variability (CV%) of 35.4%, 25.5%, 68.6% and 0%, respectively.

Conclusions

The PK of colistin havebeen characterized for the first time in burn patients after i.v. administration of CMS. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of colistin in burn patients.

Applications- Infection

PA2-4 **Establishment and Utilization of an *in vivo* Concentration-Effect Relationship for Piperaquine in Preventive Treatment of Malaria**

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Objectives

A randomized, placebo controlled trial conducted on the Northwest border of Thailand compared monthly to bi-monthly treatment with a standard 3-day treatment regimen of dihydroartemisinin-piperaquine [1]. A total of 1000 healthy adult male subjects were followed up weekly for 9 months of treatment. This project aimed to characterize the concentration-effect relationship for the malaria preventive effect of piperaquine and utilize it for simulations of dosing in vulnerable populations and in areas with piperaquine resistance.

Methods

Seasonal variations in baseline risk of malaria infection were investigated by applying one or two surge functions to a constant baseline hazard for placebo treated subjects. A mixture model was used to differentiate between a high- and low-risk subpopulation [2]. Monthly observations of piperaquine plasma concentrations were modeled using a frequentist prior [3] based on a published PK model [4]. A joint PKPD model was subsequently applied to explore the effect of piperaquine plasma concentration on malaria infection hazard. The model was sequentially extended to account for the effect of dihydroartemisinin and the delay between the malaria diagnosis and the crucial point of prevention failure.

Results

One significant seasonal peak in malaria transmission was identified from May throughout June during when the hazard was increased with 217% (RSE 27%). The concentration-effect relationship was best characterized with a sigmoidal E_{max} relationship where concentrations of 7 ng/mL (RSE 13%) and 20 ng/ml were found to reduce the hazard of acquiring a malaria infection by 50% (i.e. IC_{50}) and 95% (IC_{95}),

respectively. Simulations of monthly dosing, based on the final model and literature information about PK suggested that the one year incidence of malaria infections could be reduced by 70% with a recently suggested dosing regimen compared to the manufacture recommendations for children with a body weight of 8-12 kg [5]. Pregnant women were predicted to have a 12.5% higher incidence compared to non-pregnant.

Conclusions

For the first time a concentration-effect relationship for the malaria preventive effect of piperaquine was established. The established model has been useful in translating observed results from a healthy male population to that expected in other populations.

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Applications- Infection

PA2-5 Population Pharmacokinetic and Pharmacodynamic Modeling of Amodiaquine and Desethylamodiaquine in Women with Plasmodium Vivax Malaria during and after Pregnancy

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Objectives

Vivax malaria rarely causes mortality but is associated with multiple relapses, anemia, abortion, and a reduction of infant birth weight in pregnant women with malaria. Amodiaquine is effective for the treatment of *P. vivax* malaria but there is little information on the pharmacokinetic and pharmacodynamic properties of amodiaquine in pregnant women with malaria. This study evaluated the population pharmacokinetic and pharmacodynamic properties of amodiaquine and its biologically active metabolite, desethylamodiaquine, in pregnant women with *P. vivax* infection and again after delivery.

Methods

Twenty-seven pregnant women infected with *P. vivax* malaria on the Thai-Myanmar border were treated with amodiaquine mono-therapy (10 mg/kg/day) once daily for three days. Nineteen women returned to receive the same amodiaquine dose post-partum. Nonlinear mixed-effects modeling was applied to evaluate the population pharmacokinetic and pharmacodynamic properties of amodiaquine and desethylamodiaquine. Covariates were investigated with a stepwise and a full covariate model approach. Model selection was made with respect to physiological plausibility and model fit.

Results

Amodiaquine plasma concentrations were described by a lagged first-order absorption and a two-compartment disposition model. Desethylamodiaquine disposition was described with a three-compartment model under the assumption of constant *in vivo* conversion of amodiaquine. Body weight was implemented as an allometric function on all clearance and volume parameters. Amodiaquine clearance decreased linearly with age and absorption lag-time was shorter in pregnant patients. Estimated gestational age did not have any significant effects on the pharmacokinetics. Recurrent malaria infections in pregnant women were modeled with a time-to-event model consisting of a constant hazard function with an inhibitory effect of desethylamodiaquine plasma concentration. The simultaneous pharmacokinetic and pharmacodynamic model established a post-treatment prophylactic effect of desethylamodiaquine with a 50% risk reduction at a concentration of 7 ng/mL (68% RSE).

Conclusions

Pregnancy did not have a clinically relevant impact on the pharmacokinetic properties of amodiaquine or desethylamodiaquine. This is reassuring that no dose adjustment in pregnant women is needed. The pharmacodynamic model suggested that amodiaquine treatment can prolong the time to a recurring *P. vivax* infection and might therefore be a promising alternative as an intermittent preventive treatment in this vulnerable group.

Applications- Infection

PA2-6 **An *in vivo* Pharmacokinetic/Pharmacodynamic Model of Fecal Bacterial Resistance to Ciprofloxacin in Piglets Treated with Ciprofloxacin − Application to Design a New Study of Antibiotic Resistance**

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Objectives

The colonic flora is where antibiotic residues select resistant commensal bacteria during treatment [1,2]. In this study in piglets, we aimed to develop a pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the link between ciprofloxacin (CIP) concentrations and CIP resistant Enterobacteriaceae (EB) counts in feces. We used these results to design a future study of resistance dynamic in commensal flora.

Methods

29 piglets were randomly assigned to oral treatment with placebo (n = 9), CIP 1.5 (n = 10) or 15 mg/kg/day (n = 10) from D1 to D5. Concentrations and resistant EB counts were obtained from fecal samples at D1, D3, D5, D7, D9, D12, D16 and D27. The PK model was assimilated to a one compartment model with intravenous infusion and first order elimination. The infusion rate was the daily dose of CIP with a duration of 5 days. The PD model described the resistant EB amounts as the result of a saturable growth and an elimination. The drug effect was supposed to inhibit the elimination rate of resistant EB through an Imax model. The joint PK/PD modeling was performed by nonlinear mixed effect model (NLMEM), using SAEM algorithm [3] in MONOLIX4.1.1 [4]. From the model and estimated parameters, we used PFIM [5,6], an R function for design in NLMEM, based on the population Fisher information matrix [7,8], to plan a new study. We studied the influence of choice of sampling times, of doses and of subject number in each dose group on the estimation precision of parameters.

Results

The chosen model adequately described jointly fecal concentrations and resistant counts. Parameters were estimated with good precision. Concentrations increased sharplywith doses and resistant EB amounts increased nonlinearly with concentrations.

We found that not only choice of sampling times but also appropriate choice of different doses improved the estimation precision of parameters.

Conclusions

The proposed model adequately described the data. To our knowledge, this is the first model of in vivo dynamic of resistance in commensal flora. The next step is to model also the susceptible EB counts. These studies can be analysed through NLMEM and efficiently designed using PFIM.

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Applications- Infection

PA2-7

Evaluation of Pharmacokinetics of Chloroquine, an Anti-Malarial Agent, across Ethnicity

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Objectives

Plasmodium species cause malaria, residing in red blood cells (RBC). Therefore, the extent of distribution of chloroquine into RBC would affect the anti-malarial effect of chloroquine. This study was designed to explore pharmacokinetics of chloroquine focusing on the intra-erythrocyte concentration over time across different ethnicities.

Methods

A total of 9 healthy, adult, male volunteers of different ethnicity (4 Koreans, 2 Caucasians, 1 African, and 2 Southeast Asians) received single oral dose of chloroquine, 1,000 mg, and blood for pharmacokinetic evaluation was drawn serially, thereafter. Chloroquine and its metabolites, desethylchloroquine, bisdesethylchloroquine concentrations both in plasma and whole blood were measured by validated high performance liquid chromatography. Whole blood and plasma pharmacokinetics were analyzed using NONMEM, and simulations for Intra-erythrocyte chloroquine concentration over time on various regimens of chloroquine were performed. Intra-erythrocyte chloroquine concentration at each time point was calculated from plasma and whole blood concentrations using following equation.Intra-erythrocyte concentration = [whole blood concentration ×100 - plasma concentration × (100-Hct)]/Hctwhere Hct is hematocrit, the volume percentage (%) of red blood cells in blood.

Results

Chloroquine was rapidly absorbed with oral dosing, and 2-compartment, linear model with mixed first and zero order absorption kinetics best described the concentration data. The average values of observed concentration ratios of erythrocyte over plasma were 12.7, 12.9, 9.6, and 15.2 in Korean, Caucasian, African, and Southeast Asian, respectively. Model predicted intra-erythrocyte concentrations over time were similar between Korean and Caucasian, and lower in African, and Southeast Asian, which is thought to be due to lower chloroquine concentrations in whole blood and plasma.

Conclusions

There was no definite ethnic difference in intra-erythrocyte concentrations over time. However, since this study is limited by small sample size, and the information on the intra-erythrocyte concentrations could be important for treatment effect of chloroquine, further studies are needed.

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Applications- Infection

PA2-8 Exploration of Optimal Dosage Regimen of Vancomycin in Patients with Methicilin-Resistant Staphylococcus Aureus (MRSA) Infection by Pharmacokinetic and Pharmacodynamic Modeling and Simulation

The study was presented at the 2011 ACOP meeting

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Objectives

To develop the pharmacokinetic and pharmacodynamics methodology to explore optimal dosage regimens for antibiotics, which could be applied in clinical therapeutics, and in early characterization of antibiotics in the drug development processes

Methods

This study consists of pharmacokinetics (PK) for patients who were treated with intravenous vancomycin, 1,000 mg every 12 hours for MRSA infection, and pharmacodynamics (PD) study which was in vitro time-kill experiment for vancomycin against various MRSA strains. PK and PD models were built using NONMEM VII (ICON Development Solutions, Ellicott City, MD, USA). Monte-Carlo simulation for the bacterial titer change over time in human body on various dosing regimens of vancomycin was done with PK-PD

Results

PK analysis was done with 112 serum vancomycin concentrations from 20 patients, which was best fitted by two compartment linear model. Creatinine clearance calculated by Cockcroft-Gault equation was linearly associated with the clearance of vancomycin. PD for antibacterial effect of vancomycin was analyzed using 1,000 vancomycin concentration-bacterial titer by time data, where log transformed values of bacterial titer was used in the fitting. Monte-Carlo simulations for MRSA titer changes over time in serum, lung and CSF on various dosing regimens of vancomycin were done with the pharmacokinetic/pharmacodynamic model built in this study.The simulation results corresponded well with the clinical experiences.

Conclusions

This study characterized both PK and PD of vancomycin and predicted bacterial titer in human body over time on various dosing regimens via Monte-Carlo Simulation. This approach would be useful in finding optimal dosing regimens of antibiotics, and in making novel antibiotics development process more efficient. Using pharmacodynamic model from in vitro bacterial time-kill study and human pharmacokinetic model from phase 1 study, the possibility of therapeutic effect within tolerable dose ranges, and optimal dosing regimens could be predicted in earlier phase of clinical development.

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Applications- Infection

PA2-9 **Pharmacokinetic Modeling of Cefepime Concentration Data in Human Lung and Target-organ-specific Pharmacodynamic Simulation**

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Objectives

Cefepime is an injectable cephalosporin used for various infections such as pneumonia. The treatment of patients with pneumonia benefits from a more thorough understanding of cefepime penetration into the lung, therebyexerting its antibacterial effects which correlate with the drug-exposure time above the minimum inhibitory concentration for the pathogen (T > MIC, % of 24 h). This study performed pharmacokinetic modeling and pharmacodynamic simulation of cefepime in human lung.

Methods

Cefepime concentration data for plasma and lung were obtained from four reports including our two previous papers. Using NONMEM program, the plasma data were modeled with a standard two-compartment model (with clearances of CL and Q, and distribution volumes of V_1 and V_2). The lung data were modeled as $dX(3)/dt = QLUNG*C_1-QLUNG*C_3/KPLUNG$, where $X(3)$ is the drug amount in the lung compartment (with a distribution volume of V_3), C_1 and C_3 are the drug concentrations in the central and lung compartments, QLUNG is the plasma flow (207 L/h), and KPLUNG is the drug partition coefficient between lung and plasma.

Results

The mean (interindividual variability) parameters of this semi-physiological pharmacokinetic model were: CL = 5.81 (42.5%) L/h, V_1 = 9.77 (36.2%) L, Q = 5.97 L/h, V_2 = 5.44 (46.4%) L, V_3 = 0.47 (46.6%) L, and KPLUNG = 1.01. The pharmacokinetic model was validated with diagnostic plots and the bootstrap method. Based on the model parameters, target-organ-specific pharmacodynamic simulation (1000 times) predicted T > MIC in the lung: 80.1% ± 21.1% for cefepime 1 g every 12 h at a MIC of 2 mg/L, 78.2% ± 21.8% for 2 g every 12 h at a MIC of 4 mg/L, and 70.2% ± 24.9% for 1 g every 8 h at a MIC of 8 mg/L. These 0.5-h infusion regimeswere able to achieve the near-maximal bactericidal target (70% T > MIC) in the lung at MIC for common pathogens such as Streptococcus pneumoniae and Staphylococcus aureus.

Conclusions

The semi-physiological pharmacokinetic model helps to better understand the clinical pharmacokinetics of cefepime in the lung, while also helping to rationalize and optimize the regimens for pneumonia based on the target-organ-specific pharmacodynamic evaluation.

Applications- Infection

PA2-10 Cerebrospinal Pharmacokinetic / Pharmacodynamic Analysis of Meropenem for Pediatric Patients with Bacterial Meningitis

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Objectives

Meropenem is used for the treatment of bacterial meningitis, one of fatal infectious diseases. The pharmacokinetic (PK) / pharmacodynamic (PD) simulations (Monte Carlo simulations) for meropenem revealed that higher doses and/or longer infusion duration is effective for pediatric patients with general infections. The aims of this study are to develop population PK model which can simulate meropenem concentrations in cerebrospinal fluid (CSF) and to investigate optimal dosage regimens for meropenem in pediatric patients with bacterial meningitis.

Methods

A total number of 207 plasma concentrations and 84 CSF concentrations of meropenem were obtained from approximately 150 pediatric patients with meningitis or various infectious (0 to 4 concentrations from each). The age of the patients ranged from 29 days to 16 years. Meropenem was administered intravenously every 8 h at a dose of 10, 20, or 40 mg/kg t.i.d. by 0.5 h or more infusion duration. The meropenem concentrations in plasma and CSF were described by a 3-compartment model with zero-order input. The ability of meropenem to achieve critical PD target (target attainment at 10 to 100 percent time above minimum inhibitory concentration [%T>MIC]) was estimated using various MIC.

Results

The model evaluations suggested that the final model was adequate for predicting the concentration-time curves of meropenem in CSF which showed flatter profiles compared with ones in plasma. Focusing on the meropenem concentrations in plasma, target attainment at 50%T>MIC at a dose of 20 mg/kg t.i.d. by 2 h infusion was comparable with that at a dose of 40 mg/kg by 0.5 h infusion. However, focusing on the meropenem concentrations in CSF, target attainment rate at 50%T>MIC at a dose of 40 mg/kg t.i.d. by 0.5 h infusion was greater than that at a dose of 20 mg/kg t.i.d. with any infusion duration.

Conclusions

These results suggest that a higher dose, not longer infusion duration, was essential for achieving higher clinical effectiveness of meropenem, if the site of infection is suspected to be the cerebrospinal space. Careful attention should be paid to dosing regimen when the causative pathogen is unknown and the site of infection is suspected to be apart from blood.

Applications- Infection

PA2-11

Pharmacometrics of Antifungal Agents

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Objectives

Population pharmacokinetics/pharmacodynamic (PK/PD) analyses were performed to investigate the dose recommendations of antifungal agents. Four types of antifungal agents were selected for testing: a polyene (liposomal amphotericin B), triazoles (fluconazole, itraconazole, and voriconazole), echinocandins (capsofungin, micafungin, and anidulafungin), and a pyrimidine (flucytosine).

Methods

We predicted the pharmacokinetics parameters for antifungal agents from 1,000 virtual patients in the population pharmacokinetic model. The PK/PD parameters were: peak plasma concentration of the drug/minimum inhibitory concentration (MIC) of liposomal amphotericin B (target value of >40) and echinocandin (target value of >3); the percentage of time that the level of drug in the serum exceeded the MIC of flucytosine (target value of >40%); and the plasma concentration-time curve of the drug/MIC of azole (target value of >25). The MIC was classified as susceptible, susceptible dose-dependent, intermediate resistant, or resistant by each antifungal agent and the probability of attaining the target value of each PK/PD parameter was predicted.

Results

The relationship of dose-exposure could be clearly estimated. With a maximum dose of flucytosine and echinocandin, the probability of attaining 90% could be expected for susceptible, susceptible dose-dependent and intermediate resistant MICs. For liposomal amphotericin B and azole, the probability of attaining 90% was insufficient at the maximum dose.

Conclusions

Recently, the incidence of deep invading mycosis has dramatically increased, especially in patients who have risk factors such as broad spectrum antibiotic use, thermal injuries, neutropenia, immunosuppressive therapy, and anticancer drug administration. In order to achieve prophylaxis for fungal infection without evoking adverse side effects or drug tolerance sufficient doses must be administrated for treatment. The present results indicated that the population PK/PD analysis technique is useful for the dose selection. In conclusion, an appropriate drug selection and dose selection classified by MIC became possible based on the antifungal activity expectations from the PK/PD parameters.

Applications- Infection

PA2-12

Dose Findings of Antofloxacin Hydrochloride for Treating Bacterial Infections in an Early Clinical Trial Using PK-PD Parameters in Healthy Volunteers

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Objectives

To find an appropriate dose regimen of the concentration-dependent antibacterial agent antofloxacin for a phase II clinical trial using a population pharmacokinetic (PPK) study in healthy volunteers and the minimum inhibitory concentration (MIC) as pharmacodynamic (PD) parameters.

Methods

Twenty-four healthy volunteers were enrolled in a double-blind crossover study and received 200 or 400 mg antofloxacin daily with 10 days washout between two periods. Blood concentrations were analyzed using HPLC with a UV-Vis detector. The values of area under the curve (AUC) of antofloxacin with covariates were obtained from a PPK model and the MICs were extractedfrom previous research as the PD parameter. The dose regimen was determined for the phase II clinical trial according to the ratio (>20) of AUC/MIC, and the efficacy of the dose was evaluated by the trial.

Results

A two-compartment model best describesthe time-concentration data with first-order absorption. The PPK parameter estimates for CL, Vc, Q, Vp and KA are 8.34 L/h, 142 L, 15.9 L/h, 52.2 L, and 4.64 1/h, respectively. The covariates sex for KA, weight for CL, weight for Vc and interoccasion variability were included in the final model. The AUC/MIC was calculated according to the PPK model and the MIC of the four types of bacteria were determined in vitro. The 400 mg loading dose with 200 mg/d maintenance dose was recommended and confirmed by the phase II trial.

Conclusions

The ratio of AUC from the PPK model and MIC as the PD parameter can be applied in a dose-finding trial of bacterial infections for a concentration-dependent agent. The PPK model suggests that sex and body weight may be considerations in regards to individual therapy, which could be investigated in larger clinical trials and serve as a potential reference for clinical therapies.

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Applications- Infection

PA2-13 The Population Pharmacokinetic and Pharmacodynamic Properties of Intramuscular Artesunate and Quinine in Tanzanian Children with Severe Falciparum Malaria; Implications for a Practical Dosing Regimen

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Objectives

Parenteral artesunate is the drug of choice for treatment of severe malaria. The pharmacokinetic properties of intramuscular artesunate have not been studied in the main treatment group who carry the highest mortality; critically ill children with severe malaria. Although artesunate is superior, parenteral quinine is still widely used. A loading dose has been recommended for 30 years but is often not used. The objectives were to characterize the pharmacokinetic and pharmacodynamic properties of quinine, artesunate and dihydroartemisinin (the active metabolite of artesunate) in children with severe malaria in Tanzania and recommend practical dosing regimens.

Methods

A nested population pharmacokinetic study was conducted, as part of a large outcome trial (1), in Tanzanian children aged 4 months to 11 years. They received a standard body weight-based dose of quinine (n=75) or artesunate (n=70). Sparse capillary data were characterized using nonlinear mixed-effects modeling and outcome modeled with a time-to-event approach. The final population pharmacokinetic models were used for Monte-Carlo simulations and dose optimization.

Results

Observed mortality was 12.9% [CI.6.05-23.0] and 17.3% [CI.9.57-27.8] after artesunate and quinine dosing, respectively; relative reduction of 25.8% for artesunate treatment compared with quinine treatment. A zero-order absorption model withone-compartment disposition pharmacokinetics described all the drugs adequately. Body weight as an allometric function was a significant covariate in all models. An exposure-effect relationship was established for quinine with cumulative AUC modulating the hazard of mortality. No exposure-effect relationship could be established for artesunate/dihydroartemisinin in the pharmacokinetic cohort. Simulations using the final population pharmacokinetic models indicated a reduced quinine, artesunate and dihydroartemisinin exposure at lower body weights after a standard weight-based dosing. However, a loading dose of quinine resulted in adequate drug levels for all body weights and there was no evidence of dose related drug toxicity. An adapted dosing regimen of artesunate/dihydroartemisinin for young children was proposed, including a practical dosing table per weight band.

Conclusions

Artesunate/dihydroartemisinin and quinine pharmacokinetics were adequately described. A loading dose of quinine is recommended. Children at lower body weight had reduced artesunate/dihydroartemisinin exposure and the final model was used to develop a practical dosing table for intramuscular artesunate in the treatment of severe malaria.

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Applications- Infection

PA2-14

Mechanistic Model of Maraviroc Pharmacokinetics in Adults and Children

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Objectives

Maraviroc is a first-in-class selective CCR5 antagonist indicated for HIV-1, which prevents viral entry to host immune cells. Following intravenous administration, maraviroc clearance is linear, mainly via hepatic CYP3A4. After oral administration, maraviroc displays non-linear behaviour with low doses (due to P-glycoprotein efflux), and can exhibit double/multiple plasma concentration peaks. AUC is increased or decreased with CYP3A4 inhibitors and inducers, respectively. Due to maraviroc's complex pharmacokinetics, it may not be possible to develop a model for defining paediatric oral dosing using data derived from children alone. By pooling adult data with interim data from an ongoing paediatric trial, this study aimed to create a mechanistic model incorporating dose non-linearities, effects of drug interactions and scaling to children.

Methods

Intravenous adult data were described using an empirical 4-compartment model with allometric scaling, renal clearance fixed and scaled with expected glomerular filtration (Rhodin et al. 2008), and intrinsic clearance (CLI) estimated via a liver compartment with blood flow scaled with expected liver volume for weight (Price et al. 2003). An oral, dual-input model was used to describe single and double concentration peaks, andoral data were added in stages: adult tablet monotherapy (fed and fasted), adult solution monotherapy (fed and fasted), adult interaction (maraviroc plus protease inhibitors), and interim paediatric data. Dose non-linearity was explored with a variety of empirical functions. Food and formulation were explored as covariates on absorption parameters; drug interactions were tested on CLI and bioavailability. Model evaluation focused on prediction of AUC, which relates to efficacy.

Results

Data from 549 adults and 30 children were included. Dose non-linearity was best described using a Richard's model. Food and solution formulation significantly increased the value of the non-linearity inflection point. Food was a significant covariate on absorption lag and rate from the later input compartment. CLI was decreased by approximately 88% by protease inhibitors. AUC calculated from simulated and observed data gave good agreement in paediatric and adult subjects.

Conclusions

This model of maraviroc pharmacokinetics adequately described the data and can predict AUC in adults and children, and in patients receiving different formulations/food/interacting medicines.

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PA3-1   Population Pharmacokinetics/Pharmacodynamics of Anti-asthma Drug CJ13,610 in Phase II Study in Patients with Persistent Asthma

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Objectives

The purpose of this work was to develop a PK/PD model to describe the characteristics of the efficacy for a 5-lipoxygenase inhibitor CJ13,610.

Methods

A Run-in-Placebo-PK/PD joint model was developed based on a phase II clinical trial of CJ13,610, in patients with persistent asthma. A one compartment model with first-order absorption was used based on the prior information [1]. A mixture error model was applied to the pharmacokinetic model to simultaneously estimate the residual error distributions for both normal data and outlying data and, the proportion of the outlying points[2]. The forced expiratory volume in one second (FEV1) was used as the endpoint. During the placebo modeling, the data from a model-based meta-analysis[3] and the individual data from current clinical trial were pooled with a weight of sample size to fill the sampling time gap in the current clinical trial. The run-in phase, placebo and PK/PD models were estimated simultaneously.

Results

The oral clearance (CL/F) of CJ13,610 was 27.1 L/h, the oral distribution volume(V/F) was 468 L, and the absorption rate constant was 0.155 h-1. The estimated proportion of the outlying data points was 15.6% with a residual error high to 260%, while the normal residual error was only 26.3%. , maximum concentration at steady state reflecting both dose level and the frequency of administration, was selected as the independent variable in the PK/PD model.The run-in model was an exponential model. The population typical baseline of FEV1 at randomization was 2.32 L. The estimated maximal placebo effect (Pmax) was 0.059L, and the rate constant to approach the plateau was 0.527 wk-1. A linear PK/PD model described the increase of the drug effect with a slope of 0.118 L/(mg/L). The covariate screening showed there was no significant influence of demographic characteristics, predicted FEV1% and baseline FEV1 on the drug effect.

Conclusions

The Run-in-Placebo-PK/PD joint model was developed to describe the time course of the run-in phase, placebo effect and the effecacy of CJ13,610. To obtain a drug response of 0.15L over placebo as marketed 5-LO inhibitor, the typical subject would take 600 mcg QD.

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Applications- Inflammation

PA3-2

Contribution of Modeling & Simulation to NDA Approval by Designing Successful Phase 3 Trial for Tacrolimus Treatment in Patients with Ulcerative Colitis

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Objectives

The tacrolimus application for remission in severe or moderate patients with refractory ulcerative colitis has been approved in Japan recently based on two Phase 3 trials which were designed by intensivemodeling & simulation[1] in view of 1) rationale of the tacrolimus trough concentration being firm surrogate of the efficacy (remission of repulse by two week), and 2) reliable dose titration procedure for controlling the tacrolimus trough concentration within the target window at two week time point of treatment to ensure efficacy and safety. The Phase 3 trial has been completed and the NDA submission has been approved recently. In this presentation, we will demonstrate how precisely the modeling & simulation could predict actual clinical outcomes. (The modeling & simulation for tacrolimus has been presented in the International PKPD Symposium).

Methods

The response rate of remission at two week was predicted by established logistic model with tacrolimus trough concentration as an independent exposure variable. The mean and PI of predicted response rate were compared with the actual outcome in the Phase 3. The performance of the dose titration procedure was evaluated by the success rate of controlling simulated trough concentration within the target window of 10~15 ng/mL and compared with the actual results in the Phase 3.

Results

The mean predicted response rate was close to the actually observed rate in the Phase 3 (50%). The success rate aswell as entire distribution of trough concentration well predicted the actual success rate confirmed in the Phase 3.

Conclusions

The quite high consistency between the pre-defined predictions and the actual clinical outcomes confirmed the validity of the established models for both efficacy and dose titration procedure before conducting the confirmatory study. This is one of examples where modeling & simulation approach has significantly contributed to successful NDA by providing reproducible predictions.

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Applications- CNS

PA4-1

Impact of Aminophylline on the Pharmacodynamics of Propofol in Beagle Dogs

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Background

This study aimed to characterize pharmacodynamic interaction between propofol and aminophylline in beagle dogs.

Methods

Nine beagle dogs were randomly allocated to receive propofol at the rates of 0.75 (group A), 1.00 (group B), and 1.25 (group C) $mg \cdot kg^{-1} min^{-1}$ (n=3 each). During period 1, propofol only was infused, while during period 2, aminophylline only, at the rates of 0.69, 1.37, and 2.62 $mg \cdot kg^{-1} min^{-1}$, to group A, B, and C, respectively. From period 3 to 5, propofol and aminophylline were co-administered. The infusion rates of aminophylline were 0.69, 1.37, and 2.62 $mg \cdot kg^{-1} min^{-1}$, for period 3, 4, and 5, respectively. The durations of zero-order infusion were 20 min and 30 h for propofol and aminophylline, respectively. When co-administered, the infusions of aminophylline and propofol were started from time 0 h and 24 h, respectively. Blood samples of propofol and aminophylline for pharmacokinetic analysis and electroencephalograms for pharmacodynamic analysis were obtained at

preset intervals. Phamacokinetic and pharmacodynamic analysis were performed using NONMEM VII.

Results

In the linear regression between log-transformed dose (log-*Dose*) of aminophylline and AUC_{inf} ($AUC_{aminophylline}$), the slope was 0.6976 (95% CI, 0.5242 0.8710). Pharmacokinetics of aminophylline was best described by a one-compartment with enzyme auto-induction model. Pharmacokinetics and pharmacodynamics of propofol were best described by a three-compartment model and a sigmoid E_{max} model, respectively. Pharmacodynamic parameter estimates of propofol were as follows. k_{e0}=0.805 min^{-1}, E_0=0.76, E_{max}=0.398, $Ce_{50\ without\ aminophylline-exposure}$=2.38 ($gml^{-1}$), $Ce_{50\ with\ aminophylline-exposure}$=4.49 ($gml^{-1}$), and = 2.21.

Conclusions

Propofol became less potent with the presence of aminophylline.

Keywords

pharmacodynamic interaction, propofol, aminophylline, NONMEM

Applications- CNS

PA4-2

A Systematic Approach to PKPD Model Development to Describe Sleep Effects of Compounds with Different Mechanisms of Action Using Semi-Mechanistic Markov Chain Models

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Objectives

To describe the sleep effects of the non-benzodiazepine hypnotic agent Zopiclone (ZOP), and the selective 5-HT2A antagonist MDL-100,907 (MDL) using a semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) Markov-chain model previously developed for Zolpidem in healthy rats[1].

Methods

Experimental. Electroencephalogram (EEG) data were obtained in rats. For each 10 second interval, EEG data were converted into AWAKE, REM or NREM stages representing non-ordered categories. The data consisted of a 12 h baseline where EEGs were monitored in the absence of any type of perturbation and a 12 h period during which methylcellulose (MC), ZOP or MDL were administered. **Data analysis.** The time course of the 9 possible transition probabilities between the 3 sleep stages was described using a non-homogeneous Markov chain model based on piecewise multinomial logistic functions[2], as previously described[1]. Literature PK data was used to generate concentrations of ZOP and MDL over time[345]. Analyses were performed using NONMEM VII v2. Model evaluation was based on visual predictive checks (VPCs).

Results

Baseline model. A model selected previously[1] was used to generate VPCs for the baseline data from the new studies. Results indicated that this model was adequate to describe and predict the new data. **MC model.** The effects of MC administered orally or IP were incorporated using a Bateman function to reflect an increase in the transition probability from NREM to awake. **Drug effect model.** Exploration of the time course of transition probabilities revealed that both ZOP and MDL elicited a temporal decrease in the transition probability from NREM to awake indicating that sleep was promoted. ZOP exhibited a rebound effect approx. 8-10h after dosing, whereas such rebound phenomena were not observed in the data with MDL. ZOP effects were described using a turnover feedback model[16]. For MDL, the PKPD models that best described the data were the link[7] or indirect response[8] (IDR) models.

Conclusions

The baseline response model used to describe the underlying physiological system (a non-homogeneous Markov chain model) has been shown to be conserved across several studies, thereby supporting its application for future studies. Drug level effects need to be considered separately, contingent on their mechanism of action and the observed responses.

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Applications- CNS

PA4-3

Clinical Implications of Blood-Brain Equilibration Half-Time of Propofol

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Objectives

The aims of this study were to evaluate the pharmacokinetics and pharmacodynamics of propofol and to estimate keo of propofol for EEG ApEn (electroencephalographic approximate entropy) with varying sizes of moving window through pharmacodynamic modeling.

Methods

Microemulsion and long-chain-triglyceride emulsion propofol were administered by zero-order infusion (1.5, 3.0, 6.0 and 12.0 $mg \cdot kg^{-1} \cdot min^{-1}$) for 60 min. Each volunteer was studied twice with different formulations at an interval of 1 week. Arterial or venous concentrations of propofol were measured, and bispectral index and EEG ApEn were used as a measure of propofol effect. Pharmacodynamic parameters of a sigmoid E_{max} model and k_{eo} were estimated using a population approach with mixed effects modeling.

Results

Microemulsion and long-chain-triglyceride emulsion propofol were administered by zero-order infusion (1.5, 3.0, 6.0 and 12.0 $mg \cdot kg^{-1} \cdot min^{-1}$) for 60 min. Each volunteer was studied twice with different formulations at an interval of 1 week. Arterial or venous concentrations of propofol were measured, and bispectral index and EEG ApEn were used as a measure of propofol effect. Pharmacodynamic parameters of a sigmoid E_{max} model and k_{eo} were estimated using a population approach with mixed effects modeling.

Conclusions

Microemulsion propofol was more potent than LCT propofol. The onset of microemulsion propofol was faster than LCT propofol. The k_{eo} for ApEn calculated with moving windows of 30 s was smallest, suggesting delayed apparent onset of propofol as determined by $t_{1/2}k_{eo}$, compared with that for BIS. The size of moving window for calculating ApEn should be shorter than 30 s.

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Applications- CNS

PA4-4

The Population Pharmacokinetics and Pharmacogenomics of Lamotrigine in Thai Patients

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Objectives

Lamotrigine is approved for the treatment of several types of seizures and bipolar disorder. Lamotrigine is primarily metabolized by UDP-glucuronosyl transferase (UGT) enzymes. Whereas UGT1A4 is the main enzyme responsible for lamotrigine metabolism, UGT2B7 may also play a role [1, 2]. This study aimed to investigate the influence of UGT1A4 and UGT2B7 polymorphisms and other non-genetic factors on lamotrigine pharmacokinetics by the population approach.

Methods

Four single nucleotide polymorphisms (SNPs); UGT1A4 142 T>G, UGT1A4 70C>T, UGT2B7 372A>G, and UGT2B7 -161C>T were identified by Taqman allelic discrimination assays using Taqman probes. Data were analyzed using NONMEM. A one-compartment model with first-order absorption and elimination was used. The absorption rate constant (ka) cannot be estimated and was fixed to 1.3 hr-1. Interindividual variability was model using exponential error model. The influence of genetic and non-genetic factors was investigated in the covariate model using stepwise forward inclusion ($p < 0.05$; $\chi 2$) and backward deletion ($p < 0.01$; $\chi 2$) using the likelihood ratio test as cutoff criteria. The UGT genotypes were classified into two groups; group 1 consisted of patients with *wt/*wt and group 2 consisted of patients having at least one variant alleles.

Results

A total of 75 patients were included in the analysis. It was found that the use of enzyme inducers, valproic acid, and UGT2B7-161 C>T significantly influence lamotrigine CL/F. The final model can be defined by:CL/F = 2.49 x (1+1.04 x inducers) x (1-0.41 x valproic acid) x (1-0.18 x UGT2B7 -161 C>T)The interindividual variability of CL/F was 22.42%. The estimated volume of distribution (V/F) was 156 L. The residual unexplained variability was estimated to be 26.11% and 0.18 mg/L, respectively.

Conclusions

The results from our study showed that the use of inducers increases lamotrigine clearance by 104%. The concomitant use of VPA and the presence of at least 1 variant allele of UGT2B7 -161 C>T decrease CL/F 41% and 18%, respectively. Therefore, these factors should be considered whendosing lamotrigine. The results from this study can facilitate individualizing lamotrigine dosage regimens in this population using patient-specific covariates.

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PA4-5   Population Pharmacokinetics and Pharmacodynamics of Escitalopram in Healthy Volunteers

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Objectives

Pharmacokinetic-pharmacodynamic (PK-PD) modeling has been suggested for the prediction of brain receptor occupancy by antipsychotics. Escitalopram, a selective serotonin reuptake inhibitor, is used for depression or obsessive-compulsive disorder (OCD). This study aimed to assess escitalopram PK and PD profile using positron emission tomography (PET) data in healthy volunteers to explore the relationship between plasma drug concentration and transporter occupancy.

Methods

The population PK and PD analysis was performed using nonlinear mixed effect model (NONMEM®7.2) based on plasma concentrations and transporter occupancies from PET imaging in healthy volunteers receiving escitalopram 5-20 mg dose range. Sequential PK-PD model was developed and the first-order conditional estimation with interaction in NONMEMwas employed for model run. A one-compartment model with first order absorption and first-order elimination described the PK. The influence of demographic characteristics on PK parameters was examined. The serotonin transporter occupancy was calculated from binding potential of PET imaging. A sigmoid Emax model was employed to describe transporter occupancy by escitalopram in the caudate nucleus.

Results

Twelve subjects contributed to 144 escitalopram concentrations and 139 binding potential data for the caudate. Oral clearance was 35.9 L/h (CV 35.5%), oral volume of distribution was 1260 L (CV 12.1%) and the absorption rate constant was 10.5 hr-1 (CV 81.2%). Of the covariates including age, weight, height evaluated, none of the covariate showed an influence on escitalopram PK parameters. The transporter occupancy in the caudate was correlated with escitalopram concentration. Sigmoid Emax model was well fitted for transporter occupancy in the caudate nucleus. EC50 was 1.67 ng/mL (CV 0.01%) and Hill coefficient was 0.681 (CV 25.9%).

Conclusions

PK-PD model for escitalopram was developed for healthy volunteers. Therapeutically effective serotonin transporter occupancy for OCD is unclear although that for depression was reported about 80%[1]. Further PK-PDmodeling using occupancy for escitalopram may be useful tool to predict clinically relevant plasma concentration and drug effect in OCD patients.

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Applications- CNS

PA4-6 **Population Pharmacokinetics of Blonanserin in Chinese Healthy Volunteers and the Effect of the Food Intake**

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Objectives

Blonanserin is a novel oral atypical antipsychotic agent with potent activity of blocking dopamine D2 and serotonin 5-HT2A receptors. The purpose of this research was to better understand blonanserin population pharmacokinetics characteristics and the effect of food intake on exposure in Chinese healthy subjects

Methods

Data from two studies with fifty subjects were analyzed to investigate the population PK characteristics of blonanserin at single-dose (4mg, 8mg and 12mg) under fasting, multi-dose (4 mg bid for 7 days, then 8 mg qd for 7 days) and under food intake condition (single-dose, 8mg). Blonanserin plasma concentrations were detected using the LC/MS/MS. A nonlinear mixed-effects model (NONMEM) was developed to describe the blonanserin concentration − time profiles

Results

A two-compartment model with first-order absorption was built to describe the time-course of blonanserin. The population-predicted system apparent clearance (CL/F), volume of apparent distribution in center (V1/F) and first-order absorption rate constant (Ka) of blonanserin under fasting was 1230 L/h, 9500 L and 3.02 h-1 respectively. Food intake decreased Ka of blonanserin to 0.78h-1. The relative bioavailability between fasting and food intake estimated by the final model was 55%. No clinically significant safety issues were identified

Conclusions

Food intake increased the systemic exposure to blonanserin and the PK parameters of blonanserin can be used for simulation in further clinical trial and optimizeindividual dosage regimens using a Bayesian methodology in patients

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Applications- CNS

PA4-7 Exposure-Response Modeling of Lacosamide in Adjunctive Treatment of Patients with Partial-Onset Seizures

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Objectives

To develop a retrospective exposure-response model for lacosamide based on daily seizure counts of individual patients with focal epilepsy and to identify potential prognostic factors in reducing seizure frequency (SF) by performing a covariate analysis.

Methods

Individual daily seizure records (N=210,234) were obtained from 1308 patients who participated in three double-blind, placebo-controlled clinical trials (SP667, SP754, SP755). Probability of daily seizures was estimated by nonlinear mixed effects modeling using statistical distributions appropriate for count data. Plasma concentrations were estimated using a population pharmacokinetic model. Drug effect on seizure frequency reduction was modeled using a Hill function.

Results

A negative binomial distribution with zero-inflation and Markovian element provided the best fit for all phases (baseline, titration, maintenance). Patients not taking concomitant sodium channel blocking (SCB) anti-epileptic drugs (AEDs; 18% of population) underwent a greater SF reduction from baseline than patients on SCB AEDs (82%). The EC_{50} (trough concentration producing half the maximum SF reduction) was 4.6µg/mL (90%CI 3.5–5.7µg/mL). Median SF reduction in improving patients was 23% (placebo), 48% (lacosamide with SCB) and 70% (lacosamide with non-SCB) at lacosamide 400mg/day.

Conclusions

An exposure-response relationship was demonstrated between lacosamide plasma trough concentration and SF reduction from baseline in patients with uncontrolled focal seizures. The combination of AEDs with different mechanisms of action (SCB and non-SCB) resulted in greater reductions in SF compared with the combination of AEDs sharing the same mechanism of action (SCB and SCB), as identified previously [1].

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Applications- CNS

PA4-8 # Exposure-Response Analysis to Assess the Effect of Clozapine in Chinese Patients with Schizophrenia

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Objectives

The objective of our analysis was to develop a mathematical exposure–response model to describe the relationship between the exposure of clozapine and the time course of Positive and Negative Syndrome Scale (PANSS) response in Chinese patients with schizophrenia

Methods

Sparse PK data accompanied by PD evaluation were collected from 2 clinical studies in Chinese inpatients with schizophrenia. To assess the accurate PK characteristics, the sparse clozapine data were mixed with two sets of rich data, one of which was a single dose pharmacokinetic study in Chinese healthy subjects (study I), the other was a multi-dose study in Chinese patients with schizophrenia (study II). A two-compartment pharmacokinetic model with first order absorption and proportional error models described the PK profile of clozapine adequately using NONMEM. For the exposure-response model, accumulated exposure of clozapine was related to the PANSS scores using Emax model. The evaluation of the prediction of the final model was conducted based on 1000 simulations in visual predictive check plots and normalized prediction distribution error

Results

A total of 1410 concentrations of clozapine and 641 PANSS scores were included for this analysis. In the final model, gender and smoking status were identified as combined effect influencing the system clearance of clozapine. The time course of total PANSS scores was characterized with accumulative clozapine exposure via an Emax model. The Emax and AUC50 of accumulative exposure of clozapine was 55.9% and 368 mg · h · day/L, respectively. The results indicated that the obvious effect would be achieved after the continuous administration of clozapine for four weeks

Conclusions

The exposure-response model for the pharmacokinetic characteristics and the time course of PANSS scores of clozapine in schizophrenia patients is appropriate for use for clinical effectiveness estimate

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PA4-9 The Effect of Poor Compliance on the Pharmacokinetics of Carbamazepine and Its Epoxide Metabolite Using Monte Carlo Simulation

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Objectives

To study the effect of delayed and missed doses (poor compliance) on the pharmacokinetics of carbamazepine (CBZ) and its main active metabolite carbamazepine-10,11-epoxide (CBZE).

Methods

Monte Carlo simulation was performed to generate CBZ and CBZE time–concentration profiles in various scenarios based on a population pharmacokinetic study in epilepsy patients. The scenarios were based on patients who were administrated with multiple doses of CBZ from 100 to 300 mg three times daily or from 200 to 300 mg every 12 hours. The individual therapeutic range of CBZ and CBZE for each scenario was estimated to assess the effect of delayed or missed doses and to design corresponding rescue regimens. Moreover, the impact of body weight, absorption rate and co-therapy with other antiepileptic drugs (phenytoin, phenobarbital and valproic acid) on the dosage recommendation in the event of poor compliance was investigated.

Results

The risk for sub-individual therapeutic concentration of CBZ and CBZE was increased in a daily dose-dependent manner in both two and three times daily regimens when delayed or missed doses occurred. The effect of poor compliance is less significant on lower daily dose compared with high daily dose. The recommendation doses in the event of poor compliance were time related and dose dependent. Patient body weight, absorption rate and co-therapy with phenytoin, phenobarbital and valproic acid had no significant impact on the dose recommendation. Moreover, taking a dose 30 minutes before or 30 minutes delayed from the scheduled time has no significant impact on the concentration profile of CBZ and CBZE.

Conclusions

The patients should take the delayed doses as soon as they remember and partial missed doses should be taken when it is close or equal to the next scheduled time. The pharmacokinetic simulationis a useful tool to analyze the impact of poor compliance and provide rational information to patients in the case of delayed or missed doses.

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Applications- CNS

PA4-10

Evaluation of Exposure-Response Relationship of 3 Antiepileptic Drugs

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Objectives

The aim of this work was to compare the relationship between exposure and seizure frequency for three antiepileptic drugs (AEDs), rufinamide, zonisamide and perampanel and to seek common characteristics.

Methods

Sequential exposure-response analyses of rufinamide, zonisamide and perampanel were performed by non-linear mixed effect modeling using NONMEM. Rufinamide was administered within the range of 1000-3200 mg/day b.i.d. to patients with Lennox-Gastaut Syndrome (LGS) aged 4-37 years (active: 65 subjects, placebo: 64 subjects). Zonisamide was administered within the range of 25-500 mg/day q.d. or b.i.d. to patients with refractory partial seizure aged 6-77 years (active: 271 subjects, placebo: 208 subjects). Perampanel was administered within the range of 2-12 mg/day q.d. to patients with refractory partial seizure aged 12-76 years (active: 770 subjects, placebo: 339 subjects). All three drugs were used as adjunctive therapy. The relationship between average plasma concentration and natural log (rufinamide, perampanel) or box-cox transformation (zonisamide) of seizure frequency was modeled for each drug. The exposure-response models were qualified using goodness-of-fit plots and visual predictive check.

Results

The relationships between exposure and seizure frequency were well described by comparable structure in exposure-response models for zonisamide and perampanel in subjects with refractory partial seizuresand for rufinamide in subjects with LGS. For all three AEDs, the best model for the seizure frequency was the sum of the baseline, a placebo/time effect and a drug effect proportional to the estimated average plasma concentration. As several AEDs were co-administered adjunctively, the effect on drug term was evaluated. For each drug, neither concomitant AEDs nor demographic covariates had a significant effect on the exposure-response relationship.

Conclusions

A common empirical model characterized the exposure-response relationship for each of the three AEDs. This model may be useful to analyze exposure-response data for other antiepileptic drugs.

Applications- CNS

PA4-11   A Longitudinal Model-Based Meta-Analysis for Hamilton Rating Scale for Depression (HAMD-17) from Randomized-Controlled Trials with Patients with Major Depressive Disorder (MDD)

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Objectives

To describe the time-course of clinical response in MDD using HAMD-17, to explore the relationship between placebo response and trial-specific covariates, and to characterize the effects of selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) by performing a model-based meta-analysis (MBMA).

Methods

A systematic review of public data sources from 1986 to May 2, 2011 on studies of SSRI and SNRI with MDD (without comorbid conditions) was conducted. Only data from randomized, double-blinded, and placebo-controlled studies were included. 86 reports met the search criteria but 550 HAMD-17 observations from 15675 patients participated in 42 studies were available for the analysis (absence of HAMD-17 or baseline, etc.). NONMEM 7.1.2 was used for the analysis with consideration of inter-study, inter-arm, and residual variability that was weighted according to the sample size (Ahn and French, 2010).

Results

Overall the response measured in HAMD-17 was characterized as the sum of baseline, placebo response, and treatment effects. The non-lineardrop in HAMD-17 observed in placebo arms was described using an asymptotic exponential function. The treatment effects with delay were incorporated but dose-response was not found in most SSRI/SNRI.

MBMA estimated that it would take about 1.8 weeks to reach half of the maximum placebo effects of 9.35 points (RSE 4.73%). At week 6, the estimated typical placebo response was a 8.4 point drop in HAMD-17 scores. Taking the placebo response into account, the treatment effects were small and variable among treatments; furthermore, the half-life to reach the maximum treatment effect was long (~5 weeks) and variable from study-to-study (63% CV; RSE 50.1%). The trend in placebo response with respect to publication year was unclear partly due to limited information from the 90's in the current meta-data. However, the placebo response was dependent upon the baseline which appears to be unrelated to publication year. Posterior predictive check showed that model prediction of observed data was reasonable.

Conclusions

MBMA was performed to quantify the time course of HAMD-17 scores. As expected, placebo response was very large leaving less room for the treatment response. The tendency in placebo response over time was unclear.

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PA4-12

Correlation between Exposure to ELND005 (Scyllo-inositol) and Emergence of Neuropsychiatric Symptoms in Mild to Moderate Alzheimer's Disease Patients

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Objectives

Neuropsychiatric symptoms (NPS) in AD may reflect dysfunction in frontal areas. In patients with NPS, anterior cingulate Myo-inositol elevations correlated with NPS severity (Shinno et al., 2007). ELND005, an amyloid anti-aggregation agent, demonstrated pathological and cognitive benefits in preclinical models. In Study AD201 (Salloway et al. 2011), ELND005 treatment led to dose-dependent reductions in brain Myo-inositol, and to reduced emergence of NPS (Tariot et al. Neurology 2012).The objective of the work presented herein was to evaluate the role of change in brain levels of Myo-inositol or Scyllo-inositol in mediating the effects of ELND005 on NPS emergence.

Methods

Study AD201 evaluated 3 ELND005 doses (250mg, 1000mg and 2000mg, all BID) versus placebo in 351 patients. Brain Scyllo-inositol and Myo-inositol were assessed by magnetic resonance spectroscopy (MRS, n=104): percent changes from baseline (PCBLs) were calculated from observed MRS data. Across the four treatment groups, four quartiles of PCBL in Scyllo-inositol and Myo-inositol brain levels were plotted against the emergence probability of individual NPS. Logistic regression models were estimated to quantify the effect of exposure to 250mg of ELND005 compared to placebo.

Results

Of 12 NPS, depression, anxiety, apathy, and irritability exhibited a V-shaped pattern with lowest probability of emergence mostly at 2nd quartile of brain Scyllo-inositol AUC0-24 hr, corresponding to the 250 mg dose. Plots of NPS emergence versus Myo-inositol PCBL showed a similar V-shaped pattern for depression, anxiety, apathy with Myo-inositol PCBL of 30%- 50%, also correspondng to the 250mg ELND005 dose. Logistic regressions revealed trends (p< 0.1) at various visits for decreased emergence of agitation, depression, anxiety, disinhibition, and nighttime behavior. At some visits, trends further reached significance (p< 0.05) for agitation, depression, and nighttime behavior.

Conclusions

Decreased emergence of affective NPS was associated with specific Scyllo- and Myo-inositol changes in brain assessed by MRS. The neuropsychiatric effects of ELND005 may be partly mediated by brain Myo-inositol regulation.

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Applications- CNS

PA4-13

ELND005 (Scyllo-inositol) Reduces Brain Myo-inositol Levels in Mild to Moderate Alzheimer's Disease Patients

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Objectives

ELND005 (Scyllo-inositol), a Myo-inositol stereoisomer, is being developed as a potential disease modifying agent based on its amyloid anti-aggregation effects in preclinical models (McLaurin et al., 2000). Endogenous Myo and Scyllo-inositol concentrations in brain are ~ 4-5mM and < 1mM, respectively. Myo-inositol, through its phosphorylated derivatives, is involved in the Phospho-inositol (PI) cycle, an important signaling pathway of G protein-coupled receptors (GPCRs). Unlike Myo-inositol, Scyllo-inositol is not thought to be phosphorylated or involved in PI signaling (Fenili et al. 2007). The objective of the work presented herein was to evaluate effects of ELND005 on brain Scyllo-inositol, Myo-inositol, and total inositol levels in AD patients

Methods

Study AD201, a 78-week study, included 351 AD patients who received placebo or ELND005 (250, 1000, or 2000 mg, all BID). Brain Scyllo andMyo-inositol levels were assessed in 104 patients by proton-magnetic resonance spectroscopy (MRS), at baseline, 24, 48, and 78 weeks. MRS measurements (1.5 or 3 Tesla) were obtained from an 18 cm3 voxel in posterior medial cingulate cortex. Analyses of inositol levels were performed by a central imaging laboratory (NeuroRx Research, Montreal).

Results

Brain levels of Scyllo-inositol showed a dose-dependent increase with ELND005 treatment at 250mg and 1000mg doses, and reached apparent saturation above 1000 mg. Brain levels of Myo-inositol showed a reciprocal decrease at same time points: Percent change from baseline (PCBLs) at the 250mg and 1000mg doses were -36% to -45% and -61% to -64%, respectively, and also reached apparent saturation at doses above 1000 mg. These effects on Scyllo and Myo-inositol were observed from 24 through 78 wks, and were similar in Mild and Moderate patients. Total brain inositol levels were generally constant at any given visit, and Scyllo and Myo-inositol were highly inversely correlated (at 24, 48 wks: r= 0.86, 0.9, both p < 0.0001).

Conclusions

ELND005 dose-dependently decreased brain Myo-inositol levels, likely due to competition for active uptake by the Sodium/Myo-inositol transporter, which has similar affinity for Myoand Scyllo-inositol (Fenili et al., 2011). ELND005, through reduction of Myo-inositol levels, may play a regulatory role in the PI pathway and in signal transduction of neurotransmitter and growth factor stimuli.

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PA4-14 Model-based Meta-Analysis Demonstrating the Comparative Efficacy of Single Doses of Standard Analgesics in the Treatment of Postoperative Dental Pain

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Objectives

The purpose of this model-based meta-analysis (MBMA) was to characterize the comparative dose-response relationships for the analgesic effect of single doses of standard analgesic agents: NSAIDs, paracetamol and opioids, in the treatment of pain after third molar extraction. The overall goal was to facilitate future analgesic drug development by more fully characterizing dental pain as a model of more general post-surgical surgical pain.

Methods

A joint nonlinear mixed effects modeling was performed to analyse TOTPAR6 (time-weighted total PR 0-6 hrs) and SPID6 (time-weighted sum of the PID 0-6 hrs) data obtained from literature[1]. The correlation between TOTPAR6 and SPID6 was captured utilizing a fixed effect and both trial to trial variability and residual error models.

Results

The dose-response relationships for TOTPAR6 and SPID6 for NSAIDs were adequately described by an Emax model with same maximum efficacy (Emax) (for all except quick-release (QR) ibuprofen formulation (solution/gel/salts)) and different potency (ED50) for each drug. In comparison, a linear model with a different slope for each drug was sufficient to describe the dose-response relationships for paracetamol and opioids over studied dose range. The estimated Emax (mean [95% CI]) of TOTPAR6 over placebo for NSAIDs and QR ibuprofen were 11.4 [10.6, 12.2] and 13.5 [11.9, 15.1], respectively. The slopes for paracetamol, hydrocodone, morphine, oxycodone, tapentadol and tramadol were 0.00578, 0.0843, 0.101, 0.188, 0.0383 and 0.0100, respectively. NSAIDs showed larger effect than paracetamol and opioids. The scaling coefficient (mean(SE)) between SPID6 and TOTPAR6 was estimated to be 0.663(0.0150) across all drugs except for QR ibuprofen (0.600(0.0458)). When opioids were comedicated with ibuprofen or paracetamol, the combination effect was estimated to be additive or more than additive, respectively. The combination effect of paracetamol with NSAIDs was less than sum of their separate effect.

Conclusions

This model-based meta-analysis provided a broad overview and understanding of dose response relationship across different classes of analgesic drugs in the treatment of postoperative dental pain. It has had a key role in setting target values for go/no go decision rules in early analgesic drug development and in providing priors for designing and analysising future studies.

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Applications- CNS

PA4-15

An Exploratory Analysis of the Comparative Efficacy of Single Doses of Standard Analgesics in the Treatment of Postoperative Dental Pain

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Objectives

To conduct an exploratory analysis of the efficacy data from randomized double-blind studies that have assessed standard analgesics for acute pain after third molar extraction.

Methods

A comprehensive literature research identified randomized, double-blind, parallel-group, placebo-controlled trials investigating single doses of NSAIDs, paracetamol and opioids administered alone or in combination to healthy patients with moderate to severe dental pain after third molar extraction. Pain relief (PR) and pain intensity difference (PID) data were extracted and converted into total pain relief (TOTPAR) and sum of pain intensity difference (SPID) over 6 hours using a time-weighted trapezoid rule. Exploratory analysis was performed for the PR and TOTPAR data. Univariate meta-analysis[1] (random effects model) was undertaken for efficacy endpoints of TOTPAR6/SPID6 at one common used dose level for each compound in R.

Results

93 placebo controlled trials including 297 treatment arms with a total of 17362 patients were included in the meta-database. PR and PID were reported in 82 and 66 trials, respectively. There were 272 and 25 treatment arms for monotherapy and combination therapy, respectively. Funnel plots showed no obvious publication bias. TOTPAR6 and SPID6 of each drug were correlated (r^2=0.901) and a scaling coefficient of 0.657 was estimated. The effect sizes for TOTPAR6 over placebo (mean, [95% CI]) were estimated to be for 400mg standard ibuprofen tablets (acid) (7.79, [4.72, 10.85]), 400mg quick-release ibuprofen formulation (solution/gel/salts) (10.05, [5.90, 14.19]), celecoxib 400mg (8.41 [3.39, 13.42]), etoricoxib 120mg (11.16, [9.96, 12.36]), parecoxib 20mg (9.88 [8.52, 11.25]), rofecoxib 50mg (8.31, [4.19, 12.43]), valdecoxib 40mg (10.23, [9.13, 11.34]) and paracetamol 1000mg (5.81, [5.10, 6.52]). This suggested that NSAIDs had a larger analgesic effect than paracetamol. The analgesic effect of opioids after co-treatment with ibuprofen was larger than that of combination with paracetamol. Exploratory analysis showed that placebo response could be impacted by baseline pain intensity and trial locations.

Conclusions

This exploratory analysis and meta-analysis integrated prior knowledge of standard analgesics and provided quantitatively understanding of their effect size across standard administered doses: NSAIDs were more effective than paracetamol and opioids. Patients treated with opioids could gain greater benefit from combination with either ibuprofen or paracetamol.

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Applications- Coagulation

PA5-1

Evaluating the Influence of Different Covariates on Enoxaparin Pharmacokinetics in Neonates, Infants and Children

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[www.page-meeting.org/?abstract=2598]

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Objectives

Enoxaparin, a low-molecular-weight-heparin, is used off-label in children for prevention of symptomatic thromboembolism. However, little is known regarding its pharmacokinetics (PK) in children. The aim of this investigation was to further evaluate the PK by using additional data and covariate analysis combined with previous study data. [1]

Methods

Data from 126 patients (median age: 5.9 years; median weight (WT): 24 kg) receiving enoxaparin either as a once or twice daily dose regimen, were analysed. All studied patients received enoxaparin during secondary prophylaxis therapy. Using NONMEM, steady-state plasma concentration-time data were analysed. The following patient characteristics were assessed as covariates on PK parameters using conventional and linearised stepwise covariate model (SCM) building: age, WT, body surface area (BSA), serum creatinine, estimated Glomerular Filtration Rate (eGFR), Body Mass Index, and Antithrombin. Missing covariates were handled using: a Slope-Intercept model for WT imputation from postmenstrual age (PMA); the Boyd equation, using the imputed WT as an independent variable, to calculate missing BSA values [2]; the Mosteller formula to calculate missing heights from the imputed BSA and WT; and either the Lund-Malmöequation or the updated Schwartz equation for eGFR imputation, depending on age or height availability, respectively. [3,4]

Results

A two-compartment first-order absorption model with interindividual variability (IIV) on clearance (CL/F), central volume of distribution (V1/F), and absorption rate konstant (ka) best described the data. WT as covariate was pre-specified in the base model on CL/F and V1/F. As enoxaparin is mainly cleared renally it was hypothesised that CL might be parameterised asa sum of an eGFR-dependent renal and a WT- or BSA-dependent non-renal component. However, the SCM did not find any parameter-covariate relations statistically significant for inclusion. Final parameter estimates (IIV %) were: CL 15 mL/h/kg (54%), V1/F 169 mL/kg (24%), intercompartimental clearance (Q) 52 mL/h, peripheral volume of distribution (V2) 12 L and ka 0.404/h (68%).

Conclusions

This population PK analysis confirms our previous findings [1] that no other covariate than WT is needed for renally healthy patients to explain the PK of enoxaparin. The model describes enoxaparin disposition in all age groups in our study population from neonates to adolescents.

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Applications- Cardiovascular, QT

PA6-1 **Population Model of Blood Pressure - Based on 24-Hour Ambulatory Blood Pressure Monitoring Studies in Antihypertensive Drugs Clinical Trials in China**

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Objectives

24-hour ambulatory blood pressure monitoring (24-h ABPM) is commonly regarded as an efficacy endpoint in evaluating antipertensive drugs, but its analysis is still insufficient. The aim of this study was to depict the inter-day variations of blood pressure and assess the antihypertensive effects using pharmacometric models based on four 24-h ABPM studies without drug concentrations in Chinese hypertension patients.

Methods

The 24-h ABPM data were collected from six studies where mild to moderate hypertensive patients were recruited. All studies comprised a placebo run-in period and 8-week antipertensive treatment period, 24-h ABPM were conducted at the end of each period and no drug concentrations were measured. The cyclic fluctuations model and antihypertensive effect model were fitted using NONMEM.

Results

The final 24-h blood pressure structure model consisted of two parts. Before treatment, a double cosine function was utilized for modeling the baseline cyclic fluctuations of blood pressure. After treatment, blood pressure changes were estimated as baseline model minus antihypertensive effects which were described by a 2-exponential function. 24-h blood pressure variations before and after applying different antihypertensive drugs were well explained by the same structure model.

Conclusions

The cyclic fluctuations model and antihypertensive effect model provide a basis for individualized antihypertensive therapy, and will be beneficial for simulating and optimizing antipertensive trial designs.

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Applications- Cardiovascular, QT

PA6-2

Pharmacokinetic and Pharmacodynamic Variability of Fluindione in Octogenarians

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Objectives

Fluindione is an oral antivitamin K (AVK) agent comprising about 80% of oral anticoagulant prescriptions in France. AVK are characterised by a narrow therapeutic window: bleeding is the major adverse event, leading to a high number of hospital admissions [1]. Elderly patients suffer more often from diseases for which anticoagulant treatment is indicated such as atrial fibrillation; they also receive more concurrent medications with potential interactions, and experience morbid conditions such as denutrition. As a result, the risk of bleeding is increased in that population [2]. The PREPA observational study was designed to investigate the factors influencing pharmacokinetic and pharmacodynamic variability in the response to fluindione in a general population of octogenarians [3,4].

Methods

Measurements of fluindione concentrations and INR (International Normalised Ratio) were obtained from 131 octogenarians inpatients initiating fluindione treatment and followed over a maximum duration of one month. Treatment was adjusted according to routine clinical practice. The data was analysed using non-linear mixed effect models, using the MONOLIX software for parameter estimation. Covariate model building was performed sequentially, first for PK then for the PK/PD model, and a final joint estimation was performed. The final model was used to predict the dose of fluindione to administer to obtain an INR within a therapeutic window of 2-3.

Results

The dataset included 493 pharmacokineticand 477 pharmacodynamic measurements, mostly obtained between 8 and 15 hours after a dose. The median duration of stay in the study was 8 days (range 2-31 days). The pharmacokinetics of fluindione was monocompartmental, while the evolution of INR was modelled according to a turnover model (inhibition of vitamin K recycling). Interindividual variability was very large. Clearance decreased with age and with prior administration of cordarone. Patients who underwent surgery before the study had lower IC50, leading to an increased sensitivity to fluindione. Fluindione doses of 7.5 to 10 mg were found to be adequate in this elderly population.

Conclusions

AVK administration is challenging because of the long equilibration half-time, and could benefit from modelling-based approaches to better anticipate the fluctuations of INR. Pharmacokinetic exposure is substantially increased in elderly patients, warranting a lower dose of fluindione.

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Applications- Cardiovascular, QT

PA6-3 Prediction of Human *in Vivo* Antiplatelet Effect of
S- and R-Indobufen Using in Vitro Platelet Aggregation Test
The study was presented at the 2010 PAGANZ meeting.

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Objectives

Ibutstrin®(Indobufen), a reversible inhibitor of platelet aggregation is effective in the prophylaxis of thromboembolic events at risky patients. Ibutstrin® exists in two enantiometric forms and S-indobufen is known to be more potent. This in vitro study was done to characterize the antiplatelet effect of S- and R- Indobufen by pharmacodynamic (PD) modeling and to predict the antiplatelet effect of indobufen at steady state on recommended therapeutic dosage.

Methods

From 24 healthy subjects plasma was drawn, to which S- and R-indobufen were added individually or together to make 816 drug containing plasma of the concentrations randomly selected from concentrations of 0, 0.25, 1, 2, 4, 8, 16, 24, 32, 64, 128 mg/L. Collagen-induced platelet aggregation in platelet rich plasma was determined using a Chrono-log Lumi-Aggregometer. The data were analyzed by response surface PD model using NONMEM VI. The final model was validated via predictive check, normalized prediction distribution error, and nonparametric bootstrap procedures. Simulation was done combining the PD model built in this study and the previously reported pharmacokinetic results.

Results

Antiplatelet effect of Indobufen was well-described by inhibitory sigmoid Emax model. S-form was more potent, while the inter-individual variation was quite smaller in R-form. A significant antagonistic effect was found between the two enantiomers.

Conclusions

From simulation study on multiple administrations of indobufen, we could predict the antiplatelet effect on ibustrin®200 mg twice daily administration. Furthermore, we could predict the antiplatelet effect when S- or R-indobufen was administered alone at various doses, and by doing so we could explore the optimal therapeutic dosing regimen of S- or R-indobufen, respectively.

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Applications- Cardiovascular, QT

PA6-4

Impact of ECG Time Point in Concentration-QT Analysis with Phase I Data

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Objectives

Concentration-QT analysis has been conducted at various stages of drug development. Rohatagi et al. showed the usefulness of the analysis with data from available ascending-dose studies such as Phase I. The objective of this study was to determine the impact of ECG time point in concentration-QT analysis with Phase I data.

Methods

A concentration-QT simulation study was conducted under several conditions regarding ECG time point (dense or sparse) using SAS 9.2 (SAS Institute Inc., Cary, North Carolina). Each arm including placebo was assumed to contain 10 participants, and 5000 replicates of the trial were simulated. Simulation was conducted in both negative (no QTc prolongation) and positive (5 msec QTc prolongation at mean Cmax in the therapeutic dose) situations, and false-positive rate and power were assessed, respectively, by fitting the following linear mixed effects model for each replicate.Delta = QTc − QTc (at screening) = b0 + b1*concentration + ε

Results

In the negative (no QTc prolongation) situation, the model predictions were generally symmetric around the true value of 0 in both time points (dense and sparse). In no cases was there a false-positive declaration (95% upper confidence limit of prolongation at mean Cmax exceeding 10 msec) when a dense ECG sampling was conducted. Even in the sparse sampling, false-positive rate was 0 by sampling ECG around Tmax. However, when ECG sampling was conducted only around trough, false-positive declaration was seen in 31.3% of the simulations possibly due to the lack of ECG information around Tmax.In the positive situation, the distribution of QTc prolongation surrounded the true value of 5 msec in both time points (dense and sparse). When a dense ECG sampling was conducted, statistical significance was accomplished in almost all of the simulations (power = 95.0%). Even in the sparse sampling, power was 92.9% by sampling ECG around Tmax. However, when ECG sampling was conducted only around trough, power was at most 40%.

Conclusions

Even in the sparse ECG sampling, an evaluation around Tmax has a comparable benefit to the dense one in some cases. Sparse ECG sampling only around trough would lead to an incorrect view.

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Applications- Cardiovascular, QT

PA6-5 Development of a Longitudinal Model to Describe the QT-time Course in Healthy Volunteers Given Placebo and Moxifloxacin

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Objectives

The purpose of this work was to develop a longitudinal model to describe the time course of QT interval in healthy volunteers given placebo and moxifloxacin treatments and to examine the source of variability affecting on QT interval with a focus on the variability in demographic factors and inter-study differences.

Methods

Electrocardiograph (ECG) data from placebo and 400mg moxifloxacintreatments were analyzed using NONMEM software. The longitudinal QT interval model incorporating the variability in demographic factors and the inter-study difference was developed within a mixed effect model framework according to the following steps: individual correction, baseline correction, drug effect, inter-study difference, covariate effect, and model evaluation. The data from 12 studies were modeled together using a meta-analysis approach.

Results

The corrected QT interval estimated yielded theheart-rate correction slope of alpha being 0.35 with 16% (CV) of intersubject variation. A two-oscillator model with 24- and 12-hour period best described the circadian variation of baseline QT measurements. For moxifloxacin effect on QT interval, a Bateman function was selected to represent the elongating aspect of QT interval for the early phase followed by shortening for the later part of the observation. The difference among the 12 studies was best modeled using separate baseline mesor parameters for each study, ranging between 378 and 410. In the covariate effect, the baseline corrected QT interval and the magnitude of drug effect were found significantly higher in women than in men. The acrophase for 24-hour period circadian rhythm was estimated lower in Asian than in other ethnic groups. Age was also found to be an important covariate, showing the baseline value increased with age.

Conclusions

The present analysis was carried out as a meta-analysis using observed data across a number of QT trials. The developed longitudinal mixed-effect model well described the time course of the QT interval when the source of variability on the QT interval was appropriately included. The model provided the useful information on potential covariates such as sex, age, and race influencing the QT interval. The final model may influence future trial design and will assist in contextualizing information from future TQT studies.

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Applications- Cardiovascular, QT

PA6-6 Role of Concentration-Effect Modeling in Assessing Drug Effects on the QTc Interval from Early Phase I Data: Preliminary Results from The Pfizer Experience

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Objectives
Concentration-Effect (CE) modeling enables quantification of drug-related effects on QTc interval of electrocardiogram (ECG). Increased efficiency is afforded through inclusion of all concentration and QT data across time and treatments relative to E14 ANOVA-based methods. Early phase 1 clinical studies provide an opportunity to explore concentrations that are higher than those achieved later in drug development. The objective of this study was to assess the concordance between the thorough QT (TQT) results with the CE modeling results of Phase 1 data.

Methods
Five programs were identified retrospectively with TQT or TQT-like studies and CE modeling using Phase 1 data conducted at Pfizer since 2002. The QTcF interval (QT interval corrected using Fridericia's correction) data from TQT studies were analyzed using an intersection–union test (IUT) as recommended in the International Conference on Harmonisation E14 guidance [1] while the Phase 1 studies were analyzed using mixed-effect models. Out of five compounds, three had negative TQT study results, where the upper limit of the two-sided 90% confidence interval (CI) for all time-matched mean differences between drug and placebo were less than 10 msec [1]. Mean and 90% CIs of the CE model-predicted placebo-adjusted change from baseline QTcF intervals were evaluated at the mean Cmax of the highest dose administered in each TQT study.

Results
Three compounds with negative TQT results demonstrated that the CE modeling of Phase 1 data were in agreement with IUT analyses from the TQT studies; two compounds had 90 % CIs which included zero while one compound had a negative mean QTcF change. Two compounds with positive TQT results also showed agreement between Phase 1 CE modeling and TQT study results; the CE modeling predicted mean placebo-adjusted change from baseline QTcF increases of greater than 5 msec, however, 90% upper confidence limit excluded 10 msec for one compound.

Conclusions
The preliminary assessment showed that equivalent inferences can be drawn from IUT analysis of TQT studies and CE modeling of early Phase 1 studies. Further evaluation is warranted to include comparisons for a larger number of compounds with TQT data at Pfizer to ensure the robustness of this conclusion.

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Applications- CVS

PA7-1 **Application of a PBPK/PD Model Describing the Change in Systolic Blood Pressure Following Administration of Immediate Release and Controlled Release Nifedipine**

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Objectives

Nifedipine GITS is a controlled release (CR) oral nifedipine formulation that offers a number of benefits over immediate release (IR) nifedipine, including reduced food effects, reduced reflex sympathetic nervous system activation and reduced dosing frequency [1]. A PKPD model that relates reduction in systolic blood pressure to the slow binding kinetics of nifedipine in Japanese hypertensive patients taking IR nifedipine has previously been described [2], but it is not clear whether the response profile changes with the nifedipine GITS formulation. We aimed to integrate PBPK models developed for IR and CR nifedipine using prior physicochemical and in vitro data with a published PD model [2] within the Simcyp Simulator to assess the ability of the combined model to predict the PK and PD profiles for IR and CR nifedipine.

Methods

Simulations were performed using Simcyp V12 using the Sim-Nifedipine compound file. For nifedipine GITS, formulation effects were described by a mechanistic absorption model using in vitro data [4]. The PKPD model used a dynamic binding model [2] and was assumed to be the same for IR and CR nifedipine and all study populations. Simulated study design was matched to that reported for clinical studies, including age, ethnicity, proportion of females and fasted or fed state dosing.

Results

Simulations in Simcyp recovered the observed plasma and PD profiles for IR nifedipine in Japanese hypertensive patients [2,3]. Both the magnitude and sustained plateau (>24h) of the PK and PD profiles were well captured for 60mg nifedipine GITS, with clinical data [5] falling within the range of the mean values of simulated trials. However, clinical PK and PD data1 for a 30mg multi-dose study of nifedipine GITS were underestimated by approximately 2-fold.

Conclusions

Integration of a PBPK model for nifedipine that accounts for formulation effects with a dynamic PKPD binding model within the Simcyp Simulator provided a good match with clinical observations. Underestimation of the response to 30mg nifedipine GITS may relate to use of the dissolution profile for 60mg nifedipine GITS in simulations due to unavailability of the dissolution profile for the 30mg dose. This may have significantly impacted on PK, and subsequently PD, predictions.

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Applications- Endocrine

PA8-1 A Literature-based Integrated Glucose-Insulin Model: Application to Evaluate Dose-Titartion Schemes for LY2605541 in a Phase 2 Trial

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Objectives

LY2605541 is PEGylated insulin lispro designed as basal insulin to have a large hydrodynamic size which delays insulin absorption and reduces clearance, resulting in prolonged duration of action. An integrated glucose-insulin (IGI) model was developed to evaluate dose-titration schemes for optimal glucose control. IGI development islengthy and requires a large amount of data. Using information from the literature and simulations, these difficulties were overcome and it was possible to inform complex Phase 2 trial design earlier in the drug development process.

Methods

A previously developed literature-based IGI[1] model was extended to account for 1) LY2605541 and oral anti-diabetic drug (OAD) treatments, 2) 24-hr meal conditions, and 3) repeated dosing. Literature values were used for the physiological-related and OAD-related pharmacodynamic parameters. Using a simulation-based approach by Trial Simulator®, sub-model extensions were sequentially tested and qualified against literature results and LY2605541 Phase 1 glucose observations. The full IGI model was used to simulate dose-titration scenarios for a Phase 2 trial.

Results

The IGI model was extended to account for supplemental drugs including bolus prandial insulins, insulin glargine, LY2605541, and OADs. Model based simulations of 24-hr glucose and insulin were inagreement with literature and LY2605541 Phase I results. Simulations demonstrated that tapering insulin glargine did not influence the titration or study endpoints. The QD dosing is adequate to control average fasting blood glucose at a lower hypoglycemiarate compared to TIW dosing. Four LY2605541 dose-titration simulation scenarios were also tested with 25% titration dose increments producing the shortest number of titration steps to reach an optimal LY2605541 dose with a minimal hypoglycemia rate. The final results from the Phase 2 trial were well within expectations based on the literature based model predictions.

Conclusions

This IGI model, extended from previous work[1] is capable of handling multiple exogenous inputs of diabetes treatments. Model-based simulations informed adaptive dosing design of a Phase 2 trial to increase the success rate of anti-diabetic therapeutic agents in drug development.

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Applications- Endocrine

PA8-2 Exposure-Response Analysis from a 12 week Phase 2 Study in Type 2 Diabetics (T2DM) given QD LY2605541: Application Semi-Mechanistic Models

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Objectives

LY2605541 is PEGylated insulin lispro designed as basal insulin to have a large hydrodynamic size which delays insulin absorption and reducesclearance, resulting in prolonged duration of action. Patients were initiated for study insulin dose conversion from the pre-study basal insulin and subsequent doses were adjusted for hyperglycemia and hypoglycemia in this study. The objective of this analysis was to describe the relationship of LY2605541, self-monitored blood glucose (SMBG), fasting glucose and HbA1c data from a Phase 2 study.

Methods

Two models were applied to the Phase 2 data; an integrated Glucose-Insulin (IGI) model[1] wasadapted to describe the relationship of LY2605541 exposure and blood glucose. Fasting endogenous insulin was estimated using C-peptide. Secondly, a transit compartment model describing the interrelationship of fasting glucose, hemoglobin, and HbA1c (FG-Hb-HbA1c model)[2] was developed to mimic the underlying mechanisms of HbA1c glycosylation. Models were implemented in NONMEM version 7.2.

Results

The dataset for the IGI model comprised of 23669 SMBG and 629 C-peptide measurements from 117 T2DM patients. Each of these subjects contributed a weekly/biweekly fasting glucose and HbA1C measurement over the course of 12 weeks. The pharmacokinetics was described using a one compartment model with an additional transit compartment for subcutaneous absorption and a first-order elimination rate constant. The IGI model described the SMBG data well; the time-course of fasting glucose and HbA1C was well described using a FG-Hb-HbA1c model. Baseline glucose was a significant predictor of the magnitude of the glucose lowering effect. The FG-Hb-HbA1c model corroborated the RBC's life span (125 days).

Conclusions

The IGI and FG-Hb-HbA1c models are useful to predict short-term and long-term responses, respectively. These models can be used to simulate Phase 3 trials with alternate titration designs for insulin.

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Applications- Endocrine

PA8-3

Genetic Polymorphisms of OCT2 and MATE1 Have No Influence on the Population Pharmacokinetics of Metformin in Healthy Subjects

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Objectives

Although the pharmacokinetics of metformin is well known, pharmacokinetic characteristics regarding OCT2 rs316019 variant are controversial between Asians and Americans. MATE1 rs2252281 polymorphism was found to showreduced transport activity of metformin in vitro. This study investigates the influence of genetic polymorphisms of OCT2 and MATE1 on the population pharmacokinetics of metformin in healthy subjects.

Methods

Forty eight subjects were included in this analysis. Following the oral administration of 1750 mg metformin in healthy humans, plasma concentrations of metformin were measured using LC-MS/MS. We estimated the population pharmacokinetics of metformin using a nonlinear mixed effects modelling (NONMEM) method and explored the possible influence of genetic polymorphisms in OCT2 rs316019 and MATE1 rs2252281 on the population pharmacokinetics of metformin.

Results

A two-compartment model with first-order absorption described the plasma metformin concentrations well. Population estimates (relative standard error, RSE) of apparent clearance, apparent volume of distribution, and the absorption rate constant were 102 L/h (7.33%), 309 L (7.47%), and 1.01 h-1 (7.33%) ,respectively. Covariate analyses revealed that genetic polymorphism of OCT2 MATE1 did not influence metforminpharmacokinetics. The predicted plasma glucose concentration values were similar to the previous results reported in the literature.

Conclusions

The results of the present study indicate that a two-compartment model with first-order absorption described plasma metformin concentration adequately. OCT2 and MATE1 polymorphisms had no significant influence on substantial inter-individual variability of metformin.

Applications- Endocrine

PA8-4

Body Weight, Body Fat Mass and Body Mass Index are Associated with the Pharmacokinetics of Letrozole

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Objectives

To characterize pharmacokinetics (PK) of letrozole by noncompartmental and mixed effect modeling analysis with the exploration of effect of body compositions on the PK

Methods

The PK data of 52 normal healthy male subjects with intensive PK sampling from two separate studies were included in this analysis. Subjects were given a single oral administration of 2.5 mg letrozole (Femara®), an anti-estrogenic aromatase inhibitor used to treat breast cancer. Letrozole concentrations were measured using validated high-performance liquid chromatography with tandem mass spectrometry. PK analysis was performed using NONMEM®7.2 with first-order conditional estimation with interaction method. The association of body composition (body mass index, soft lean mass, fat free mass, body fat mass), CYP2A6 genotype (*1/*1, *1/*4), and CYP3A5 genotype (*1/*1, *1/*3, *3/*3) with the PK of letrozole were tested.

Results

A two-compartment model with mixed first and zero order absorption and elimination best described the letrozole concentration-time profile. Body weight and body fat mass were significant covariates for central volume of distribution and peripheral volume of distribution (Vp), respectively. In another model that was built using more readily available bodycomposition measures, body mass index was also a significant covariate of Vp. However, no significant association was shown between CYP2A6 and CYP3A5 genetic polymorphism and the PK of letrozole in this study.

Conclusions

Our results indicate that bodyweight, body fat mass, body mass index are associated with the volume of distribution of letrozole. This study provides an initial step toward the development of individualized letrozole therapy based on body composition.

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Applications- Endocrine

PA8-5

Effect on Hypoglycemic Activity of Glipizide Tablets on Addition of Okra Seed Pod Mucilage as Excipient

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Objectives

The objective of the work is to use okra seed pod mucilage for development of glipizide tablets and check the effect on its hypoglycemic activity due to addition of mucilage. Okra seed pod has been shown to possess hypoglycemic activity in various literatures. Glipizide is an oral hypoglycemic drug usually prescribed for diabetic patients

Methods

The mucilage was extracted using whole okra pod and water as solvent. The dried mucilage powder was subjected to various physicochemical studies to assess its suitability to be used an excipient. Glipizide tablets were prepared by wet granulation technique using okra mucilage as binder and matrix forming agent. The amount of mucilage was varied between the formulations prepared. Another formulation was prepared using hydroxyl propyl methyl cellulose (HPMC) 15cps as matrix forming agent and starch. The formulated tablets were subjected to various evaluations like weight variation, hardness, thickness, friability, in vitro drug release. Diabetes was induced in Wistar albino rats by using streptozotocin at 60mg/kg body weight i.p in freshly prepared citrate buffer pH 4.5.

Results

The preliminary phytochemical analysis shows the presence of carbohydrate by Molisch's test. The physicochemical analysis like ash value, water soluble ash, acid insoluble ash, swelling index, pH, moisture content, angle of repose, bulk density, compressibility index, loss on drying were found to be satisfactory. FTIR spectrum indicates that there is no chemical incompatibility between glipizide and the excipients used. The thickness, hardness, friability, weight variation were found to be within the limits as prescribed in United States Pharmacopoeia. The tablets formulated with mucilage showed better antidiabetic effect than the tablets in which HPMC was used as matrix forming agent.

Conclusions

The okra pod mucilage powder have the property to be used as excipient in tablet formulation. It also has ability to potentiate the hypoglycemic activity of glipizide. This calls for recognizing the dual role of mucilage, as active pharmaceutical ingredient (API) & bioactive excipients. However, further studies must be carried out to optimize the dose of glipizide along with okra seed mucilage powder so that one can achieve optimum glucose level or else it may also lead to reduced glucose level

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Applications- Oncology

PA9-1 **A Frequency-Domain Based Analysis Linking Schedule and Toxicity of Anticancer Therapeutics**

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Objectives

Neutropenia is a common side effect of cytotoxic and targeted antineoplastic agents, as neutrophils are derived from a rapidly dividing, drug-sensitive progenitor pool. Since neutropenia is also a reflection of drug effect and pharmacologic activity in the peripheral compartment, mathematical modeling of neutropenia has been useful for simulating anticancer schedules in the clinic, and can capture the time course of treatment as well as the variability observed in the population.

Methods

Several well-characterized mathematical models exist to describe the kinetics of neutropenia in the clinical setting. Here, we utilize these models to develop a fundamental, first-principles understanding of the the relationship between dose schedule and neutropenia, framed in terms of pharmacokinetic (PK) parameters such as Area Under the Curve (AUC) or peak plasma concentration (Cmax). We simulate the effect of treatment schedules with different dosing frequency on absolute neutrophil count (ANC) in a population for a variety of drugs. While each cytotoxic agent induces different degrees of neutropenia, the underlying dynamics of stem cell differentiation provide a common set of principles for the prediction of neutropenia.

Results

We find that for equal dosing density, short bursts of high doses induce a nadir that is lower than constant low levels of dosing. The same relationship is found to hold for the probability of inducing grade 4 neutropenia, with short bursts of high doses being more effective at inducing neutropenia. While this finding runs counter to the conventional view of widely spaced high doses for minimization of neutropenia, clinical evidence to support this view can be found in the published literature with several antineoplastic agents. Based on first-principles, we derive PK measures that correlate with the induction of neutropenia, and demonstrate a strong relationship with neutropenia across a range of treatment schedules.

Conclusions

The results presented here represent a first attempt at deriving a fundamental understanding of the underlying pharmacokinetic drivers of neutropenia, and provide insights that can be leveraged in a translational setting in schedule selection. This novel approach is applicable to any toxicologic endpoint allowing one to link schedule and pharmacological effect of anticancer therapeutics.

PA9-2 Population Pharmacokinetic (PPK) Analysis for 5-FU, Tegafur (FT), Gimeracil (CDHP) and Oteracil Potassium (Oxo) in the Eight Clinical Studies of S-1 in Western Patients with Solid Cancer

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Objectives

This analysis was performed to establish the PPK model of S-1, and to identify the intrinsic or extrinsic factors that influence S-1 exposure in the Western patients with advanced solid tumor.

Methods

PK data obtained in seven phase I and one phase III (FLAGS)[1] studies were combined for PPK analysis. The total number of patients was 315, and the number of data points for FT, CDHP, 5-FU and Oxo were 2,860, 2,625, 2,492, and 2,484, respectively. The two-compartment model was used for FT, CDHP and Oxo, whereas for 5-FU, inhibitory effect of CDHP on 5-FU clearance was incorporated into a two-compartment model to describe its non-linear PK. The final models were validated by visual predictive check and bootstrapping.

Results

The individual fit and the stability of four models were acceptable. The predicted daily AUCs (at steady state) were calculated to evaluate the effect of covariates. The daily AUC of 5-FU strongly correlated with oral clearance (CL/F) of CDHP, but not with that of FT. The ethnic difference in exposure to 5-FU was not apparent despite the significantly lower CL/F of FT observed in the Asian patients. Co-administration with food delayed the absorption of S-1 but exhibited no or limited effect on the AUC of FT, CDHP and 5-FU, whereas the bioavailability of Oxo decreased to approximately 30%. Renal function primarily influenced CDHP exposure and, in turn, 5-FU. The model simulation suggested that the S-1 dosages of 30, 25 and 20 mg/m²BID could achieve similar daily AUC of 5-FU in the Western patients with normal renal function (CLcr>80 mL/min), mild (50-80 mL/min) and moderate (30-50 mL/min) renal impairment, respectively. Other factors such as age, gender, liver function, serum albumin, PS, gastric cancer, gastrectomy, combination with cisplatin and liver metastasis, had little or minimal impact on the daily AUC of 5-FU.

Conclusions

This analysis suggests that the daily AUC of 5-FU after S-1 administration is primarily affected by the CDHP levels, and hence renal function remains the primary factor for 5-FU PK in patients. Other factors as well as CL/F of FT had little impact on 5-FU.

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Applications- Oncology

PA9-3 **PKPD-Modeling of Standard Uptake Value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) Patients Treated with Sunitinib**

Encore presentation: Poster at the 21st PAGE meeting, Venice, Italy, June 5-8, 2012

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Objectives

A change in tumor glucose utilization, as determined by the maximal standardized uptake value (SUV), may be a significantly better predictor of early tumor response and clinical outcome compared with conventional tumor size measurements (RECIST) in patients treated with the multi-targeted tyrosine kinase inhibitor sunitinib [1]. The aim of this analysis was to characterize the time-course of SUV and investigate potential longitudinal relationships between sunitinib dose, AUC, biomarkers (VEGF, sVEGFR-2 and sKIT), and SUV in patients with gastro-intestinal stromal tumors (GIST).

Methods

SUV measurements ([18F]-fluorodeoxyglucose uptake determined by PET corrected for body weight, n=158) were available from 47 patients followed for a median time of 14 weeks of treatment with three different oral doses of sunitinib under three different treatment schedules. Dose, daily AUC and relative change in the three biomarkers from baseline over time, predicted by earlier developed models [2], were evaluated as drivers for the change in SUV in a longitudinal tumor growth inhibition model previously applied for tumor size (SLD, sum of longest diameters) [3].

Results

The longitudinal SUV data were well characterized by the tumor growth inhibition model with a fast initial decline in SUV, followed by a more static phase. Daily AUC was found to be the best predictor for SUV response and the model showed no additional improvement when also including model predicted sKIT, VEGF or sVEGFR-2 time courses as predictors.

Conclusions

The present results indicate that the daily AUC can potentially be used to predict early metabolic tumor response, as determined by SUV. In a previous analysis [3], sKIT was shown to be the best predictor of tumor size [4]. However, because of the rapid SUV response, it is not surprising that sKIT, with a turnover time of 14 weeks, didn't characterize the SUV data. It remains to be shown if SUV response is a better predictor of survival than response in SLD or angiogenic biomarkers. Acknowledgement: This research was performed as part of the DDMoRe project.

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Applications- Oncology

PA9-4 PKPD Modeling of Predictors for Side Effects and Overall Survival in Patients with Gastro Intestinal Stromal Tumor Treated with Sunitinib

Encore presentation: Poster at the 21st PAGE meeting, Venice, Italy, June 5-8, 2012

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Objectives

To describe the association between sunitinib exposure, candidate biomarkers (VEGF, sVEGFR-2, sVEGFR-3, sKIT) and side effects (myelosuppression, hypertension, fatigue and hand-foot syndrome) by the development of longitudinal pharmacokinetic-pharmacodynamic (PKPD) models. A further objective was to investigate relationships between side effects and overall survival (OS) in a model based analysis.

Methods

Data were available from 303 patients receiving sunitinib for the treatment of imatinib resistant gastro-intestinal stromal tumor (GIST). Longitudinal PK/PD models were developed to characterize the exposure-side effects data and to assess relationships with potential biomarkers earlier characterized by indirect response models [1]. The model-predicted time-courses of the side effects were evaluated as predictors of OS.

Results

Neutropenia was well characterized by a semi-physiological model [2] and hypertension with an indirect response model [3]. Proportional odds models with a first order Markov model [3, 4] described the time-course of the incidence and severity of fatigue and hand-foot syndrome (HFS). The relative change in sVEGFR-3 over time best described myelosuppression, fatigue and HFS. Hypertension was best predicted by sunitinib exposure. Baseline tumor size, neutropenia and the relative time-course of diastolic blood pressure (dBP) were identified as predictors of OS using a parametric time-to event model with a Weibull distribution.

Conclusions

The relative change in sVEGFR-3 over time was identified as a predictor of the occurrence and severity of myelosuppression, fatigue and HFS following sunitinib treatment. Furthermore, sunitinib induced elevation of dBP and neutropenia were identified as predictors of OS in GIST. The developed model has a potential to be used for early monitoring of treatment response thereby facilitating dose individualization.

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Applications- Oncology

PA9-5 Evaluation of Tumor-Size Response Metrics to Predict Survival and Progression Free Survival in Western and Chinese Patients With First-Line Metastatic Colorectal Cancer

PAGE 21st Meeting, Venice, Italy, June 2012

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Objectives

End-of-cycle 2 change in tumor size (TS) from baseline end-of-cycle 2 has been proposed as a predictor of overall survival (OS) in metastatic colorectal cancer (CRC) (1, 2) and other tumor types (1, 3, 4). The goal of this project was to assess new metrics of TS response to predict OS and progression free survival (PFS), and to test for any ethnic differences in the link between TS response and clinical endpoints in CRC.

Methods

Various metrics of TS response were estimated using longitudinal TS models developed from two Phase III studies comparing bevacizumab plus chemotherapy vs. chemotherapy in Western (923 patients) (5) and Chinese patients (203) (6) as first-line CRC therapy. Effect of baseline prognostic factors and estimates of tumor TS metrics were assessed in multivariate models to predict OS and PFS. Predictive performance of the models were assessed by simulating OS, PFS and hazard ratios (HR) of bevacizumab vs. chemotherapy.

Results

Time to tumor growth (TTG) was the best metric to predict OS and PFS in 991 evaluable patients. In the OS model, TTG fully captured bevacizumab effect, performance status and the number of metastatic sites were significant baseline prognostic factors. In the PFS model, TTG did not fully capture bevacizumab treatment effect and PS was a significant baseline prognostic factor. In both models, when other covariates like PS and TTG were accounted for, there was no impact of Chinese ethnicity on any of the endpoints, or on the TTG-OS or PFS relationships (no interactions). The models correctly predicted OS and PFS distributions in each study arm and each patient population as well as bevacizumab HRs (e.g. model prediction [95% prediction interval]: 0.78 [0.52 - 1.13] vs. 0.63 observed for OS in Chinese patients).

Conclusions

TTG is a better TS metric to capture drug effect and predict OS and PFS in first-line CRC patients than previously proposed ones. There is no impact of Chinese ethnicity on TTG survival or PFS relationships. Longitudinal TS data coupled with model-based approaches may offer a powerful alternative in the design and analysis of early clinical studies in both Western and Chinese patients (7).

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Applications- Oncology

PA9-6 **Pharmacokinetics and its Relation to Toxicity of Pegylated-liposomal Doxorubicin in Chinese Patients with Breast Tumors**

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Objectives

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin encapsulated with polyethylene-glycol coated liposomes, which has prolonged circulation time and unique toxicity profile. This study deals with the pharmacokinetics and its relation to toxicity in Chinese patients with breast tumors.

Methods

Twenty-two Chinese female patients with breast tumors were receivedtwo PLD products in single dose of 50 mg/m2 with a randomized, two-period, and cross-over design. Blood was sampled immediately before and at 15 minutes, 30 minutes, 60 minutes, 1.17 hours, 2 hours, 5 hours, 13 hours, 25 hours, 49 hours, 73 hours, 97 hours, 121 hours, 145 hours and 241 hours after the PLD infusion. The plasma level of doxorubicin was determined with LC-MS.

Results

The pharmacokinetics of PLD was best described by a one-compartment linear structural model with a long elimination $T_{1/2}$ (64hours), a slow clearance (0.025 L/hour/m2), and a small volume of distribution (2.310 L/m2). The main toxicities were neutropenia (22/44), nausea (22/44), vomiting (8/44), and pigmentation (4/44). The nausea and neutropenia were positively correlated with AUC while negatively correlated with CL ($P<0.05$).

Conclusions

The study confirms the different pharmacokinetic and toxicity profiles of PLD compared with non-liposomal doxorubicin. The pharmacokinetic profile in Chinese patients with breast tumors is significantly different from those reported for European patients with metastatic breast cancer. The correlation between toxicities, neutropenia grade and nausea, and two of the pharmacokinetic parameters, AUC and CL, may be useful for guiding the dosing of the agent.

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Applications- Oncology

PA9-7 **Pharmacokinetics and Tissue Distribution Study of the Nanoporous Octanuclear Cu(II) Wheel Complexes in Rats by High-performance Liquid Chromatography**

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Objectives

Nanoporous Octanuclear Cu(II) wheel complexes(N-Cu) is a new complex by Department of Chemistry, Zhengzhou University. And have been proven to be strong antiproliferative and apoptotic effect in human cancer cells[1]. The N-Cu emulsion has been prepared in order to overcome its poor water solubility to reach the appropriate concentration of drug[2].

Methods

To examine the potential of the N-Cu, we established HPLC method for analysis and pharmacokinetic study in rat. The N-Cu was separated using Agilent ODS column(250×4.6mm,5μm) with a mobile phase consisting of methanol and 0.01M potassium dihydrogen phosphate buffer solution (70:30,v/v) at a flow rate of 0.8ml•min-1. The UV detection was seted at 293 nm. For tissue distribution and pharmacokinetic studies, SD rat were starved for 12h, injected with different dose of the N-Cu emlsion(1.38 mg/kg 2.75mg/kg, 5.50 mg/kg),The blood samples were collected at 0min,5min,15min,30min,50min,1.5h,2.5h,4h, 6h,10hand14h. SD rats (n=3)were treated with the N-Cu emulsion by intravenous injection at a dose of 2.75 mg/kg, After administrated, heart, spleen, liver, lung, kidney, stomach were collected at 30 min and1,2,4, 6,8h,respectively.The N-Cu of the plasma and the desired tissue were extracted with ethanol. Tissue were homogenized and then by HPLC analysis[3]. The pharmacokinetic parameters and the compartment model were analyzed by software 3P97.

Results

The results showed that the N-Cu plasma concentration-time curve was fitted into open two-compartment model. The main pharmacokinetic parameters AUC, T1/2(alpha),T1/2(beta)andCLwere 891(ug/ml)*min,41(min), 237(min),1.23(L/h・Kg) respectively.Tissue distribution showed the highest level was observed in liver.

Conclusions

We developed HPLC method of analysis provided a reliable,reproducible and specifi assay for the N-Cu emulsion on plasma and tissue,and our study clearly demonstrates the bioavailability of the N-Cu in plasma and its target organs, suggesting further studies to evaluate the chemopreventive efficacy of the N-Cu in different rat cancer model.

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Applications- Oncology

PA9-8

Population Pharmacokinetics of Paclitaxel
in Indian Breast Cancer Patients

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Objectives

The present study was aimed to study the population pharmacokinetics of paclitaxel in breast cancer patients who are undergoing paclitaxel therapy after AC (adriamycin + cyclophosphamide) chemotherapy

Methods

When the patients were started on paclitaxel infusion, blood samples were collected during and after the completion of infusion up to 48 hours. The collected data was modeled using NONMEM (Version 7). 102 female patients were enrolled in the study. The mean age of the patients was 49±9 year with a range of 28 to 68 years. The mean body weight, height and body surface area of patients was 54±7kg (range 35 to 77), 152±4cm (range 138 to 168) and 1.50±0.11m2 (range 1.22 to 1.86). Total of 383 blood samples were collected and analysed from 102 patients. Average dose administered in the study population was 260mg (range 220 to 330) paclitaxel. Age, Body weight and Body surface area were tested as covariates by forward addition and backward deletion procedure. Final model was developed using weight as covariate on V and VM.

Results

A three compartment non-linear model was developed as the structural model and for the covariate model the effect of body weight on VM and V was selected as the final model. The values of the parameter estimated were: V1: 3.28 L, VM: 63.3μmol/h, KM: 0.326 μmol/L, Q2:0.104 and V3 was 3.46 L

Conclusions

The developed paclitaxel model estimated the key population pharmacokinetic parameters with good precision. The values estimated in the present study were different from reported literature for other population (Caucasians) The developed model might serve as a tool of dosage adjustment in the indian population

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Applications- Oncology

PA9-9 Population Pharmacokinetics and Pharmacogenomic Analysis of Methotrexate in Patients after Hematopoietic Stem Cell Transplantation

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Objectives

Methotrexate (MTX) is often used to prevent graft-versus-host disease after allogeneic haematopoietic stem cell transplantation (HSCT). However, MTX has large variability in its pharmacokinetics and it can affect fatal complications, GVHD, and infections after transplantation. The purpose of this study was to build a population pharmacokinetic model of MTX in patients that have undergone HSCT, and to identify covariates, including genetic polymorphisms, that affect MTX pharmacokinetic parameters.

Methods

Clinical characteristics and MTX concentration data for 20 post-HSCT patients were collected. ABCB1, ABCC2, ATIC, GGH, MTHFR, and TYMS genotyping were performed. A population pharmacokinetic analysis was conducted by using the NONMEM program. Analysis of the pharmacokinetics of MTX was accomplished using a two-compartment pharmacokinetic model with first-order conditional estimation (FOCE) methods with interaction. The effect of a variety of demographic and genetic factors on MTX disposition was investigated.

Results

The final estimate of mean MTX clearance (CL) was 7.08 L/h, and the mean central compartment volume (V1) of distribution was 19.4 L. The glomerular filtration rate, the use of penicillins, and the presence of the ABCB1 3435 genotype significantly affected MTX CL. The inter-individual variability for CL and V1 were 21.6% and 73.3%, respectively. A 10 mL/min increase of GFR was associated with a 32% increase in population mean CL of MTX , while the use of penicillins decreased in 61% of MTX CL. The MTX CL value significantly increased, to approximately 21%, in patients with the ABCB1 3435 CC or CT genotypes compared to that in ABCB1 3435 TT genotype patients ($p < 0.001$).

Conclusions

There was a large inter-individual variation in MTX pharmacokinetics in patients after HSCT and the glomerular filtration rate, the concomitant drug of penicillins, and the presence of the ABCB1 3435 C<T genotype significantly affected MTX CL.

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Applications- Oncology

PA9-10 Population Pharmacokinetic and Pharmacodynamic Analysis of Docetaxel; Hematologic Side Effects in Japanese Lung Cancer Patients

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Objectives

Docetaxel is used for the treatment of many cancers (e.g. breast cancer, lung cancer), but neutropenia is the dose-limiting factor. In this study, we tried to develop a population pharmacokinetic-pharmacodynamic (PK-PD) model with regard to docetaxel-induced side effects, especially focused on neutropenia, in cancer patients.

Methods

This study was approved by the Institutional Review Board of Kyushu University Hospital and Kitakyushu Municipal Medical Center, and all patients gave written informed consent. Forty-seven advanced or recurrent non-small cell lung cancer patients, who were treated by docetaxel as monotherapy, were enrolled. Docetaxel was infused intravenously over 1.0 to 1.5 hr. Thirty-six patients received the approved dose of 60 mg/m^2 and remains received 50 mg/m^2. Blood sampling for PK analysis was carried out before docetaxel infusion, at the end of the infusion, and 0.17, 1, 5, 10, 24 hr after the infusion. The laboratory test values and pharmacogenomic information were used to develop population PK-PD model. The population PK-PD model was built sequentially: population PK model was developed and then the time-course of neutrophils was modeled, with each individual empirical Bayesian estimated PK parameters. Population PK-PD modeling was performed by NONMEM 7.2 with first order conditional estimation with interaction method (FOCE-INTER).

Results

Three-compartment model was used to describe the pharmacokinetic data of docetaxel. In population PK-PD modeling for neutrophils, a semi-mechanistic model, previously developed by Friberg et al., was applied to the present data. The constructed model gave an adequate characterization of time-course of absolute neutrophil count. Now, we are evaluating the utility of pharmacogenomic information into the PK-PD model.

Conclusions

The semi-mechanistic model was appropriate to describe changes in individual neutrophil count after docetaxel treatment.

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PA9-11 Use of Modeling and Simulation in the Early Clinical Development of a Novel Oral Paclitaxel, DHP107
The study was presented at the 2011 ACOP meeting.

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Objectives

To characterize pharmacokinetics (PK) of DHP107, a novel oral paclitaxel by PK modeling and to predict maximum tolerated dose and its treatment efficacy in comparison with intravenous (IV) paclitaxel using Monte-Carlo simulation.

Methods

Phase I study was conducted with modified Fibonacci escalation design where each of 20 subjects received DHP107 at dose ranges of 60-400 mg/m2 on day 1 and IV paclitaxel at 175 mg/m2 on day 22 and thereafter. Serial plasma concentrations for both of DHP107 and IV paclitaxel were measured by validated LC/MS/MS. PK of DHP107 and IV paclitaxel were analyzed using NONMEM VII (ICON Development Solutions, USA) and compared with each other. Using the PK model for DHP107 and IV paclitaxel built in this study and previously published paclitaxel-neutropenia model [1], phase 1 clinical trials for DHP107 with modified Fibonacci doseescalation design, beginning at 60 mg/m2 were simulated by Trial Simulator 2.12 (Pharsight, USA), where maximum tolerated dose (MTD) was predicted. In the clinical trial simulation, patients were treated with weekly regimen (1 treatment cycle, treatment on day 1, 8, 15 and rest on day 22), and the difference in the free fraction of paclitaxel between taxol and paclitaxel without cremophore was taken into account from a literature [2]. Another subsequent simulation was done using NONMEM to predict whether the DHP107 will show the comparable treatment efficacy on at the MTD in the clinical trial simulation with that of a standard treatment regimen of IV paclitaxel, 175 mg/m2. Simulation for the efficacy comparison is based on the previous report that the treatment efficacy of paclitaxel is related with the time of the plasma concentration over a threshold concentration of 42.7 ng/ml.

Results

In the clinical trial simulation with neutropenia as dose-limiting toxicity, DHP107 was administered with single or split doses in the weekly regimen, and 480 and 780 mg/m2 were predicted as MTD for DHP107. In the subsequent simulation for the treatment efficacy indicated that the possibility of equal treatment effect of the novel oral paclitaxel to the current standard intravenous paclitaxel.

Conclusions

This study showed the possibility that DHP107 could have clinically significant treatment effect in cancer patients.

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Applications- Oncology

PA9-12   **Glutathione S-transferase A1 Genetic Variants Reduce Busulfan Clearance in Korean Adult Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation**

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Objectives

Busulfan which is a commonly used conditioning agent in allogeneic hematopoietic stem cell transplantation (alloHSCT) has a narrow therapeutic range and large inter-individual variability. The aim of this study was to construct the population pharmacokinetic model of intravenous busulfan in Korean adult patients undergoing alloHSCT.

Methods

A total of 101 blood samples from 36 patients receiving intravenous busulfan for conditioning of alloHSCT were taken. All patients were genotyped for the GSTA1, M1, P1, and T1. Nonlinear mixed-effects modeling (NONMEM) according to one compartment pharmacokinetic model with first-order elimination was used for analysis. A number of covariates including demographic features, transplantation characteristics, laboratory values, GST genotypes, and drug interaction were screened for their influence on the pharmacokinetic parameters of busulfan. Model stability and performance were verified using bootstrap simulations.

Results

The population estimates from the base model for clearance (CL) and volume of distribution (V) were 10.8 L/h and 43.1 L, respectively. Body weight (BW) and GSTA1 -52G/A polymorphism were identified as significant covariates for both clearance and volume ($P < 0.05$). None of the other covariates studied significantly influenced any of the pharmacokinetic parameters. The final model is as follows; $TVCL = 4.48\ e\ 0.0153\ BW - 0.176\ A$, $TVV = 20.7\ e\ 0.0138\ BW - 0.311\ A$; where TVCL = typical value of clearance, TVV = typical value of volume of distribution, BW = body weight, and A=0 for GSTA1 wild type and 1 for GSTA1 heterozygous variants. Inter-patient variability, expressed as coefficient of variation, was 14.9% for CL and 17.3% for V.

Conclusions

To our knowledge, this is the first population pharmacokinetic analysis that reports the significance of GSTA1 polymorphism on busulfan in adult alloHSCT patients. With more information confirming ourstudy, genotyping of recipient GSTA1 could assist in individualizing of busulfan dosing in alloHSCT.

PA9-13 **Preclinical Pharmacokinetic/Pharmacodynamic Models to Predict Schedule-dependent Interaction between Erlotinib and Gemcitabine**

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Objectives

To investigate the pharmacological effects of different erlotinib (ER) and gemcitabine (GM) combination schedules *in vitro* and *in vivo*, and to develop pharmacokinetic/pharmacodynamic (PK/PD) models to characterize and quantify the anti-cancer effects of combination therapies using time-dependent data.

Methods

Firstly, H1299 cells were exposed to six different ER combined with GM schedules. Cell growth inhibitionand cell cycle distribution were analyzed to evaluate the pharmacological effects of different schedules, and combination index was calculated to assess the interaction between two drugs[1]. Based on the *in vitro* results, we further designed an interval combination schedule, and conducted a preclinical *in vivo*study to compare the tumor inhibition rates of ER monotherapy, GM monotherapy, ER and GM used simultaneously, ER and GM used with interval in H1299 xenografts in female BALB/c nude mice. Then pharmacokinetic/ pharmacodynamic (PK/PD) models were developed to characterize and quantify the anti-cancer effects of combination therapies, with an interaction term φ, using time-dependent tumor growth data[2,3]. The parameters in these models were used to simulate the tumor growth delay of each schedule and tumor inhibition effect of long duration treatments.

Results

In the *in vitro* study, strong synergism was observed when ER preceded GM, but other sequences showed antagonism. In the *in vivo* study, interval group was significantly better than simultaneous group after drugs administered for 12 days, and the PK/PD models fitted well the observed data from mono- to combination-therapies. φ of simultaneous treatment and interval schedule were 0.961 and 1.82 respectively, which implied that interaction of the two drugs was additive in simultaneous treatment but synergistic in the interval schedule. The results of simulation showed that interval schedule can delay tumor growth for the longest time among all the tested schedules, and demonstrated more evident anti-tumor effect compared with simultaneous group if the treatment durations were longer.

Conclusions

Interval schedule of the two drugs can achieve synergism in anti-tumor effect, and it is superior to traditional simultaneous treatment. The interval schedule has some potential to be tested in clinical trials.

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Applications- Oncology

PA9-14

Population Pharmacokinetic Analysis of Free and Bound Aflibercept in Patients with Advanced Solid Tumors

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Objectives

Aflibercept (VEGF-Trap) is a fusion protein of human vascular endothelial growth factor (VEGF) receptor domains that binds to VEGF and inhibits tumor growth [1,2]. We aimed to develop a mechanism-based pharmacokinetic model for aflibercept to characterize its binding to VEGF and its pharmacokinetic properties in healthy subjects and cancer patients with advanced solid tumors.

Methods

Model building was conducted with data from two phase I clinical trials with aflibercept administered as a single intravenous infusion of 1, 2 or 4 mg/kg in healthy subjects. Two-compartment pharmacokinetic models with central/peripheral binding to VEGF under linear binding, target-mediated drug disposition (TMDD) [3] or reduced approximate TMDD [4] were used to describe pharmacokinetics of free and VEGF-bound aflibercept, using a nonlinear mixed-effects modeling approach with MONOLIX 3.1. The final model was applied to the data collected from 1506 cancer patients in 9 clinical trials, containing 7916 free aflibercept and 6977 VEGF-bound aflibercept concentrations. Aflibercept was administered as multiple intravenous infusion doses ranging from 2 mg/kg to 9 mg/kg and was given every 2 weeks or 3 weeks. Simulations of concentration-time courses of free and VEGF-bound aflibercept for typical and extreme patients with given doses were conducted to evaluate the optimal dosing regimen for achieving VEGF blockade.

Results

The best structural model involved two compartments for free aflibercept and one for VEGF-bound aflibercept, with a Michaelis-Menten (MM) type binding of free aflibercept to VEGF from the peripheral compartment [5]. This TMDD model with MM approximation described reasonably well the observed concentrations of free and VEGF-bound aflibercept in both healthy subjects and patients. Following the simulated dosing regimens, the recommended doses of 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks were sufficient to saturate circulating VEGF in most patients.

Conclusions

The present pharmacokinetic model for aflibercept characterizes well the underlying mechanism of disposition of aflibercept and its nonlinear binding to VEGF. It was used in support of the rationale for the aflibercept dose in the q2w and q3w regimens.

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Applications- Paediatrics

PA10-1 The Utility of a Population Pharmacokinetic-pharmacogenetic Model in Predicting Tacrolimus Dosage in Pediatric Kidney Transplant Recipients: A Clinical Validation

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Objectives

We conducted a clinical and external validation of a developed population pharmacokinetic-pharmacogenetic (POPPK-PG) model on predicting tacrolimus individual dose requirements in kidney transplant children.

Methods

Three cohorts from French and Canadian hospitals were used. The developed model integrated patients' weight, hematocrit and CYP3A5 genotype.

Results

Fifty children with a mean age of 11.7years (range 3.3–17.6) were included. The developed model could accurately predict an individual dose without age-related misspecification. The observed and predicted doses were significantly correlated (correlation coefficient of 0.49 (95%CI: 0.24-0.68)) with a mean difference of -0.2mg.

Conclusions

The developed POPPK-PG model can support tacrolimus C0 monitoring by providing an individualized dose before initiation of therapy in order to shorten the trial period with dose-level fluctuations.

Applications- Paediatrics

PA10-2 **A Time-to-event Model for Acute Rejections in Paediatric Renal Transplant Recipients Treated with Ciclosporin A**

Encore: 5-7 June 2012, PAGE, Venice, Italy: A Time-to-event Model for Acute Rejections in Paediatric Renal

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Objectives

Ciclosporin A (CsA) immunosuppression after paediatric renal transplantation remains challenging due to a narrow therapeutic range and limited information in children. Also, the target CsA exposure (AUC) is under debate. The aim of this study was to develop a model for the time to first acute rejection (AR) including exploration of predictive factors.

Methods

Data was extracted from patient records at the hospital for Children and Adolescents in Helsinki, Finland (1995-2006). A parametric survival model implemented in NONMEM 7.2 was applied. The influence of predictive factors on the hazard was explored using stepwise covariate modelling (SCM)[1], bootstrap-(boot-) SCM[2] and cross-validated (XV-) SCM[3]. The clinical relevance of the potential effects was assessed with the time at which 90% of the patients were AR-free (T90), accounting for parameter uncertainty and covariate distributions.

Results

Data from 87 patients (0.7-19.8 years), whereof 54 experienced an AR, was analysed. An exponential survival model based on a function of discrete constant hazards changing in steps over time, (peak hazard day 5-8 after transplantation), described the data best. Dialysis time, sex and baseline weight were identified in the SCM as potential, but were not statistically significant covariates (p>0.01), which was confirmed by boot- and XV-SCM procedures. The boot-SCM demonstrated low inclusion rates for all relationships and selection bias in covariate effect sizes. The XV-SCM showed the best predictive performance for a model without covariates. The median T90 changed by about 1 day for different covariate values; for the strongest covariate found, dialysis time, median T90 was 5.8 days (90% confidence interval 5.1-6.8) for long (90th percentile) and 7.4 (6.4-11.7) days for short (10th percentile) dialysis times.

Conclusions

The data was described in a survival model based on a step function of hazards. Covariate effects were not statistically significant and the predicted clinical relevance of the effects was low.Boot-SCM and XV-SCM methods were successfully applied and discouraged inclusion of any covariates into the model. Daily CsA AUC was not identified as a covariate, suggesting that within the observed range (90% interval 1.13–8.40 h*mg/l), it could not be demonstrated that a rise in AUC increases protection from AR.

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Applications- Paediatrics

PA10-3 Population Pharmacokinetics of Intravenous Itraconazole in Pediatric Cancer Patients

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Objectives

Intravenous itraconazole in pediatric patients undergoing hematopoietic stem cell transplantation has recently been used for empirical treatment. A clinical study was conducted to identify PK parameters for repeated dose intravenous itraconazole with 6 pediatric patients who were switched from oral prophylactic treatment to empirical treatment for persistent neutropenic fever. The purpose of this study was to investigate the population pharmacokinetics of pediatric intravenous itraconazole.

Methods

Total 78 plasma concentrations of itraconazole and the metabolite, hydroxyitraconazole, from 6 patients were used for model building. Nonlinear mixed effects modeling methodology was implemented in the population pharmacokinetic analysis using NONMEM®(version 7.2.0). A two stage, stepwise forward selection and backward elimination procedure was used to identify relationships between population PK parameters and selected covariates including baseline body weight, age, gender, and co-medication such as proton-pump inhibitors.

Results

A two-compartment model with hydroxyitraconazole, allocated to the peripheral compartment was chosen as the basic model for PK parameters.

Conclusions

This model can be used for modeling and simulation and to predict itraconazole exposure in pediatric patients.

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Applications- Paediatrics

PA10-4   # Physiologically-based Pharmacokinetic Modeling of Bosentan (Tracleer®) to Support Pediatric Drug Development

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Objectives

Bosentan (Tracleer®) - a dual endothelin-receptor antagonist - was the first oral treatment approved for treatment of pulmonary arterial hypertension (PAH) in adults. The pediatric dispersible formulation of Tracleer®(bosentan) for the treatment of PAH in children from two years of age has been approved in the European Union.Further pediatric development is ongoing including clinical studies in children below 2 years of age. The objectives of this analysis were to develop a human physiologically-based pharmacokinetic (PBPK) model for bosentan in adult and pediatric patients, to compare model predictions to observed data in adults and children, and to use the PBPK model to simulate exposures in different age ranges (including neonates and infants) to support further pediatric drug development [1].

Methods

A whole-body human PBPK model for bosentan in adults and children was developed using the software PK-Sim® and MoBi®. Physicochemical properties, in vitro data on drug metabolism and transporters, as well as data from clinical studies performed in adults and pediatric patients [2] wereincorporated during model development. For simulations, the PK-Sim®-generated PBPK model was exported to the MoBi® population wrapper to simulate different doses and age groups. The simulation results were analyzed to provide plasma concentration-time profiles and age-dependent data for PK parameters such as C_{max}, AUC, and clearance.

Results

The developed adult and pediatric PBPK model for bosentan considered hepatic clearance processes via CYP3A4 and CYP2C9, hepatic uptake processes via OATP1B1/1B3 as well as physiological and clearance changes with age. The PBPK model was qualified by observed data from clinical studies in adults and children. Subsequent simulations for several age ranges showed that the PBPK model predicts lower exposures in children, but similar or slightly higher exposures in neonates compared to adults when doses were normalized for body weight.

Conclusions

The PBPK model expanded to the pediatric population was able to adequately predict observed data in the pediatric population(in the age range 2 to 11 years) and to explain observed differences to adults. Simulations of different age ranges and for different doses provided meaningful exposure predictions. These results provided substantial support for further development of bosentan in the pediatric population.

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Applications- Paediatrics

PA10-5 Estimation of Doses for Infants and Premature Infants Based on Physiological Development of Hepatic and Renal Functions

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Objectives

In fetus, the hepatic functions including drug metabolism are extremely restricted, and they are fully relied on functions of the maternal liver. Analogously, the renal function is insignificant being closed in the amniotic fluid. After birth, these situations are changed dramatically, and both hepatic and renal functions develop promptly within several months. During this period, the dose adjustments for infants and also for premature infants are a matter of serious concern since clinical evidences are almost unavailable. In the present study, theoretical considerations are given to predict clearance and appropriate doses for infants and premature infants based on physiological development of hepatic and renal functions.

Methods

In this study, clearance of infants and prematureinfants were estimated from age, post-conceptional age (PCA), serum creatinine, and pharmacokinetic information available from adults (oral and hepatic clearances and protein binding). Body weight was estimated from statistical data obtained from Japanese. Protein binding was estimated from concentrations of albumin and alpha-acid glycoprotein in infants[1]. Renal clearance for infants of less than two months was calculated from the protein binding and GFR in infants[2]. A development function of hepatic metabolism was constructed considering expression of CYP enzymes in fetus and infants[3] in addition to an adjustment for premature infants.

Results

In the present study, oral clearances of 15 drugs, of which 6 eliminated mainly through the kidney and 9 by hepatic metabolism, were successfully predicted for infants and premature infants. It was suggested that conventional dose estimations for infants, principally based on body surface area, may tend to be overdose, especially for drugs mainly eliminated by hepatic metabolism in newborns and premature infants.

Conclusions

Considering the physiological development of hepatic and renal functions, doses for infants and premature infants need to be carefully determined. Clinical studies would be required to confirm predictions calculated by the present method.

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Applications- Paediatrics

PA10-6 Warfarin Dose Prediction in Children Using Pharmacometric Bridging

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Objectives

To evaluate how well a mechanism-based population-model developed on data from warfarin-treated adults predicts the dose-response relationship in children, and to compare accuracy in maintenance dose prediction between the bridged population-model and three published warfarin dosing algorithms for children [1-3].

Methods

A previously developed population model for warfarin [4], with *CYP2C9* and *VKORC1* genotype, age and target INR as covariates, was bridged from adults to children by taking into accountexpected changes in pharmacokinetics due to growth and maturation. The bridged population-model was used to predict the dose-response relationship in 64 warfarin-treated children (median age 4.3 years, range 0.06-18.9 years) that were genotyped for *CYP2C9* (*1/*1 n=47, *1/*2 n=8 *1/*3 n=7, *2/*2 n=1, *2/*3 n=1) and *VKORC1*(G/G n=24, A/G n=31, A/A n=9). Prediction corrected visual predictive checks were used to assess the model's predictive performance in children [5]. Accuracy in maintenance dose prediction, defined as the proportion of children with a predicted dose within 20% of the actual dose, were compared between the bridged population-model and the three published algorithms in 49 children with data available on stable maintenance dose (median age 7.2 years, range 0.33-16.9 years).

Results

The bridged population-model showed good agreement between model-predicted and observed INR. Stratified by age, there was a tendency that the model over predicted the INR, or conversely underestimated the dose, in the youngest age group (children ≤2 years). With *a priori* dose predictions using the bridged population-model, 41% of the children were predicted within 20% of their actual dose, which increased to 70% with *a posteriori* dose predictions. Corresponding figures for *a priori* dosing with published algorithms were 33% [1], 35% [2] and 41% [3], respectively.

Conclusions

Maintenance dose predictions from the bridged population-model were at least as accurate as predictions from algorithms developed on pediatric data. This supports that mechanism-based population-models developed on adult data are useful as a basis for individualized dosing recommendations also in children. Work is currently ongoing to transform the model into a user-friendly tool for dose predictions of warfarin to both children and adults. The current version of the tool will be available for demonstration.

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Applications- Paediatrics

PA10-7 Dose Selection of Doripenem for Pediatric Patients Based on the Pharmacokinetic Profiles Predicted from Adults

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Objectives

Doripenem (DRPM) is a parenteral carbapenem antibiotic, exhibits broad spectrum of anti-bacterial activity against any aerobic gram-positive and gram-negative bacteria and anaerobes. The aim of this study was to select dosing regimens for pediatrics before start of a pediatric clinical trial by using simulation approaches based the predicted pharmacokinetic profiles in pediatrics.

Methods

The pharmacokinetic parameters and profiles of DRPM in pediatric patients were predicted by using the previously reported approach for beta-lactam antibiotics from adult pharmacokinetic data (1,2). Monte-Carlo simulation was employed to assess the dosing regimens in pediatric patients based on the predicted pharmacokinetic profiles and the MIC distributions of H. influenzae and S. pneumoniae which were frequently isolated in pediatric patients with infectious disease. The probabilities of attaining target time above MIC (%T>MIC [40%]) were calculated for dosing regimens of 1 - 30 mg/kg with q12h or q8h dosing based on the simulations of 5000 virtual pediatric patients and MICs. In addition, the predicted pharmacokinetic profiles were compared with the observations after the completion of a pediatric clinical trial (3).

Results

Simulations suggest that 15 and 5 mg/kg q8h would give approximately 90% or more probability of target (40%T>MIC) attainment against H. influenzae and S. pneumoniae, respectively. The q12h dosing regimens would give insufficient probabilities of target attainment, especially against H. influenzae. The observed plasma concentrations in the pediatric clinical trial were comparable to the predictions.

Conclusions

The bactericidal effect of DRPM was expected at 5 - 20 mg/kg q8h in pediatric patients, and the dosing regimen of 20 mg/kg q8h was evaluated in the pediatric clinical trial. The framework of dose selection for pediatric clinical trials based on prediction of pharmacokinetic profiles can be applied to other beta-lactam antibiotics.

References

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Applications- Paediatrics

PA10-8

Functional Characterization of MDR3 Variants in PFIC3 Patients

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Objectives

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a rare liver disease which caused by mutation of the ATP-binding cassette, subfamily B, member 4 gene (ABCB4) also known as multidrug resistance 3 (MDR3). MDR3 is hepatocellular canalicular transporter associated with not only billiary phosphatidylcholine secretion but also efflux of drugs and xenobiotics. This study was to investigate the functional characterization of several variants of MDR3 found in PFIC3 patients.

Methods

Thirteen nonsynonymous variants found in PFIC patients were selected. To constructthe plasmid containing reference MDR3 gene, pBluescriptR-hMDR3 vector was purchased from Open Biosystems and was subcloned into pcDNA3.1 vector. Variants were constructed using the QuikChange II site-directed mutagenesis kit. Plasma inside-out membrane vesicles were made from the harvested cells after transfection of MDR3 plasmids into HEK293T cells and transport activity of MDR3 was measured using ATP-dependent uptake of paclitaxel.

To determine the mechanism through which MDR3 variants change transport activity, cell surface biotinylation, immunoblotting and immunofluorescence staining were performed.

Results

Eight variants (M1, M5, M7, M8, M9, M11, M12, M13) of MDR3 showed significantly reduced transport activity, compared to the reference ($p<0.05$). Through cell surface biotinylation, we found that M1 and M11 showed altered protein size and the others showed decreased cell surface expression levels, compared to the reference ($p<0.05$). Four of them (M5, M7, M8, M9) also resulted in lower total protein levels in immunoblotting ($p<0.05$).

Conclusions

Our studies revealed several MDR3 variants result in changes in the transport activity of MDR3. Decreased transport activity can be explained by protein truncation (M1, M11), decreased total protein levels (M5, M7, M8, M9), or impairment of membrane trafficking (M12, M13).

PA10-9   Top-Down Modeling Meets Bottom-Up Modeling: The Physiological and Physicochemical Basis for the Ontogeny of UGT2B7-Mediated Drug Glucuronidation

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Objectives

Despite the multi-factorial nature of the ontogeny of drug clearance, paediatric population models oftendescribe this process with a limited number of descriptive covariate relationships. These covariate models quantify the influence of underlying physiological changes for a given drug and preliminary proof-of-concept studies suggest that these covariate models can, in specific cases, be used for between drug extrapolations[1,2]. The current study examines the physiological and physicochemical basis of a paediatric covariate model for the ontogeny of UGT2B7-mediated glucuronidation in young children (top-down model)[1,3], by untangling the underlying maturational processes with a physiologically-based model (bottom-up model).

Methods

The physiologically-based modeling software Simcyp version 11 was used to simulate glucuronidation clearance of morphine and zidovudine (both selective UGT2B7 substrates with intermediate hepatic extraction ratios) in 1000 children younger than three years. In vivo clearance predictions by the physiologically-based model were compared to clinically observed clearance ontogeny profiles. Additionally, the main physiological and physicochemical drivers of the ontogeny profile of UGT2B7-mediated in vivo clearance were identified by changing system and drug specific parameters and evaluating the influence of these changes on the clearance ontogeny profile.

Results

Using currently available in vitro data, morphine and zidovudine clearances were under-predicted by the physiologically-based model, while the predicted ontogeny profile in glucuronidation clearance was similar to the clinically observed profile across the first three years of life, with the exception of the first two weeks of life. Developmental changes in system-specific parameters explained 79% and 41% of the increases in morphine and zidovudine clearance, respectively, with the influence of liver size and UGT2B7 ontogeny being most pronounced. Physicochemical drug parameters did not affect the developmental glucuronidation profile, although logP and pKa both influenced the absolute value of clearance.

Conclusions

For drugs with intermediate extraction ratios liver volume and UGT2B7 ontogeny drive the ontogeny of in vivo glucuronidation. For drugs with similar extraction ratios, physicochemical drug properties do not influence the ontogeny profile, but only the absolute value of clearance, allowing for the extrapolation of paediatric population covariate models between these drugs. Situations involving extrapolation between drugs of varying extraction ratios and situations with non-linear drug metabolism need further investigation.

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Applications- Other diseases

PA11-1   # A Population Pharmacokinetic Analysis of Sildenafil Citrate in Korean Healthy Male Adults

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Objectives

The objective of this analysis was to develop a population pharmacokinetic model in from Korean healthy male adults in comparision with those reported in the western population.

Methods

A total of 25 subjects received 50 mg single dose of sildenafil citrate (Viagra®, Pfizer). Blood sampling for full pharmacokinetic study was done just before and 0, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 24 hours after dosing. LC/MS/MS was used for plasma concentration measurement of sildenafil. A population pharmacokinetic analysis was performed using NONMEM (Ver. 7.2).

Results

The mean age and weight of subjects were 24.7 years and 65.6 kg, respectively. A two-compartment model with first-order absorption gave the best description for time-concentration profile of sildenafil. Absorption lag time was included in the model. The population parameter estimates were 59.9 L/h for clearance (CL/F), 134 L for volume of central compartment (V2), 31.9 L for volume of peripheral compartment (V3), 6.85 L/hr for intercompartmental clearance (Q), 4.97 hr-1 for absorption rate constant (ka) and 0.17 h for lag time (ALAG1). The between-subject variabilities were 30.1% for CL, 30.7% for V2, 93.1% for ka, and 36.0% for ALAG1. No covariates were found significant for any model parameter.

Conclusions

Even after the effects of age and body weight on the pharmacokinetic parameters were taken into consideration, Korean healthy male adults showed relatively smaller estimate of clearance as well as the volume of distribution compared to Caucasian population. Genetic factors including CYP3A4 genotype and different hepatic function by the population might contribute to this interracial difference. According to the result, it was expected that the efficacious plasma level of sildenafil might be achieved in Korean population with relatively lower dose of sildenafil citrate than that need in western population.

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Applications- Other diseases

PA11-2

A Pharmacokinetic-Pharmacodynamic Model of the Weight-Reducing Effect by Sibutramine: As a Post Factum Reference for its Weak Efficacy

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Objectives

Sibutramine had been marketed in Korea for 10 years since 2001. However, there has been no published data on its weight-reducing effect in comparison with that of placebo. Although it is no longer prescribed in Korea since 2010, we report its meager weight-reducing effect simulated in Korean patients as a post factum reference that may help justify the decision to stop its marketing by regulatory authorities in many countries.

Methods

A clinical study was conducted in 8 hospitals and 120 abdominal obesity patients with metabolic syndrome according to the ATP III definition were enrolled. The treatment arm received daily 11.51 mg sibutramine mesylate (8.37 mg as sibutramine) for 4 weeks initially and the dose was maintained if the body weight showed $\geq$2kg decrease. In case the weight loss was not sufficient (<2 kg), the dose was escalated to daily 17.26 mg (12.550 mg as sibutramine) until study completion (24week). Bdy weights were assessed every 4 weeks throughout the study. Sparse pharmacokinetic sampling was done at weeks 0, 4, 8 and 24. A mixed effect analysis of the PK-PD relationship was performed using NONMEM (ver. 7.2).

Results

According to the simulated results using our final PK-PD model, it was expected that more than 1 year of sibutramine therapy would be needed to attain the maximum weight reduction by the drug. The weight loss expected by sibutramine over placebo effect was 1.87% and 2.41% forrepeated 8.37 mg and 12.55 mg sibutramine dose, respectively. When 12.55 mg sibutramine was assumed to be given for 1 year, the propoprtion of patients who lost more than 5% of their weight was 58.4 ± 6.35 (Mean ± SD) %, while that of placebo group was 44.6 ± 4.33 %.

Conclusions

These simulated results tell us that sibutramine may not show sufficient efficacy to meet the current criteria for approval as a weight control drug.

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Applications- Other diseases

PA11-3

Toxicokinetics of Paraquat in Korean Self-poisoned Patients

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Objectives

Paraquat (PQ) self-poisoning with suicidal attempt or accidental ingestion is highly fatal due both to its inherent toxicity and the lack of anyeffective treatment. Many studies had been carried out to elucidate the mechanism of toxicity of PQ at various cellular and molecular levels. It is also important to understand the mechanisms of PQ induced injuries but toxicokinetic knowledge in human is crucial for developing and/or designing potential therapeutic treatment in poisoned patients.

Methods

9 patients were admitted to the Institute of Pesticide Poisoning, Soonchunhyang University Cheonan Hospital (SCH). All the patients had swallowed one to three mouthfuls of 24.5% PQ solution in order to commit suicide. Standardized medical emergency procedures were conducted according to the Treatment Guideline for PQ Poisoning of SCH. Blood samples were taken from time of arrival up to 31 hours after ingestion of PQ. PQ plasma concentration-time data were analyzed using a non-compartmental method with WinNonlin software version 6 and compartmental analysis using NonMEM software version 7.2. Because patients had ingested wide range of PQ amount (4.9 − 49 g), maximum concentration (C_{max}) and area under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}) were normalized by PQ amount ingested and body weight or body mass index (BMI) to evaluate dose linear toxicokinetics.

Results

C_{max} and AUC_{inf} were 20.8 ± 25.7 mg/L and 172.5 ± 160.3 hr·mg/L, respectively. Weight or BMI-based dose normalized C_{max} and AUC_{inf} did not show linearity. Apparent volume of distribution and clearance were 84.1 ± 108.6 L/kg and 235.0 ± 170.2 L/hr, respectively.

Conclusions

Toxicokinetics of PQ was best described with a two-compartment model. Because obtaining exact information regarding PQ amount ingested or demographic characteristics was not possible, interindividual variations were large enough to show no dose-linearity in toxicokinetic parameters.

Applications- Other diseases

PA11-4   Population Pharmacokinetics of Oltipraz and Its Active Metabolite (RM), in Patients of Liver Fibrosis or Cirrhosis

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Objectives

Transforming growth factor-$\beta 1$ (TGF-$\beta 1$) has an important role in liver fibrosis to causes synthesis of extracellular matrix proteins and their receptors and inhibition of collagenase activity. Oltipraz shows a possibility to repress TGF-$\beta 1$ and resulted inresolving accumulated fibers and regenerating the cirrhotic liver. The aim of this study was to describe pharmacokinetics of Oltipraz by population approach following single and multiple oral doses in patients with liver fibrosis or cirrhosis

Methods

The pharmacokinetics of Oltipraz and its active metabolite (RM) were investigated after oral single dose (30, 60 and 90 mg) and multiple dose (60 mg bid and 90 mg qd for 24 weeks) in liver fibrosis or cirrhosis patients. The population pharmacokinetic analysis was performed by nonlinear mixed-effect modeling software (NONMEM®, version 7.1.2). The first-order conditional estimation with interaction method was used to fit the plasma concentration-time data. The influence of demography (age, sex, weight, height) and liver function test results (ALT, AST, albumin, total bilirubin, prothrombin time) on pharmacokinetic parameters was examined. Standard goodness-of-fit diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and predictions

Results

A one-compartment model with first-order absorption, and first-order elimination characterized the pharmacokinetics of Oltipraz in 644 concentrations from 78 patients with liver fibrosis or cirrhosis. A one-compartment model satisfactorily described the pharmacokinetics of RM. For covariate selection, the effect of body weight was found significant for apparent clearance of Oltipraz. Typical estimates of oral clearance (CL/F) and volume of distribution (V/F) were 88.5 L/h and 321 L for Oltipraz, 0.76 L/h and 2490 L for RM, respectively. Most of the data were within the 5th and 95th percentiles upon visual predictive check, which indicated that the model describes the pharmacokinetics of Oltipraz adequately

Conclusions

The pharmacokinetics of Oltipraz and RM were each characterized adequately by one- and one-compartment model with first-order elimination, respectively. The developed population pharmacokinetic model can be used for finding an optimal Oltipraz dose for patient population

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Applications- Other diseases

PA11-5 **Quantitative Assessment of Drug Response in Male Patients with Severe Nocturia Receiving a Combined Medication of Solifenacin and Tamsulosin**

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Objectives

Nocturia, defined by the International Continence Society as the complaint that an individual has to wake at night more than once to void [1], is a common disorder affecting both elderly men and women[1-3]. It is known that increased urination frequency and change in urine volume are two major symptoms of nocturia.However, there still has been no method that can quantitatively evaluate the drug effect on the improvement of symptoms. A nonlinear mixed effects model approach, by quantitatively describing the time course of drug response and incorporating random individual differences, can become a solution for this problem.

Methods

We selected a total of 20 male patients over the age of 18 with more than 3 times of nocturia a day who were treated with the same daily dose amount oftamsulosin q.d. for 3 month in outpatient clinics. Data were collected using the frequency volume chart, daily recorded by patients themselves.To predict the time-course of the urination frequency, a count model involving Poisson distribution was used[5], where the data were analyzed using the number of frequencies included in the time interval equally spaced and the interval midpoint. For the urine volume, the excretion flow rate (mL/hr) instead of the volume itself was analyzed to enable to predict the urine volume at anynon-urination time points as well as urination times. Modeling was performed using NONMEM 7.2.

Results

For urination frequency, when the time interval of 2 hours was chosen, the model with a 4-hour periodic cosine function best described the response before the medication (Placebo model). The baseline of lambda in Poisson distribution or mean urination frequency was estimated to be 1.03/2hrs. After the treatment, the baseline declined by the drug effect and was well described by an inverse Bateman function adjusted for steady-state. The rate constants associated with the onset and offset of drug effects were 12.1(1/time) and 1.44 (1/time), respectively, and magnitude of drug effect was 0.751.

Urine excretion flow rate (mL/hr) before the treatment was best described by the combination of 6- and 24-hr periodic cosine functions, yielding its baseline estimate of 86.4 (mL/hr) for daytime urination (awakened time) and 64.7 (mL/hr) for nocturia (after sleep).

Conclusions

In this study, we analyzed the two major symptoms of nocturia, urination frequency and volume. Further analyses will be needed to better understand the relationship between urination frequency and volume in this clinical population.

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Applications- Other diseases

PA11-6

Population Pharmacokinetics of Tanezumab in Patients with Osteoarthritis in the Knee and Hip

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Objectives

Tanezumab is a recombinant humanized monoclonal IgG2 antibody against human nerve growth factor. Tanezumab is under development for the treatment of joint pain associated with osteoarthritis (OA). The aims were to describe the PK of tanezumab administered intravenously and assess the influence of selected demographic factors on its clearance and distributive properties (V1, V2), and to explore the impact of a fixed versus a body weight (WT) adjusted dosing regimen.

Methods

A population pharmacokinetic analysis was conducted using pooled data from four Phase 3 studies (7592 observations,1608 patients, 61% females) in patients with OA of the knee and hip.

Results

The data were appropriately described by a two-compartment model with a parallel linear (CL, Q) and non-linear (VM, KM) elimination process. WT was added as a power function on CL, V1 and V2 to form the base model. The final model included sex, renal function and dose as predictors of CL, and sex as predictors of V1 (p<0.001). For a typical patient (female, 84.7 kg, 93.5 mL/min, 10 mg dose), final parameter estimates (RSE) for CL, V1, V2, Q, KM and VM were 0.135 L/day (0.021), 2.71 L (0.009), 1.98 L (0.067), 0.371 L/day (0.24), 27.7 µg/L (0.37) and 8.03 µg/day (0.15), respectively. Simulations showed that the fraction of a 2.5 mg and 10 mg dose eliminated via the non-linear pathway by a typical individual were 18% and 5%, respectively. Inter-individual variability (IIV expressed as %CV) in CL, V1, V2 and VM ranged from 20% (V1 and V2) to 41% (VM). WT was the most influential covariate decreasing IIV in CL from 35% to 27%; addition of the other covariates further reduced it to 26%. Residual variability was described using two additive terms on the log-scale (13% and 54%), combined using a mixture model with a mixture probability of 76% in favour of the low residual error.

Conclusions

The small increase in exposure variability for fixed versus weight-adjusted dosing was not considered clinically relevant given the tanezumab acceptable toleration profile over the studied dose range in large clinical trials and the higher risk of administration errors with weight-adjusted dose regimens.

Applications- Other diseases

PA11-7

Population Pharmacokinetics of Etanercept in Healthy Korean Male Volunteers

This abstract was presented as a poster at the 21st PAGE Meeting in Venice, Italy (June 07, 2012)

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Objectives

Etanercept is a soluble recombinant human tumor necrosis factor receptor (TNFR) fusion protein which is used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis and other inflammatory diseases. A model characterizing the population pharmacokinetics (PKs) of etanercept was explored. The aim of this study was to evaluate the relationships between PK parameters and explanatory covariates of etanercept in healthy Korean.

Methods

Plasma concentration data from 35 individuals were used receiving single dose of etanercept (Enbrel®) 25 mg by subcutaneous injection into the abdomen. A total of 476 concentration data obtained before dosing and 3, 6, 12, 24, 36, 48, 60, 72, 96, 144, 216, 312 and 480 hour after drug injection. The population PK analysis was conducted using nonlinear mixed effect modeling approach NONMEM®(version 7.2) based on the plasma concentrations. The first order conditional estimation (FOCE) with interaction method was employed to fit the model run. The demographic characteristics including age, weight, and height were examined as covariates. Standard goodness-of-fit diagnostics, visual predictive checks (VPC) and bootstraps were used to evaluate the model.

Results

A two compartment disposition model with first-order absorption and elimination was best characterized the PKs of etanercept. The parameter estimates of central volume of distribution (VC/F), oral clearance (CL/F), inter-compartment clearance (Q), and peripheral volume of distribution (VP) were, 8.65 L, 0.0837 L/h, 0.431 L/h, 3.34 L, respectively. The influence of covariates on PK parameters was insignificant. The VPC results indicated that the simulation properties of the model described the pharmacokinetics of etanercept appropriately.

Conclusions

PK model for etanercept was developed in healthy Korean population. The PKs of etanercept was adequately fitted by a two-compartment model with first-order absorption and elimination. This PK model can be used for PK-PD modeling studies to predict etanercept exposure and time course of clinical improvement in Korean patients.

PA11-8   Prediction of Human Platelet Response of ONO-7746/NIP-022, an Agonist of Thrombopoietin Receptor, Based on Pharmacokinetic-Pharmacodynamic Modeling Using Preclinical Data

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Objectives

The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of ONO-7746/NIP-022 in humans were estimated using preclinical data in order to provide essential information to better design the future clinical studies.

Methods

The relationship between plasma concentration of thrombopoietin receptor agonist and platelet counts in blood was described by the semiphysiological model of eltrombopag, the existing drug of the same class[1]. This model consists of PK, platelet lifespan, and PD (stimulation of platelet production by plasma concentration) models. The human PK parameters of ONO-7746/NIP-022 were estimated using an animal scale-up approach. The human parameters of the platelet lifespan model were obtained from the literature of eltrombopag since they are physiological factors independent of the drug. The E_{max} model, which includes the E_{max} and EC_{50}, was utilized as the PD model. The EC_{50} in humans were estimated in the following order: 1) determine the relationship between platelet counts and plasma concentration of ONO-7746/NIP-022 in NOD/Shi-scid, IL-2Rγ^{null} (NOG) mice that were transplanted with human cord blood CD34+ cells, 2) estimate the PD parameters of eltrombopag in NOG mice and humans to determine the species difference, 3) correct the EC_{50} of ONO-7746/NIP-022 in NOG mice by the species difference estimated by

the eltrombopag data. The human E_{max} of ONO-7746/NIP-022 was assumed to be the same using the estimated human E_{max} of eltrombopag. Based on these estimated human semiphysiological parameters, platelet count profiles following administration of ONO-7746/NIP-022 in humans were simulated.

Results

The PK/PD model-based estimate of the EC_{50} for ONO-7746/NIP-022 in NOG mice was 574 ng/mL. Accounting for species difference in eltrombopag, the NOG mice EC_{50} of ONO-7746/NIP-022 provided an estimated human EC_{50} for ONO-7746/NIP-022 of 82.4 ng/mL. The simulated platelet count profiles showed good agreement with the actual profiles obtained from the clinical data.

Conclusions

The simulation of human platelet counts based on preclinical data led to the acquisition of useful information for designing future clinical studies, and supported early development of ONO-7746/NIP-022.

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Applications- Other diseases

PA11-9 Population Pharmacokinetic Modelling of Chloroquine and Desethylchloroquine in NONMEM

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Objectives

The aim of this study was to describe the population pharmacokinetics of chloroquine (CQ) and its active metabolite, desethylchloroquine (DCQ), using sparse, retrospective CQ and DCQ pharmacokinetic data.

Methods

Plasma CQ and DCQ concentrations were obtained from 669 healthy male and female adults who orally ingested CQ base 300mg (chloroquine phosphate 500mg) daily for 7 days, followed by 300mg weekly for 10 more weeks. One or two blood samples were obtained from each subject no less than 7 days after the completion of the weekly dosing regimen. A total of 909 and 1147 CQ and DCQ concentrations, respectively, were collected. The sparse data in this study for CQ and DCQ analysis combined with the availability of information from a previous population pharmacokinetic analysis with CQ and DCQ [1] led to the usage of NONMEM's PRIOR functionality in the combined CQ and DCQ pharmacokinetic data model development.

Results

Both CQ and DCQ pharmacokinetics were described by a two-compartment model, with clearance and volume terms scaled allometrically by bodyweight. Parameter estimates were 5.52 L/h for CQ clearance (CL/FCQ), 1.46 L/h for DCQ clearance (CL/FDCQ), 1220 L for CQ central compartmental volume of distribution (V/FCQ) and 14.3 L for DCQ central compartmental volume of distribution (V/FDCQ). The interindividual variability in CL/FCQ, CL/FDCQ and V/FCQ were 38.3, 33.5 and 122.9% respectively. The residual variability in CQ and DCQ unexplained by the population model were 62.8 and 55.3% respectively. A limited nonparametric bootstrap (n=50) was performed to obtain the standard errors of the parameter estimates. Reductions in CL/F and V/F for both CQ and DCQ compared to [1] may be explained by an increase in bioavailability, namely increased systemic absorption via decreased presystemic metabolism of CQ. Our findings are supported by previous published experimental data on the autoinhibition of cytochrome P450 (CYP) 2D6 activity in human, both in vivo and in vitro, after repeated exposures to CQ.

Conclusions

The final population pharmacokinetic model adequately described the CQ and DCQ data. Low CL/F and V/F values for both CQ and DCQ are attributed to decreased systemic elimination via reduced CYP2D6 hepatic metabolism as a result of chronic CQ exposure.

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Applications- Other diseases

PA11-10 Pharmacokinetic/Pharmacodynamic Analysis of the Role of CYP2C19 Genotypes in Short-term Rabeprazole-based Triple Therapy against Helicobacter Pylori

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Objectives

The eradication rates of rabeprazole-based triple therapy for 3-4 days vary among studies, but without taking into account the CYP2C19 genotype. This study was to explore the role of CYP2C19 polymorphism in short-term rabeprazole-based triple therapy against H. pylori infection.

Methods

Patients with H. pylori infection were tested for CYP2C19 genotype as poor metabolizers (PM) or extensive metabolizers (EM) and given rabeprazole for 7 days. Antibiotics (clarithromycin and amoxicillin) were given on days 1-4, days 4-7, or days 1-7. A direct link model with an effect compartment was used in the population pharmacokinetic/pharmacodynamic analysis. The eradication of H. pylori infection was compared.

Results

Rabeprazole clearance was lower in CYP2C19 PM than in EM in days of treatment, resulting in higher plasma levels in the former group. The values of EC_{50} and keo of gastrin response increased with multiple doses of rabeprazole. The keo values were lower in CYP2C19 PM than in EM on day 1 (0.012 vs. 0.017, 10-4 1/min), and higher than in EM on day 4 (0.804 vs. 0.169, 10-4 1/min), of rabeprazole treatment. The predicted gastrin-time profile showed a higher response in CYP2C19 PM than in EM on days 4 and 7. H. pylori was eradicated in all CYP2C19 PM except in one patient infected by a resistant strain. In contrast, in CYP2C19 EM the eradication rates ranged from 58% to 84%.

Conclusions

CYP2C19 genotypes play a role in H. pylori eradication therapy. Rabeprazole-based short-term triple therapy may be applicable in CYP2C19 PM for H. pylori eradication.

Applications- Other diseases

PA11-11 An Exposure-Adverse Event Analysis to Explore Tolerable Dosing Regimen for S-0139 Using Time to Event Modeling of Nausea and/or Vomiting

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Objectives

S-0139 is a selective endothelin A receptor antagonist given by intravenous infusion and has been suggested as potential therapy for ischemic stroke. During clinical trials, headache, nausea and vomiting were frequently observed as CNS-related adverse events, and vomiting would be critical for stroke patients. These adverse events increased in both frequency and intensity at higher infusion rate and/or longer infusion duration time of S-0139, requiring infusions to be stopped early and analgesic and antiemetic therapy to be given in some subjects. The aim of this study was to develop an exposure-adverse event model and to explore tolerable dosing regimens.

Methods

The exposure-adverse event analyses were conducted using data from the following 2 clinical studies; a single dose study with infusion rates from 1 to 6 mg/kg/hr as 6 hours continuous intravenous infusion; and a prolonged infusion study with infusion rates from 0.47 to 1.4 mg/kg/hr as 12 or 24 hours continuous intravenous infusion. A 2-compartment model with Michaelis-Menten elimination from the central compartment ($V_{max,Elim}$, and Km_{Elim}) and distribution from the central to peripheral compartment ($V_{max,Dist}$, and Km_{Dist}) was used to describe nonlinear S-0139 pharmacokinetic (PK) profiles. The time to the first occurrence of nausea or vomiting was evaluated by using a parametric time to event model (Hazard function). Visual predictive check (VPC) was used to evaluate model performance using simulated and non parametric estimates (Kaplan-Meier plots) of the time to event profiles regarding nausea and vomiting.

Results

The 2-compartment Michaelis-Menten model suitably described the S-0139 PK profiles which exhibited supra-proportional increases at high dose. Hazard function for nausea or vomiting was estimated as: 0.00219 + 0.00154 × (S-0139 Concentration). The adverse event model suggests tolerable dosing regimens, for example, when S-0139 is administered over 6 hour infusion, the dose of S-0139 can be increased up to 2.32 mg/hr/kg which yields a steady state plasma concentration of 5.93 μg/mL.

Conclusions

The exposure-adverse event model adequately predicted the risk of nausea and/or vomiting. The results would support selection of the optimal dosing regimen.

Applications- Other diseases

PA11-12   Ishak Stage Progression Model in Post Liver Transplant (POLT) Patients with Chronic Hepatitis C Virus (HCV) Infection

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Objectives

The Ishak Stage (IS) Score is a commonly used 7-point staging system to describe architectural changes and fibrosis in patients with chronic HCV infection. It is commonly accepted that IS progression rates may be different in POLT HCV patients.To build an IS progression model for POLT HCV patients and explore potential patient characteristics affecting disease progression rates.

Methods

Longitudinal IS together with demography, HCV genotype, medical and immunosuppressive therapy from 219 POLT HCV patients were analyzed. IS was treated as ordered categorical data and modeled with proportional odds method. Nonlinear mixed effects modeling technique was used to estimate model fixed effect parameters and inter-subject variability (ISV). Acute HCV, donor sex and age, steroid treatment, presence of diabetes, genotype and overall survival were investigated as potential covariates. A stepwise forward inclusion (p<0.05) and backward exclusion (p<0.005) method was used to assess covariate effect. Model fit was evaluated by graphical and numerical diagnostic tools.

Results

Probabilities (IS>=m for m=0, 1, to 6) of POLT HCV patients' IS progression can be described as the following equations:$P=\exp(base+ISprog+ETA)/(1+\exp(base+ISprog+ETA))$ $ISprog = (Emax+AHC+DAGE)*Time/(T50+Time)$ where base corresponds to a baseline probability, ISprog represents IS progression, and ETA accounts for the inter-patient variability. AHC and DAGE represent acute HCV and donor age, respectively.Estimated Emax and T50 were 16.6 and 1.42 yrs, respectively. AHC and DAGE were 5.1 and 2.29 respectively.

Conclusions

An IS progression model developed for POLT HCV patients suggests that in the first 1-2 years POLT the disease stage progression rate to IS 2 is more than the subsequent progression rate to more advanced stages. Analysis of rate of collagen deposition with liver tissue collagen quantification may offer a more robust indication of actual liver fibrosis progression in these patients. Acute HCV and donor age appeared to be important covariates in determining Ishak stage progression.

Drug/disease modeling

PD-1

Joint Longitudinal and Dropout Model for Disease Progression in Multiple Sclerosis

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Objectives

Joint longitudinal and dropout model can increase the statistical power when analyzing clinical trials. The objectives of this analysis were to understand and quantify dropout rates in multiple sclerosis (MS) clinical trial and to identify potential predictors of dropout.

Methods

Data were collected from a 96-week Phase III clinical study, involving 14359 disease disability measurements (Expanded Disability Status Score, EDSS) from 1319 patients with relapsing-remitting MS, treated with placebo or cladribine. A dropout model was developed and merged with the existing disease progression model [1]. Logistic regression was used to describe the dropout. Different dropout assumptions, such as missing completely at random, at random and not at random, were tested [2]. Potential predictors of dropout such as baseline score, last observed score and total cumulative received dose were investigated [3]. Dropout patterns were first characterized in the placebo arm and then extended to the cladribine arm. All data were fitted simultaneously using NONMEM 7.1.2. In order to evaluate the appropriateness of our model, simulations based diagnostics were performed.

Results

Observed dropout rate was 11% with no significant trend over time.Logistic regression showed that both, magnitude of change in EDSS between two neighboring visits as well as magnitude of change from baseline were the best predictors of dropout. For example, patients having an overall increase of 2 EDSS points between two neighboring visits had more than 2-fold higher probability for dropout compared to those with a 0.5-pointincrease. In the case of cladribine data, higher maximal cumulative dose was associated with lower probability for dropout; patients receiving 600mg of total dose had more than 2-fold lower probability of dropping out compared to those receiving 300mg. Visual predictive checks of the disease progression model were improved after the dropout component was introduced.

Conclusions

We provide some evidence that dropout in MS trials is associated with faster disease progression and lower cumulative dose (in the treatment groups), which is consistent with expectations that lack of or lower treatment effect will lead to higher dropout rates. Further, this model is a valuable tool to mimic dropout pattern in MS trials, and hence could be used for clinical trial simulations.

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Drug/disease modeling

PD-2 **Placebo Effect Model in Asthma Clinical Studies: Longitudinal Meta-analysis of Forced Expiratory Volume in 1 Second**

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Objectives

Our objective was to describe the time course of the placebo effect in asthma and quantitatively investigatethe affective factors of the placebo effect for theplacebo response simulation during the asthma clinical study design.

Methods

We conducted a systemic search of public data sources for the study-level forced expiratory volume in 1 second (FEV1) to build the placebo effect model for studies by oral or inhaled administrations imultaneously. The administration routes, types of inhalation device, mean patient age, mean male proportion, baseline FEV1, disease severity, year of publication, inhaled corticosteroid status during the treatment, and dropout rate were tested as covariates.

Results

There are 34 literature sources containing 178 mean values for FEV1 presenting the individual observations from about 3,703 patients. The exponential models adequately described the time course of placebo effect with the typical value of the maximum placebo effect (Pmax) of 0.060 L. Dropout rate incorporated in the residual error model and the disease severity (mild to moderate and moderate to severe) at baseline were covariates that remained in the final model.

Conclusions

The placebo effect is adequately described by an exponential model over time. By incorporating the dropoutrate in the residual error model, the estimation precision was improved. The model could predict the placebo response profile in mild to severe asthmatic patients for the asthma clinical study design and could also be a structure model of the placebo effect for the pure drug effect evaluation in the asthma clinical trials.

References

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Drug/disease modeling

PD-3 # Population Pharmacokinetics of Alcohol in Korean Healthy Volunteers with ADH/ALDH Genotypes

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Objectives

Alcohol is metabolized predominantly in the liver by alcohol dehydrogenase (ADH) to acetaldehyde that is then converted to acetate by aldehyde dehydrogenase (ALDH). Both ADH and ALDH exhibit genetic polymorphisms among racial populations. The effect of genetic polymorphism on alcohol is not yet clearly understood. This study aimed to develop the population pharmacokinetic model with the effect of genetic polymorphism in Korean.

Methods

Forty-two healthy Korean volunteers participated in this study. A Single dose of alcohol was orally administered 0.5 g/kg in twenty volunteers and 0.8 g/kg in other twenty-two volunteers. Blood concentrations were measured at 30, 60, 90, 120, 150, 180, 240, 300, 360, and 420 minutes after the end of drinking. Population pharmacokinetic modeling was performed with nonlinear mixed-effect model using NONMEM (version 7.2). Demographic data such as age, height, weight and genotypes for ADH1B, ADH1C, and ALDH2 were collected as covariates. Goodness-of-fit (GOF) diagnostics and visual predictive checks (VPC) were used to evaluate the adequacy of the model fit and predictions.

Results

Forty-two subjects contributed to 420 alcohol concentrations. Alcohol concentrations were best described by a one-compartment model with first-order absorption. The Michaelis-Menten kinetics model was adopted due to its enzymatic rate-limiting elimination. The structural model with genetic variance was validated through the VPC.

Conclusions

A population pharmacokinetic model considered genetic polymorphism was developed in healthy Korean and adequately characterized the pharmacokinetics of alcohol. Further studies will be needed to validate the proposed results.

Drug/disease modeling

PD-4

Population Pharmacokinetics of Oxcarbazepine after Oral Loading in Patients with Epilepsy

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Objectives

Oxcarbazepine is the 10-keto analog of carbamazepine and has comparable antiepileptic effect than carbamazepine with better safety tolerability. As carbamazepine is an effective for rapid oral loading for rapid seizure control. We investigated the pharmacokinetic characteristics of oxcarbazepine by population model development.

Methods

A total of 78 patients had been orally administered single dose of oxcarbazepine 30 mg/kg with a formulation of tablet or suspension, respectively. Blood samples were collected before dosing and at 2, 4, 6, 8, 10, 12, 14, 16 and 24 hours after dosing. The 737 plasma concentration-time points were used to analyze the population pharmacokinetics with NONMEM VII. The demographic and clinical data were screened to find significant covariates which explain intersubject variability of pharmacokinetic parameters. Diagnostic methods such as goodness of fits and predictive check were applied in the assessment of models.

Results

Oxcarbazepine was rapidly absorbed and reached its peak concentration within 2-4 hours after oral loading. The pharmacokinetics of oxcarbazepine was well-described by 2 compartment model with first order absorption. The estimates and standard errors of model parameters were statistically and physiologically acceptable. Intersubject variability was found to be moderate in magnitude and the size of unexplained intrasubject variability of each parameter was also evaluated.

Conclusions

The population model was described the pharmacokinetic characteristics of oxcarbazepine after oral loading in patients with epilepsy, such as typical values of parameters, size of intersubject and intrasubject variability. Further analysis is planned to develop the extended population model by including the pharmacokinetics of MHD, its active metabolite.

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Drug/disease modeling

PD-5

A Population Pharmacokinetic Analysis of Oseltamivir in Patients with Renal Impairment

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Objectives

Oseltamivir is a potent and selective inhibitor of neuraminidase inhibitor for the treatment and prophylaxis of influenza. The aim of this study was to establish a population pharmacokinetic (PK) model of oseltamivir in renal impairment patients on hemodialysis (HD), after single oral administration.

Methods

A total of 384 serum concentration measurements were obtained in adult patients undergoing thrice-weekly HD after single oral dose of oseltamivir from 2 studies. In the first study, 4 patients received oseltamivir for 3 periods of single dose of 2.5, 5 and 10 mg. In the second study, 10 patients administered single dose of 2.5 and 35 mg through 2 periods. One week of wash-out was between each period and blood samples were collected up to 72 hours after the administration. PK model of oseltamivir and its active metabolite, oseltamivir carboxylate, were established using non-linear mixed effect model (NONMEM® 7.2).

Results

A two-compartment PK model with a first-order absorption fitted well to serum concentration-time curve for oseltamivir. Oseltamivir carboxylate was well described by a one-compartment model as an extension of the parent drug model with first-order elimination and absorption from the central compartment of oseltamivir. The estimate of PK parameter for absorption rate constant was 0.08 hr^{-1} (CV 20.5%). The oral clearance (CL/F), clearance of metabolite (CLm), and inter-compartment clearance (Q) were 37.3 L/h (CV 116%), 0.42 L/h (CV 32.6%), and 198 L/h (CV 140%), respectively. The central volume of distribution (Vc/F) was 54.7 L (omega was fixed to 0), and peripheral volume of distribution (Vp) and metabolite volume of distribution (Vm) was 359 L (20.9%) and 7.7 L (CV 34.2%), respectively.

Conclusions

PK model for oseltamivir was developed for patients with renal impairment. Since limited information of the oseltamivir PK is available in these patients, this model may be a useful toolto predict clinically relevant plasma oseltamivir concentration in HD patients.

Drug/disease modeling

PD-6 **Population Pharmacokinetics of a New Proton Pump Inhibitor, Drug X, in Healthy Volunteers**

*This abstract was presented as a poster at the 20th PAGE Meeting in Athens, Greece (June 09, 2011).

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Objectives

A new proton pump inhibitor (Drug X) is under clinical development for management of gastroesophageal reflux disease. The aim of this study was to characterize pharmacokinetics of Drug X by population approach following single and multiple oral doses in healthy volunteers.

Methods

In the first-in-human study of Drug X, healthy volunteers were administered orally single or multiple dose of Drug X (single dose, 30 to 800 mg; multiple dose, 100 to 400 mg once daily for 7 days). The effect of food intake on the pharmacokinetics was evaluated following single dose ofDrug X 600 mg. Nonlinear mixed effects modeling methodology was implemented in the population pharmacokinetic analysis using NONMEM® (version 7.1.2). The first-order conditional estimation (FOCE) with interaction method was used to fit the plasma concentration-time data. After the Drug X model was developed, food effects on drug absorption were investigated. The influence of age, weight, height, dose group and function of CYP2C19 on pharmacokinetic parameters was examined. Standard goodness-of-fit diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and predictions.

Results

A two compartment model with first-order absorption, absorption lag time, and first-order elimination characterized the pharmacokinetics in 1946 concentrations of Drug X from 79 healthy male volunteers. None of screened covariates affected pharmacokinetics of Drug X significantly. Population mean estimates (standard error) of oral clearance (CL/F), central volume of distribution (V/F), inter-compartment clearance (Q/F), and peripheral volume of distribution (V2/F) were 492 (29.3) L/h, 193 (32.4) L, 318 (24.5) L/h, and 5150 (382) L, respectively. Between-subject variability (CV%) of CL/F, V/F, Q/F and V2/F were 48.8%, 119.6%, 61.9% and 58.7%, respectively. At fed status, absorption rate constant (ka) was decreased from 0.981 h^{-1} to 0.204 h^{-1}, and oral bioavailability was increased 3.18-fold compared to those at fast status. Most of the data were within 5th and 95th percentile in visual predictive check, which indicated that the model describes the pharmacokinetics of Drug X adequately.

Conclusions

The pharmacokinetics of Drug X was characterized adequately by a two-compartment model with first-order elimination, and food intake affected the absorption of Drug X.

Drug/disease modeling

PD-7

Effect of Renal Function on the Population Pharmacokinetics of Drug X

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Objectives

Drug X is a new angiotensin II receptor antagonist for the treatment of mild to moderate hypertension. Since clinical studies had already suggested that renal angiotensin system inhibitors provide renoprotection independently of blood pressure lowering, drug X is expected to be used in renal impairment patients. [1] The aim of this study was to compare the population pharmacokinetics of drug X in renal impairment patients and healthy volunteers

Methods

Eight patients with estimated glomerular filtration rate (eGFR) lower than 30 mL/min/1.73m^2 but not dialyzed and eight healthy volunteers matched with the renal impairment patients were enrolled in a single dose, open-label, healthy volunteer-controlled study. A 120-mg oral tablet of Drug X was administered to subjects with renal impairment and healthy volunteers. Venous blood samples were collected over 48 hr after dosing. Plasma concentration of drug X was determined using a validated liquid chromatography-tandem mass spectrometry method. Nonlinear mixed effects modeling methodology was implemented in the population pharmacokinetic analysis using NONMEM®(version 7.2.0). The parameter estimates were obtained using the first-order conditional estimation with interaction.

Results

The pharmacokinetics was adequately described by a two compartment model. Elimination clearance (CL) was dependent to eGFR. The population pharmacokinetic parameters were as follow: CL/F = 35 x (eGFR / 90) $^{0.276}$ L/hr ; volume of central compartment, V_c/F = 41.3 x (Body weight / 70) $^{0.995}$ L ; CL (distribution), Q/F = 2.87 L/hr ; and volume of peripheral compartment, V_p/F = 28.7 L

Conclusions

The pharmacokinetics of drug X was characterized adequately by a two-compartment model. Since the renal function which is represented as eGFR, influenced the elimination of drug X, more research is needed for dose adjustment of drug X in renal impaired patients.

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Drug/disease modeling

PD-8

Population Pharmacokinetics Analysis of Two Different Formulations of Megestrol Acetate in Healthy Volunteers

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Objectives

Megestrol acetate is a synthetic active progesterone, which is used to improve appetite and to increase weight in cancer-associated anorexia. The aim of this study was to analyze population pharmacokinetics of megestrol acetate in healthy volunteers and to evaluate the effects of formulation on bioavailability of megestrol acetate.

Methods

Ninety-eight male healthy volunteers were enrolled in an open-label, randomized, single-dose, crossover study. In part 1, participants received nanocrystal megestrol acetate (Megace F®) in the fasted or fed state. In part 2 and 3, participants were taken micronized megestrol acetate (Megace OS®) or Megace F®in the fed (part 2) or fasted state (part 3) respectively. Mixed-effects modeling (NONMEM VII) was used to determine the typical population pharmacokinetic parameters and their respective variabilities. The first-order conditional estimation (FOCE) with interaction method was used to fit the plasma concentration-time data. Standard goodness-of-fit diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and predictions.

Results

Megestrol acetate concentrations were best described by a two-compartment model with first-order absorption. Apparent volumes (V/F) were 211 L (CV 18.9%) and 658 L (25.9%) for V2/F and V3/F, respectively. Oral clearance (CL/F) was 28.6 L/h (21.3%) and intercompartmental clearance (Q) was 34.1 L/h (15.4%). The formulation of megestrol acetate was a significant covariate for absorption rate constant (ka). Compared to the Megace OS®, absorption rate constant (ka) of Megace F®was increased from 0.141 h^{-1} to 0.213 h^{-1}. Most of the data were within 5th and 95th percentiles of prediction intervals in visual predictive check, which indicated that the model describes the pharmacokinetics of megestrol acetate adequately.

Conclusions

The pharmacokinetics of megestrol acetate was best described by a two-compartment model, and nanocrystal formulation of megestrol acetate showed improved absorption.

Drug/disease modeling

PD-9

Race Difference: Model-based the Pharmacodynamics of Rosuvastatin in Western and Asian Hypercholesterolemia Patients

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Objectives

To evaluate race differences in the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients using a population pharmacodynamic (PPD) model generated and validated using published clinical efficacy trials.

Methods

Published studies randomized trials with rosuvastatin treatment for at least 4 weeks in hypercholesterolemia patients were used for model building and validation. Population pharmacodynamic analyses were performed to describe the dose-response relationshipwith the mean values of LDL-C reduction (%) from dose-ranging trials using NONMEM software. Baseline LDL-C and race were analyzed as the potential covariates. Model robustness was evaluated using the bootstrap method and the data-splitting method, and Monte Carlo simulation was performed to assess the predictive performance of the PPD model with the mean effects from the one-dose trials.

Results

Of the 36 eligible trials, 14 dose-ranging trials were used in model development and 22 one-dose trials were used for model prediction. The dose-response of rosuvastatin was successfully described by a simple Emax model with a fixed E0, which provided a common Emax and an approximate twofold difference in ED50 for Westerners and Asians. The PPD model was demonstrated to be stable and predictive.

Conclusions

The race differences in the pharmacodynamics of rosuvastatin are consistent with those observed in the pharmacokinetics of the drug, confirming that there is no significant difference in the exposure-response relationship for LDL-C reduction between Westerners and Asians. The study suggests that for a new compound with a mechanism of action similar to that of rosuvastatin, its efficacy in Western populations plus its pharmacokinetics in bridging studies in Asian populations may be used to support a registration of the new compound in Asian countries.

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Drug/disease modeling

PD-10

Population Pharmacokinetics of Prothionamide in Korean Tuberculosis Patients

This abstract was presented (poster) in the 2012 American Society of Clinical Pharmacology and Therapeutics (ASCPT) 113th annual meeting from 14 to 17 March in Maryland, USA.

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Objectives

Prothionamide (PTH) is a thioamide drug that has been used for multidrug-resistant tuberculosis (MDR-TB). It is bactericidal and is prescribed as second-line anti-TB medications. The population pharmacokinetic (PK) modeling of PTH has not been developed. The aim of this study was to investigate the population PK of PTH in Korean patients with MDR-TB.

Methods

Seventeen Korean patients with MDR-TB participated in thisstudy. All patients had received multiple oral doses of PTH for at least 2 weeks, with other second-line anti-TB drugs. Plasma samples were collected before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after dosing. The concentration of plasma PTH was analyzed with high performance liquid chromatography. The population PK data were analyzed using NONMEM (Ver. 6.2).

Results

A 1-compartment model with Weibull-type absorption described the best fit to a total 221 concentrations of PTH from TB patients. The major population parameter estimates were as follows; ka, 0.509 h-1; Vc (volume of central compartment), 104 L; and CL, 34 L/h. The 1-compartment structural model was validated through visual predictive check (VPC) with no serious model misspecification.

Conclusions

A population PK model was developed and reasonable parameters were obtained from the data of Korean pulmonary TB patients. Further study will be required to develop a final PK model through comparison with other compartment PK models and to evaluate the usefulness of dose-response relationship using bootstrap simulation.

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Drug/disease modeling

PD-11

Population Pharmacokinetics of S-Amlodipine in Healthy Korean Male Subjects

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Objectives

Amlodipine, a third-generation dihydropyridine calcium channel blocker that has been used for hypertension and angina pectoris, is known to have large inter-individual pharmacokinetic(PK) variability. The aims of this study were to develop a population PK model of S-amlodipine in healthy Korean subjects and to compare estimated parameters between two amlodipine formulations.

Methods

A randomized, open-label, two-period, crossover bioequivalence study in 30 healthy male adults was performed. All subjects were received either the test or reference formulation as a single 2.5-mg oral dose of S-amlodipine, followed by a 3-week washout period and administration of the alternate formulation. Blood samples were drawn at 0 (pre-dose), 1, 2, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, and 216 hours after dosing. Plasma S-amlodipine concentrations were analyzed using HPLC/MS/MS. A population PK analysis was conducted using NONMEM (Ver. 7.1).

Results

A 2-compartment model with zero-order absorption provided the best fit to a total of 383 concentrations from healthy subjects. Estimates of the population PK parameter were as follows; ke, 0.019 h-1; Vc, 1940 L; Vp, 515 L; Q, 102 L/h; D1 (Duration of zero-order absorption), 4.99 h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model. No significant difference in the PK parameter estimates was observed between the two amlodipine formulations.

Conclusions

A population PK model was successfully developed and reasonable parameters were obtained. Both formulations were identical in the aspect of PK behavior. There were no significant covariates affecting PK parameters. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of amlodipine.

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PD-12   # Integrative Pharmacokinetic - Pharmacodynamic Modeling and Simulation of Amenamevir (ASP2151) Using Pre-clinical Data and Clinical Data from Studies in which Patients Were Treated for Recurrent Genital Herpes

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Objectives

Amenamevir is a novel non-nucleoside oxadiazol-phenyl-containing drug that targets the viral helicase-primase complex. Efficacy differences for different doses was seen in the statistical analysis of data from a phase II study. On the other hand, dose-dependent efficacy was observed from in vitro experiments using human embryonic fibroblast (HEF) cells and in vivo experiments using rats. To discuss the unexpected clinical study results that were contradictory to that predicted from the non-clinical studies, additional PK/PD analyses have been conducted with the built-in biomarkers that connect the PK model to the endpoint based on the pharmacological mechanism

Methods

PK models for guinea pig non-clinical data and for genital herpes patients in a phase II study were built separately. HEF cell treatment data that were used to evaluate the relationship between the duration of time above a specified drug concentration and the number of virus plaques was used as the bio-marker linking PK and lesion score as the PD marker. Virus plaque time profiles among different durations of time above some specified levels were modeled to explain the time-dependent drug efficacy. Each of the virus plaque time profiles for guinea pigs and humans were simulated based on each of their PK profiles. The lesion score time profile was analyzed using the same logit model for guinea pigs and humans.

Results

Non-clinical and clinical lesion scores were explained by the same logit model using estimated PK and virus plaque time-profiles. The amount of the virus time-profile was highly related to the lesion score. The efficacy difference between the guinea pigs and the humans was mainly caused by the natural healing ability.

Conclusions

The integrative pharmacokinetic - pharmacodynamic modeling and simulation enabled to clarify the main reason for the efficacy difference between the non-clinical and clinical setting was the natural healing effect of the human immune system. In this therapeutic area, the rational and precise evaluation of the healing effect is critical for achieving the clear dose-efficacy response in humans.

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Drug/disease modeling

PD-13

An Efficacy-Oriented Approach for Comparison of Antibiotic Drug Regimens

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Objectives

The determination of an optimal dosing regimen is a critical step to enhance the drug efficacy and avoid toxicity. Rational dosing recommendations based on mathematical considerations are increasingly being adopted in the process of drug development and use.

Methods

We propose a quantitative approach to evaluate the efficacy of antibiotic agents by integrating both in vivo pharmacokinetic (PK) and in vitro pharmacodynamic (PD) information into a unified formalism. In this way, the dosing regimens, including doses and associated timings, can be mathematically defined as a causal variable that influences the therapeutic effect. Realistic drug models, representatives of concentration- and time- dependents antibiotic agents, were used to investigate the proposed approach for several typical dosing regimens, including QD, BID, TID and QID.

Results

We succeeded to reveal unexpected, but relevant behaviours of drug performance when different drug regimens and drug classes are considered. First, this new pharmacometric formalism allows covering a whole range of antibiotics, including the two well known concentration and time dependent classes, through the introduction of the Hill-dependency concept. Second, we found that the doses required to reach the same therapeutic effect, when scheduled differently, exhibit completely different tendencies for concentration- and time- dependent drugs. Moreover, we theoretically confirmed the previous experimental results of the superiority of the once daily regimen of aminoglycosides.

Conclusions

The proposed methodology is appealing for its computational features and can easily be applicable to design fair clinical protocols or rationalize prescription decisions.

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Drug/disease modeling

PD-14

Literature Model for FEV1 in COPD Trials –
Separating the Dynamic Components of Placebo Effect, Disease Progression and Interacting Drug Effects

(Presented at 21st PAGE meeting, Venice, Italy, 2012)

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Objectives

In chronic obstructive pulmonary disease (COPD) the forced expiratory volume in one second (FEV1) is used for diagnosis and dose selection.[1] The objective of this work was to develop a longitudinal model for FEV1 based on literature (summary level data) on COPD trials, to quantify placebo effect and disease progression, as well as treatment effects and their interaction in combination treatment.

Methods

Criteria for inclusion were a) randomised, blinded COPD maintenance trials b) treatments class: LABA, LAAC, ICS or PDE4i c) FEV1: troughs were used when available. Pre-study-drug measurements occurring after administration of a short-acting bronchodilator (post-SABD) were otherwise used.Background therapy was allowed and any interaction was handled by drug-drug interaction models. Estimation was performed in NONMEM.

Results

The database included 89 studies, totalling 62 946 patients across 235 treatment arms. These trials reported 1118 FEV1 values, each representing the mean in an arm, at a certain time during the study. Study durations ranged: 1 week to 4 years.The final structural model included components which described the baseline and the time course for: a) placebo response b) disease progression c) drug effect. The drug-effect model included separate estimates for 13 compounds and described dose-response where possible. Drug interactions were estimated for the combination LABA+LAAC as well as for LABA or LAAC measured post-SABD. An anti-inflammatory agent (ICS or PDE4i) in combination with a direct bronchodilator (LABA or LAAC) provided efficacy as the sum of the two mono components. Random inter-study variability was included in all four structural components and inter-arm variability in baseline. Important covariates were identified.

Conclusions

This exercise a) consolidated relevant information across compounds, in terms of efficacy, dose-response and time course for drug-effect b) positions each published trial result into a broader evidence-basedcontext c) illustrates the impact of PD interactions and other covariates.Furthermore our FEV1 model will predict trough FEV1 even for trials that only measured FEV1 post-SABD, and will be developed to predict exacerbations. This is an important efficiency gain since the late phase exacerbation trials require thousands of patients and at least one year duration.

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Drug/disease modeling

PD-15

A Modeling and Simulation Approach to Optimize the Design of a Phase 2 Study Evaluating Tofacitinib in Japanese Patients with Rheumatoid Arthritis

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Objectives

Tofacitinib is a novel, oral Janus kinase inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for rheumatoid arthritis (RA). One objective of Phase 2 trials is to produce data which support dose selection for Phase 3 multinational trials. One of the most important challenges is to design a Phase 2 study which can evaluate the similarity of dose-response relation among different ethnic groups (eg between Japanese and Western patients), with the minimum number of patients. This study presents an optimization method to design the Phase 2 study in Japanese patients with RA, by application of a modeling and simulation approach.

Methods

A longitudinal, logistic-normal, mixed effects, dose-response model on American College of Rheumatology 20% (ACR20) response has been used in clinical trial simulations (Hutmacher et al 2008). A design that would allow the estimation of the potency (dose that corresponds to 50% of maximum effect, ED_{50}) of tofacitinib in Japanese patients with RA was simulated. This estimate was derived from a pooled, longitudinal analysis of a Japanese Phase 2 study and a previous Western Phase 2 study (placebo and five tofacitinib doses, n~70 per arm). A longitudinal maximum effect (E_{max}) model was used for dose-response assessment of observed efficacy data.

Results

According to the simulation of various combinations of sample size and dose, if the ratio of ED_{50} (Japanese/Westerners) were changed from 0.66 to 1.5, placebo and tofacitinib doses of 1, 3, 5, and 10 mg twice daily with 24 Japanese patients per arm yielded >80% probability that the ED_{50} could be estimated appropriately. The analysis of observed efficacy data demonstrated that the dose-response curve and time course change were generally similar between Japanese and Western patients.

Conclusions

The simulation revealed that sample size in the Japanese Phase 2 study could be reduced to about one third of the number comparing the Western Phase 2 study by pooled analysis. Observed data from the Japanese Phase 2 study supported the dose selection for Japanese patients with RA in a multinational Phase 3 study.

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Drug/disease modeling

A Semi-Mechanistic Model of Fibrosis Progression Using Collagen Proportionate Area (CPA) in Post Liver Transplant (POLT) Patients with Chronic Hepatitis C (CHC)

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Objectives

Quantitative measurements of collagen proportionate area (CPA) by digital image analysis quantifies fibrosis in the liver. A semi-mechanistic model was developed to describe CPA progression in POLT CHC patients. The objective is to build a semi-mechanistic model of progression of CPA for POLT CHC patients and explore potential patient characteristics affecting quantity of liver fibrosis.

Methods

Longitudinal CPA data together with demography, HCV genotype, medical and immunosuppressive therapy from 185 consecutive POLT CHC patients were included in the model Assumptions regarding generation and degradation mechanisms for collagen were made for CPA modeling. Fixed effects and inter-subject variability (ISV) were estimated by a nonlinear mixed effects modeling technique. Acute HCV, basic immunosuppression, and donor age were potentially associated with CPA progression. The covariates in the model were selected by a stepwise forward inclusion ($p<0.05$) and backward ($p<0.005$) exclusion method. The model was evaluated using graphical and numerical diagnostic tools.

Results

The analysis showed that acute HCV, basic immunosuppression, and number of immunosuppressive regimens impacted collagen generation rate while donor age was correlated with collagen degradation rate. After covariate forward inclusion and backward exclusion steps, the following model best fitted patients' CPA progression data:$dCPA/dt = (Kin+AHC+BI)*(100-CPA)-Kout*CPA$where Kin is generation rate, Kout is degradation rate, AHC = acute HCV status, and is a binary variable (0=NO; 1=YES), BI = basic immunosuppression, and is binary (0=cyclosporine, 1=tacrolimus).Estimated Kin and Kout were 0.019 and 0.48, respectively. ISV was 67% and 92% for Kin and Kout, respectively. Patients with tacrolimus treatment appeared to have their collagen generation rate increased by 0.027 compared to those with cyclosporine treatment. Patients with acute HCV appeared to have their collagen generation rate increased by 0.016 compared to those without acute HCV.

Conclusions

A mechanism-based methodology could be applied to model CPA progression. A semi-mechanistic CPA progression model developed from POLT CHC patients suggests that use of tacrolimus and acute HCV infection significantly increase the rate of collagen generation. The CPA model may evolve with further investigation of mechanisms of collagen generation and degradation and exploration of variations of immunosuppression.

Drug/disease modeling

PD-17 Development of a Population Model to Describe Diurnal and Seasonal Variation in Cilostazol Pharmacokinetics

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Objectives

Diurnal variation, characterized by higher C_{max} and shorter T_{max} after the morning dose in oral b.i.d. treatment, has been reported in many lipophilic drugs.[1,2] In addition, seasonal variation has been recently observed in cilostazol pharmacokinetics (PK) study.[3] The primary aims of this work are to develop a population model to describe such PK variations in cilostazol and its metabolite OPC-13015 and to design an optimal dosing time to reduce drug adverse reaction.

Methods

A total of 1,856 cilostazol plasma concentrations ware obtained from a 2-part PK study recently conducted in healthy Korean subjects, Part A conducted in 26 subjects in February and Part B conducted in 37 subjects in August.[3] A population model was developed using NONMEM7, with diurnal variation modeled using cosine functions incorporated into the absorption rate constant (K_{12}). Seasonal effect was described as a covariate influencing PK parameters. The developed model was validated using visual predictive check (VPC) using 1000 simulated datasets, which was then used as a basis to design an optimal dosing time that minimizes peak-to-trough concentration ratio in cilostazol and OPC-13015.

Results

A two compartment model with first order absorption was selected for cilostazol and proportional residual error was selected for cilostazol and OPC-13015. The final estimated values (RSE%) of K_{12}, K_{23}, K_{32}, K_{20} and central volume (V_2) were 0.239 hr^{-1} (13%), 0.167 hr^{-1} (23%), 0.139 hr^{-1} (14%), 0.216 hr^{-1} (15%), and 55.0 L (14%), respectively. The circadian rhythm was best described by the combination of cosign functions with amplitude and acrophase of 0.299 (20%) and 7.27 hr (5%) for 24 hour period and 0.403 (11%) and 1.59 (21%) for 12 hour period. The seasonal difference was found significant in K_{12} and K_{20} (p<0.001). VPC showed the good performance of the model. The optimal dosing time (morning/evening) showing least peak-to-trough fluctuation in concentrations were 11AM/5PM for winter and 10AM/7PM for summer.

Conclusions

These results show that cilostazol PK in Korean population are influenced not only by diurnal variation but also by seasonable variation and such variations need to be considered in cilostazol treatment. To validate our results, further study with more patients will be necessary.

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Drug/disease modeling

PD-18

Development of an Interaction Model for Co-administratin of Simvastatin and Amlodipine

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Objectives

Simvastatin is often used in combination with amlodipine to treat hypercholesterolemia accompanied by hypertension. Amlodipine is known to inhibit the activity of cytochrome P450 3A4 by which simvastatin is metabolized. Therefore, co-administration of both drugs can increase simvastatin concentrations, thereby raising the risk of adverse drug reaction such as rhabdomyelosis. This study is to develop a population model to describe genetic characteristics in simvastatin pharmacokinetics (PK) and its interaction with amlodipine.

Methods

Plasma samples were obtained from 48 Korean healthy volunteers given a single-dose of simvastain 40mg and a combination-dose of simvastatin 40mg and amlodipine 10mg, each dose given q.d. for 9 days. First, amlodipine concentrations were modelled, and then, simvastatin and simvastatin acid concentrations were modelled together, conditioned on amlodipine parameter estimates. The CYP3A4/5-dependent clearance of simvastatin and simvastatin acid was inversely related to amlodipine concentrations via KI, the inhibition constant denoting the amlodipine concentration yielding 50% of maximum inhibition. Differences in oral bioavailability and baseline clearance between poor (PM) and extended metabolizers (EM) and their proportions were estimated using a mixture model. Inter-occasion variability was also included. The final model was used to find an optimal simvastatin dose minimizing the interaction with amlodipine. All analyses were performed using NONMEM 7.2.

Results

Amlodipine concentrations were best described by a two-compartment model with first-order absorption, and simvastatin and simvastatin acid by a two- and a one-compartment model, respectively. KI was estimated to be 91.9 ng/mL, about 4-fold of observed Cmax of amlodipine. In EM subjects, estimated to be 20% of entire subjects, simvastatin PK were characterized by the increases in bioavailability (5.3-fold), drug clearance (4.7-fold), and metabolite clearance (1.6-fold), as compared to PM group. Simvastatin bioavailability was found to decrease by about half when co-administered with amlodipine. The final model, when evaluated by VPC, well matched with the data. Simvastatin dose of 25mg was found to minimize the influence by amlodipine.

Conclusions

The proposed model can be used to design the optimal dose in the combination therapy of simvastatin and amlodipine. It can also be applied to the case where other CYP3A4/5 substrates are used in combination with simvastatin.

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Drug/disease modeling

PD-19   **Disease Progression Model for Angiotensin II-Angiotensin-(1-7) Counterbalance and Effects of Perindopril in Spontaneously Hypertensive Rats**

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Objectives

To develop mechanism-based disease progression models to characterize the up/down-regulation of angiotensin II/angiotensin-(1-7) (Ang II/Ang-(1-7)), and the effects of perindopril on hypertension progression in spontaneously hypertensive rats (SHR).

Methods

SHR were randomly assigned to the control group (n=6) and treatment group (n=6). Rats in the treatment group received oral perindopril (5 mg · kg-1 · day-1). Systolic blood pressure (SBP) was measured by the tail-cuff method. Serum Ang II and Ang-(1-7) concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Three linked turnover models weredeveloped to describe Ang II, Ang-(1-7) and SBP profiles. All parameters were estimated using nonlinear mixed-effects modeling.

Results

The results showed that Ang II, Ang-(1-7) and SBP gradually increased in the control group. These counterbalance mechanisms were reflected in the models with two feedback cycles. It was assumed that the Ang-(1-7) production rate constant (kin_Ang17) was stimulated by Ang II, and the Ang II output rate constant (kout_Ang2) reflecting Ang II degradation was stimulated by Ang-(1-7). The decrease in Ang II and increase in Ang-(1-7) were observed in rats treated with perindopril.

Conclusions

The models described the counterbalance relationship of Ang II and Ang-(1-7) well, and provided insights into ACE inhibition using perindopril. The models could be extended to incorporate other biomarkers and the effects of various ACE inhibitors (ACEIs).

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Methodology- Algorithms

PM1-1 A Genetic Algorithm Based Global Optimum Search Algorithm for Nonlinear Mixed-effects Models

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Objectives

NONMEM is one of the most popular softwares for the PK/PD analysis for fitting nonlinear mixed-effect models. NONMEM still uses the optimization method of BFGS quasi-Newton algorithm, whose derivatives are computed by finite difference method [1, 2]. The local optimization method such as the Newton and its similar methods usually requires initial parameter values to lie within a relatively small neighborhood of the true optimum in order to ensure any desired accuracy. The sensitivity to the initial value selection in the local optimization algorithm has been documented in the nonlinear mixed-effect model literatures [3].As a local optimization algorithm, NONMEM usually uses an initial value close enough to the global optimum. A global optimization approache is required to search the global optima in nonlinear models.One of the interesting evolution- based global optimization approaches is Genetic Algorithm (GA). GA is very popular due to its simplicity and robust convergence capability of global optimum search [4]. GA is well suited to solve complex optimization problems because it can handle both discrete and continuous variables, and nonlinear objective and constrain functions without gradient information. This paper proposes a global optimum search algorithm called GA-NONMEM. It combines the global search strategy of GA and the local estimation strategy of NONMEM.

Methods

GA-NONMEM is implemented to estimate the global optima for the fixed-effects. Firstly, initial values (genomes) are randomly generated by GA, and NONMEM is implemented for each genome to find a local optimum for fixed effects. GA-NONMEM utilizes NONMEM for calculating the fitness (by object function value from model fitting), and updating the current position with the convergent position of NONMEM for each genome. Then, GA-NONMEM employs GA to search for a global optimum based on every genome's fitness.

Results

In the simulation, GA-NONMEM was insensitive to initial value selection. Even when the initial values are far away from their global optima, GA-NONMEM almost guarantees the global optimization.

Conclusions

GA-NONMEM has improved convergence performance and leads to a global optimization for random effects of NONMEM. Futhermore, GA can be implemented directly to optimize the objective function in NONMEM of nonlinear mixed effects models without any local optimization-based estimation.

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Methodology- Design

PM2-1   # Handling Limit of Quantification Data in Optimal Trial Design

Presented at PAGE 21 (2012-06-08)
*Both first and second authors contributed equally to this work.
Acknowledgement: This work was part of the DDMoRe project.

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Objectives

Methods for including limit of quantification (LOQ) data exist in NLME models [1-3].The aim of this work was to provide new methods of handling LOQs in Optimal Design (OD).

Methods

Seven different methods were implemented in PopED [4]: • D1: Ignore LOQ. • D2: Non-informative Fisher information matrix (FIM) for median response below LOQ (FO) i.e. set the contribution to the FIM to zero if a design point gives a median response below LOQ.•D3: Non-informative FOCE linearized FIM for individual response below LOQ i.e. set the individual contribution to the FIM to zero if a design point gives an individual response below LOQ. • D4: Addition of a homoscedastic variance to account for the LOQ. • D5: Simulation & Rescaling i.e. Scale FIM with the probability of BLQ predicted from simulation. • D6: Integration & Rescaling i.e. Scale FIM with the probability of BLQ calculated from the FO approximated joint density. • D7: Calculation of FIM by integrating over simulated data with a joint likelihood for data above(normal likelihood) and below LOQ (M3 method) using the Laplace approximation.Performance of D1-D7 was assessed using a 1-cmp IV bolus model. Sampling times optimizations using a 2-cmp IV bolus model for 4 LOQs (20, 41, 57, 73% ≤ LOQ) were performed using the fastest methods. Resulting designs were evaluated for bias and precision, robustness and predictability from multiple stochastic simulations and estimations (SSE) in NONMEM using the M3 method [1-2].

Results

Evaluated determinants of the FIM for all methods, except D1 and D4, were in good agreement with SSE-derived covariance. Methods D3 and D7 were impractical for optimization due to long FIM calculation times. In optimization, D6 provided the most accurate and precise parameter estimates and expected prediction intervals matching with the empirical predictions from the true model under the M3 method. Methods D1 and D2 resulted in the least robust designs for estimation. Method D4 was shown to be insensitive to LOQ levels.

Conclusions

The use of OD methods anticipating BLQ data in planned designs allows better parameter estimations. For the scenarios investigated, method D6 showed the best compromise in terms of speed and accuracy.

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Methodology- Design

PM2-2   # Simulation-Based Design in Population Pharmacokinetics and Pharmacodynamics

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Objectives

The study design of sample size and observation period is important to reduce a patient's burden. Recently, disease progression is the target of pharmacometrics modeling, and some examples were publicated in non-small-cell lung cancer (NSCLC) ([1]Wang et al., Clin. Pharmacol. Ther. 2009, 86:167-). The aim of this study is to utilize the disease model to calculate the sample size from the aspect of parameter estimate and statistical power.

Methods

The design was simulation-based. At first, percentage tumor reduction, and interindividual variability were varied for simulation in the tumor size model. The several scenarios for sample size, observation time and drop-out rate were investigated by using NSCLC tumor size model, and the accuracy and precision of parameter and predictability of tumor size at 8 weeks were assessed. At second, for each scenario, overall survival was simulated and the power was calculated for a Log-rank test. The simulation and estimation were conducted using NONMEM 7.2 and SAS.

Results

The success rates of simulated clinical trials were investigated by using the disease model. For the overall survival evaluation, the result is influenced by the patient population, sample size, observation period, and drop-out. Although it is possible to design by using disease model, the simulation setting and results should be interpreted with cautious. Actually, the trials that were already investigated were not always according to simulated results.

Conclusions

Simulation-based design was useful for optimization of sample size. The appropriate performance indicator should be selected for this design. However, some actual trials were not consistent with simulation. The model was supposed to need the improvement for each treatment.

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Methodology- Design

PM2-3   # Bioequivalence Evaluation with Sparse Pharmacokinetic Data Using Mixed-Effects Modeling

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Objectives

We can evaluate the impact of specific population pharmacokinetic design choices (variable sampling point, variable sampling time, andvariable sample size, etc.) on the bias and precision of PK parameter estimates. From this modeling result, we can offer helpful direction in designing BE studies for cytotoxic agents. The purpose of this study is to find out the optimal study design with least blood sampling point and least sample size for BE study with cytotoxic agent.

Methods

In order to simulate PK parameters, a hypothetical drug is given orally to 100 subjects. Samples in each simulation experiment are varied with 1-point incrementfrom 1 point to 3 points. All simulations are done using the standard one-, two-, and three-compartment open model according to the drug characteristics. The parameter values for the "true" one-, two-, and three-compartment models are obtained from previous clinical trial data or published data. The simulated concentration-time profiles are employed to estimate the model parameters using either the "true" (identical to the simulation model) or an alternate model. In all of the scenarios investigated, the data are fitted using two estimation methods: first order and first-order conditional estimation with interaction between the between-subject and residual errors.The bias and precision of the estimated model parameters are expressed as the mean relative prediction error and mean relative absolute error, respectively. The bias and precision of the parameter estimates are determined separately for the subjects with dense and sparse data. With these obtained PK parameters, we simulate a parallel-design BE study. The formulations are considered bioequivalent if the 90% confidence intervals of the geometric mean ratios of test to reference formulations for AUC and Cmax are within the BE limits of 0.8–1.25. Then, we calculate the optimal sample size for the simulated BE study. Finally, we evaluate individual least sampling points and sampling time which could estimate a similar with original PK parameters (AUC and Cmax) of a drug. Our experiments would suggest that how sparse sampling point and sample size design would be the optimal parallel design for assessing the bioequivalence of certain cytotoxic drugs.

Methodology- Design

PM2-4

Prediction of Precision of Individual Parameter Estimates and of Shrinkage via the Bayesian Fisher Information Matrix in Non-linear Mixed-effects Models with Application in Pharmacokinetics

Presented at PAGE, 5-8th June 2012, Venice

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Objectives

In population pharmacokinetics (PK), precision of population parameter estimates depends on design and are evaluated using Fisher information matrix [1]. Individual parameters are usually estimated by the Maximum A Posteriori (MAP) and precision of individual estimates can be evaluated using the Bayesian Fisher information Matrix (BMF) [2]. Shrinkage of individual parameters towards the mean occurs when information is sparse and can be quantified as a reduction of variance of the estimated Random Effects (RE) [3]. This study aims at 1) exploring the relationship between BMF and shrinkage in order to propose a prediction of shrinkage and 2) evaluating by simulation the prediction of individual parameter precision and shrinkage.

Methods

We first derived the BMF for additive RE and constant residual error and then extended it for exponential RE and combined residual error. From the formula of shrinkage in linear mixed effects models, we derived the predicted shrinkage (W) from BMF. Regarding the evaluation by simulation, we simulated data from sparse and rich design for two PK examples: a simple one (one compartment) with six different scenarios (additive or exponential RE, with low and high variabilities, additive or combined residual error); a more complex example derived from a real case study [4] (two compartment, linear and non-linear elimination). We used NONMEM7.2 and MONOLIX4.0 to perform individual estimation via MAP assumingknown population parameters. We also recorded individual standard errors (SE). We then compared predicted and estimated SE as well as the predicted and estimated shrinkage, evaluated using the formula with ratio of variances.

Results

For the simple example, considering all scenarios and designs, predicted SE of the two parameters using BMF were close to the estimated SE with both software and varied as expected with the richness of the design and the variabilities. There were also a very good agreement between estimated (which varies from 0 to 70%) and predicted shrinkage. Similar results were observed for the real example.

Conclusions

The Bayesian Information Matrix allows to evaluate impact of design on precision of individual parameters and to predict shrinkage. This can be used for design optimization and will be implemented in PFIM.

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Methodology- Estimation methods

PM3-1

Evolving Population Pharmacokinetic Models with Gene Expression Programming

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Objectives

A population pharmacokinetic (PPK) model is one of empirical models that are derived from observation or experiment. Due to the lack of generalized formulated equations, it is labor intensive for modelers to develop PPK models. The use of machine learning techniques such as genetic algorithm is a promising approach to automatically develop models, as have been applied to quantitative structure-activity modeling.[1] It has been reported that genetic algorithm is available to select structural, inter-individual random effects, covariate effects and residual error models in nonlinear mixed-effect models.[2] Covariate modeling is the most difficult in PPK analysis, because not only selection of covariates but formulation of equation must be done. Recently, we proposed the use of gene expression programming for automatically building an equation and optimizing their parameters, as exemplified with in vitro-in vivo correlation of drug formulations.[3] The present study aimed to develop a fully automatic PPK modeling system, including selection of covariates, formulation of the model, and parameter optimization, by using gene expression programming.

Methods

Covariate model equations for each pharmacokinetic parameter were expressed as a genetic code, where genetic elements include operators, functions, parameters, and variables (e.g., "+v*pEt" can be translated to "v+p*exp(t)"and vice versa, according to a predefined rule). In an optimization process, a computer (1) generates a population of individual models, (2) translates their genetic code to the corresponding mathematical covariate model, (3) optimizes their parameters to evaluate an OBJ value, (4) selects a pair of individuals and recombines with each other, (5) mutates the recombinants, (6) repeats the 3rd and 4th processes until reaching a predetermined population number, and (7) goes back to the 2nd process.

Results

A program source code for the system was written in JAVA. Performance of the evolutionary modeling technique was tested using data sets available from public domains.

Conclusions

The program software would be a powerful tool for preliminary PPK modeling.

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PM4-1 Importance of Peptide Transporter 2 on the Cerebrospinal Fluid Efflux Kinetics of Glycylsarcosine in Wild-type and PEPT2 Knockout Mice

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Objectives

To develop a population pharmacokinetic model to quantitate the distribution kinetics of Glycylsarcosine (GlySar), a substrate of peptide transporter 2 (PEPT2), in blood, CSF and kidney in wild-type and PEPT2 knockout mice.

Methods

PEPT2 transporters are expressed at the blood-cerebrospinal fluid (CSF) barrier in brain pumping out drug molecules from CSF to blood, and also play an important role in the reabsorption process in the kidney. In this study, Glycylsarcosine (GlySar) was used as a model compound of PEPT2 substrate and the pharmacokinetics (PK) of GlySar in PEPT2+/+ and PEPT2-/- mice were compared. The concentration profiles of GlySar in blood, CSF, and kidney were modeled simultaneously using nonlinear mixed-effects modeling (NONMEM) and the final model was selected based on the likelihood ratio test and graphical goodness-of-fit.

Results

GlySar concentrations in the blood and kidney tissue were lower in the knockout compared to the wild-type mice, whereas CSF concentrations were higher in the knockout mice. The PK profiles of GlySar in blood, CSF, and kidney were best described by a four-compartment model with measurement of systemic elimination clearance (CL), volume of distribution of the central and peripheral compartments (V1 and V2), the active efflux CL in brain by transporters, and the volume of distribution of CSF and kidney. The estimated systemic CL, V1 and V2 are 0.239 vs 0.447 ml/min, 3.79 vs 4.75 ml, and 5.75 vs 9.18 ml for wild-type versus knockout mice. Total CSF efflux clearance (CL) was 4.3 fold higher for wild-type compared to knockout mice. NONMEM parameter estimates indicate that 77% of efflux CL is mediated by active CL of PEPT2 and the rest 23% is mediated by diffusional CL and bulk CL.

Conclusions

Due to the availability of PEPT2 knockout transgenic mice, we were able to quantitatively determine the significance of PEPT2 in the efflux kinetics of PEPT2 substrate at the blood-cerebrospinal fluid barrier (BCSFB). Our findings suggest that given the relevant transporter expression level, it may be feasible to quantitatively predict the transfer kinetics of CNS drugs at BCSFB and to adjust the dose based on this quantitative prediction approach.

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Methodology- Modeling approaches

PM4-2

Dissecting the Underlying Pharmacokinetic Drivers of Antitumor Activity Using Mathematical Modeling

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Objectives

Translating pharmacological information from the preclinical to clinical setting represents a fundamental challenge in Oncology drug development. The identification of the fundamental pharmacokinetic (PK) parameters (e.g. AUC, Cmax or time above threshold (t>T)) driving antitumor efficacy greatly facilitates the translation of optimal schedule. For numerous anticancer drugs in our pipeline, xenograft dose-fractionation studies have pointed to AUC-proportional, schedule-independent antitumor efficacy. We thus examine whether this is supported from a first-principles standpoint.

Methods

In this work, we derive the relationship between fundamental properties of a dose-response curve (such as the Hill slope,gamma, and the concentration of half-maximal drug effect, IC50), simple PK descriptors (including drug half-life, t1/2) and optimal dose density. Using the derived analytical equations, we simulate the optimal dosing schedule for a given total dose or exposure, relative to drug half-life and achieved drug concentration (stated as a multiple of the IC50)

Results

For PK/E relationships captured by an Emax model (gamma =1) , we demonstrate that the inherently concave Emax concentration-response curve predicts

frequent dose schedules as optimal. When gamma>1, the sigmoidal dose response curve is convex for low doses, and gradually transitions into a concave profile for concentrations above IC50. When the achieved concentration is in the convex region of the dose-response curve, less frequent dose schedules are predicted tobe optimal, whereas in the concave region frequent dosing is optimal. For drugs with a linear PK/E relationship, we predict schedule-independent efficacy. These fundamental relationships are not dependent on drug half life, when the exposure (AUC) is matched across different schedules for the duration of the experiment. We then relate our findings back to the observed relationships for Oncology compounds with well-characterized PK/Efficacy relationships in vivo (all with AUC-proportional efficacy), findingno schedule-dependent difference in efficacy for these compounds as they tend to follow a linear PK/E relationship. The narrow therapeutic windows of most Oncology compounds lead to a linear PK/E relationship as high concentrations are unattainable due to toxicity.

Conclusions

This work thus provides a fundamental explanation of schedule-independent efficacy typically observed preclinically for Oncology drugs, and provides a rational basis for preclinical-to-clinical translation of optimal clinical schedule.

Methodology- Modeling approaches

PM4-3 Mixed-Effect Circadian Rhythm Model for Human Erythrocyte Acetylcholinesterase Activity – Application to the Proof of Concept of Cholinesterase Inhibition by Natural products

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Objectives

This study was to develop a non-linear mixed effect circadian rhythm model of acetylcholinesterase (AChE) activityvariation and to evaluate the inhibitory effect of natural products in comparison to that of a positive control (16 mg galantamine) on human AChE in red blood cells (RBC).

Methods

A series of clinical studies to evaluate the AChE inhibition of natural products including acorn extract and Hericium erinaceus (Lion's Mane Mushroom) extract was conducted. Both of the studies employed 3-way crossover design where no treatment, natural product and galantamine were alternatively given to more than 12 subjects. RBC AChE activity was measured using peripheral blood samples serially taken up to 24 h after dosing with 1-2 h intervals. Non-linear mixed effect modeling was performed using NONMEM (Ver. 7.2).

Results

The circadian variation of AChE activity was bestdescribed using 2 mixed effect cosine functions, with periods of 24 h and 12 h, respectively. The amplitude of fluctuation was estimated as 5.86% for the 24 h component and 1.20% for the 12 h component. When the inhibitory effect terms were added, the model was significantly improved for both of acorn extract and galantamine. With regard to the effect, 2 g single dose of acorn extract showed AChE inhibition (about 5%) similar to that of 16 mg single dose of galantamine, in the first 24 h after administration.However, Hericium erinaceus did not show meaningful inhibition to the AChE activity.

Conclusions

Because both the inter-day and intra-day variation of AChE activity in RBC were quite pronounced, we concluded that the model-based approach was essential for the proof of concept for the AChE inhibition in healthy subjects.

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Methodology- Modeling approaches

PM4-4

A Full Random Effects Model for Characterising Covariate Relations

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Objectives

To further characterise the properties of this approach using real and simulated data and suggest strategies for its use.

Methods

A full random effects model (FREM) for characterising parameter-covariate effects has recently been presented [1]. In this approach covariates are entered into the data set as observed variables, and their distribution are modelled as random effects. A full covariance matrix between random effects for parameters and covariates is estimated together with the other model components.The full random effects model was implemented for a range of data sets and models. The number of covariates introduced was varied within data sets. Comparisons with the full fixed effect model (FFEM) approach [2] were made. The approach was expanded to include time-varying covariates and illustrations of methods for making predictions, simulations and interpretations were made.

Results

The FREM was successfully implemented for a range of models. Although a model where all parameters-covariate relations are simultaneously estimated is the main strategy, more selective characterisations of parameter-covariate relations could be implemented. Relations between parameters and time-varying covariates could be successfully implemented by relating the change in covariate values with interoccasion variability components for the parameters. The precision in covariate-parameter relations of the FREM was as good or superior to the FFEM. Correlation between covariates did not impact on the precision of estimated parameter-covariate relations. Predictions from the FREM could be obtained both from the full set of covariates or and subset of these. Simulations could be achieved using either a predetermined set of covariate vectors or a random sampling of covariate vectors from the FREM. A conditional covariance matrix was implemented to investigate the explanatory value of any subset of covariates.

Conclusions

The FREM shows advantages in characterizing covariate relations and standard uses of covariates models can be achieved.

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Methodology- Modeling approaches

PM4-5

Multiple Imputation of Missing Covariates in NONMEM and Evaluation of Its Sensitivity to η-shrinkage

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Objectives

Multiple imputation (MI) is an approach widely used in statistical analysis of incomplete data. However, its application to missing data problems in nonlinear mixed-effects models is limited. A MI method is suggested for handling missing covariate data where the imputations are based on individual estimates [1]. The objective was to implement a MI method for handling missing covariate data in NONMEM and to evaluate the method's sensitivity to η-shrinkage.

Methods

The MI method was implemented in NONMEM and automated using PsN. Three NONMEM models were needed; a base model without the partly missing covariate, a regression model and an imputation model. Empirical Bayes estimates (EBEs) of the parameter are obtained for all individuals from the base model. These estimates are used in the regression model to describe the likelihood of the covariate values given the EBEs. The parameters in the regression model are estimated using data records where the covariate is observed. In the imputation model the missing covariate is imputed, using the regression model and the EBEs, and the imputed dataset is analysed. The imputation followed by estimation is repeated and the analyst can choose number of imputations. The method's sensitivity to shrinkage in EBEs was evaluated in a simulation study. Data was generated for 200

individuals with a 20% difference in clearance between males and females. Sex was made missing at random for 50% of the individuals. The η-shrinkage was increased in steps from <10% to approximately 65%. 200 datasets were simulated and analysed for each scenario. For comparison purposes estimations with all data was also carried out.

Results

When shrinkage was low the MI method gave unbiased and precise estimates of all population parameters. With increased shrinkage the estimates became less precise but remained unbiased. At the highest shrinkage level the covariate was found significant in less than 50% of the simulated datasets. All results obtained with the MI method were similar to those received when no data was missing.

Conclusions

The MI method was successfully implemented in NONMEM. Despite the use of EBEs in the imputations the method gave unbiased parameter estimates even when shrinkage was high.

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Methodology- Modeling approaches

PM4-6

Necessity of Reducing Complexity of Model for Inter-Occasional Variability

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Objectives

It has been well investigated the harm of ignoring inter-occasional variability (IOV) in terms of obtaining biased parameter estimates in population analysis 1). Incorporating IOV is getting a standard procedure of population model building. Usually IOV is modeled by added to inter-individual variability (IIV) in parameter(s) as the same level of random effect in NONMEM 1). Therefore there is a potential of un-distinguishable issue between IOV and IIV. It is suggested by the fact that individual sum of post-hoc IOV is always almost completely correlate with post-hoc IIV under any conditions. In the presentation, potential cases where the un-distinguishable issue actually derives biased estimates leading a false conclusion as well as possible turnaround modeling to avoid the false conclusion is discussed.

Methods

A simulation and estimation approach was utilized to evaluate effect of model for IOV under various conditions. A one compartment model with first-order absorption was used to simulate individual concentrations with assuming different magnitudes of IOV and IIV in bioavailability (F). The simulated data were analyzed by various models with different simplifications. The performance was evaluated by bias in parameter estimates especially magnitude of IOV.

Results

IOV was fairly well estimated by true model analyses. However, some simplifications, e.g. ignoring IIV on F but not IOV, caused positively biased IOV with significant improvement of OFV regardless of magnitude of IOV used in the data simulation. Models with reducing parameters from the typical model for IOV provided better results with regard to IOV.

Conclusions

It was demonstrated that there is a possibility that usual model for IOV could lead false positive conclusion on existing of IOV. Unless dense profiling data for each occasion are available, which would be realistic in the clinical setting, reducing complexity in IOV model should be considered case by case.

References

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Methodology- Modeling approaches

PM4-7
Discrimination of Hepatic and Intestinal Contributions to Drug-Drug Interaction Mediated by Inhibition of CYP3A4
(Presented at 26th JSSX annual meeting, Hiroshima, Japan, Nov, 2011)

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Objectives
It is recognized that the intestinal metabolism by CYP3A4 contributes significantly in lowering oral bioavailability of many drugs, and hence inhibition of the intestinal metabolism often causes serious drug-drug interactions (DDIs). However, there was a lack of reliable and quantitative method for evaluation of its contribution. The purpose of this study is to develop a method to quantitate the contribution of intestinal metabolism, discriminating from the hepatic one, in various DDIs occurred between a series of inhibitor and substrate drugs of CYP3A4.

Methods
Previously, we successfully predicted degree of various DDIs with two parameters, CR (contribution ratio for a substrate) and IR (inhibition ratio) (ref 1). And we also evaluated Fg (intestinal availability) in some DDI situations assuming complete inhibition of the intestinal metabolism (ref 2). In this study, a theory was constructed in which a degree of DDI is explained with four parameters, CRh (hepatic CR), IRh (hepatic IR), Eg (extraction by GI tracts, i.e. 1-Fg) and IRg (IR in GI tracts) by extending previous studies. These parameters were sequentially obtained from changes in the AUC and plasma half-life associated with DDI which were reported in the literature.

Results
The present analysis revealed that the intestinal metabolism contributes greatly to some DDI situations. However, overall accuracy of the prediction was improved only moderately by considering the intestinal contribution separately, since the previous CR-IR method implicitly accounts also for the intestinal metabolism. An advantage of the present method is that both changes in AUC and plasma half-life are predictable.

Conclusions
The present method was proposed as a robust technique to evaluate contribution of intestinal metabolism in various DDIs mediated by inhibition of CYP3A4.

References
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Methodology- Modeling approaches

PM4-8 **Modeling Hepatitis C Viral Kinetics to Compare Antiviral Potencies of Two Protease Inhibitors: A Simulation Study under Real Conditions of Use**
Presented at PAGE meeting, June 2012, Venice, Italy.

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Objectives

2011 has marked a milestone in HCV therapy with the approval of two protease inhibitors (PI), telaprevir (TVR) and boceprevir (BOC), inaddition to current treatment. However the antiviral potency of BOC has never been estimated. Ongoing MODCUPIC-ANRS trial will provide for the first time a description of viral kinetics under tritherapy in real conditions of use. Objectives were to evaluate the estimation performance for the chosen MODCUPIC's design and the power to detect a difference of potency between both PIs using an HCV dynamic model.

Methods

Neumann's[1] biphasic viral kinetics model considers initial viral load (VL), free virion and infected cells clearance rate (c and δ), and antiviral potencies (ε which is the percentage of blockage of virion production. Values of parameters and their inter-individual variations were those proposed by Guedj et al[2]. We assumed ε^{TVR}=99.9% and ε^{BOC}=99%, 99.5% or 99.8%. We simulated 500 datasets using MODCUPIC's design as reference (N=30 patients per PI and VL measurements at 0, 0.33, 1, 2, 3, 7, 14 days) and we varied number of patients and VL measurements. Nonlinear mixed-effects models (NLMEM) were used to estimate parameters using SAEM algorithm in MONOLIX v4.1 taking into account below limit of detection data[3,4]. We performed Wald tests (with empirical threshold correction) and Wilcoxon tests to detect a difference between PIs.

Results

With MODCUPIC's design, all parameters were well estimated with relative bias <5% for fixed effects and relative RMSE was <8% for fixed effects and <35% for variances. Power to detect a difference between PIs were 100%, 100% and 94% with ε^{BOC}=99%, 99.5% and 99.8% respectively with corrected Wald test and 67%, 31% and 7% respectively with Wilcoxon test. With corrected Wald test these powers remained high without VL at 0.33 and 1d (100%, 100%, 83%, respectively) or when N=10 per PI (100%, 98%, 44%, respectively).

Conclusions

The use of viral dynamic modeling approaches along with NLMEM validates MODCUPIC's design to estimate parameters and to compare the antiviral potencies between both PIs, even with sparse initial sampling or small number of patients. Compared with standard approach (Wilcoxon test), modeling approach (Wald test) provides a more powerful tool.

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PM4-9 Application of the Target-Mediated Drug Disposition Approach within a Minimal PBPK Model to Investigate Pharmacokinetics of Therapeutic Proteins

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Objectives

We demonstrate how an equivalent dynamic representation to the target mediated drug disposition (TMDD) model proposed by Mager and Jusko [1] can be achieved through 'embedding' the TMDD model within the systemic compartment of the minimal-PBPK model with single adjusting compartment (SAC) employed in the Simcyp simulator [2].

Methods

The TMDD model was 'embedded' into the systemic compartment of the minimal-PBPK model by coupling the drug concentration within that compartment with the input concentration into the TMDD model. The TMDD and minimal-PBPK models were parameterized with data obtained for therapeutic proteins AMG317 (human monoclonal antibody) from [3] and Erythropoetin (glycoprotein hormone) from [4]. Profiles of free drug, drug-target complex and free target concentrations in plasma versus time were generated for each drug.

Results

A comparison of the PK profiles generated by the minimal-PBPK with embedded TMDD model with those of the separate TMDD model confirmed that both representations are equivalent. The plasma concentration profiles gave good matches to the published clinical data for AMG317 for doses ranging from 10 to 1000 mg (clearance rate 0.035 L/hour) and for Erythropoetin for doses ranging from 0.0625 to 3.125 microg/kg (elimination rate constant 0.0949 per hour). The linkage established between these representations implies the minimal-PBPK model within the Simcyp simulator can be directly utilized to facilitate the study of TMDD in therapeutic proteins.

Conclusions

This study demonstrates that the minimal-PBPK model with SAC as used within the Simcyp simulator can be parameterized for therapeutic proteins to be dynamically equivalent to the TMDD model of Mager and Jusko (2001) [1]. Hence the minimal-PBPK model within the Simcyp simulator can be employed to explore the influence of key TMDD parameters such as kpt and ktp (which are typically unmeasurable but correspond to SAC parameters kin and kout) defining flows into and out of tissue and which may impact upon targeted mediated drug disposition. The systems approach adopted here will enable semi-mechanistic modelling of many therapeutic proteins.

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Methodology- Modeling approaches

PM4-10 Population Pharmacokinetic Analysis to Assess the Effect of Fasting Status on Absorption Characteristics of Pregabalin in Healthy Male Subjects

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Objectives

Pregabalin is an anticonvulsant used for the treatment of neuropathic pain and partial seizures in adults. The aim of thisstudy was to develop a population pharmacokinetic (PK) model to adequately describe the absorption characteristics of pregabalin according to fasting status.

Methods

Data from three phase I clinical trials with single or multiple oral dose of 150mg pregabalin (n=46) were used for this analysis. Pregabalin was administered twice daily, without meal or 30 min after meal in the morning and 30 min or 4 h after the meal in the evening. Serial plasma samples were collected up to 36 h after the last dose for PK analysis. Non-linear mixed effect modeling was performed using NONMEM (ver.7.2).

Results

A two-compartment model with first-order absorption with lag time provided the best fit to a total 835 concentrations of pregabalin. K_a(absorption rate constant) changed by the length of fasting time (10.2 h^{-1} after overnight fasting, 0.663 h^{-1} for 4 h after meal and 0.479 h^{-1} for 30 min after meal). When bioavailability (F) of overnight fasted status were regarded as 100%, the relative F estimates of 30 min and 4 hafter meal were 95.2% and 109%, respectively.

Conclusions

We modeled the changes in the rate and extent of pregabalin absorption by meal time using mixed-effect analysis. The after-meal change in the extent of absorption (F) estimated herein fell within the variability range indicated in the label.

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Methodology- Modeling approaches

PM4-11   Evaluation of Effect of Zoletil® (Tiletamine-Zolazepam) on Pharmacokinetics of Paeoniflorin in Rats after Multiple Administration of SsangHwaTang Using ADAPT II and Monte Carlo Simulation

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Objectives

Zoletil®(tiletamine-zolazepam) is a dissociative anesthetic-tranquilizer, and is used to anesthetize laboratory animals. The purpose of this study is to identify the effect of Zoletil®on pharmacokinetics of paeoniflorin in rats after multiple administration of SsangHwaTang.

Methods

1 g/kg of SHT-autoclaved (SsangHwaTang after autoclaved) and SHT164 (fermentation by Lactobacillus fermentum with SHT-autoclaved) were administered to male Sprague-Dawley rats orally 10 times every 8 hours, and blood samples were collected at 25, 35, and 56 hr. After administration of Zoletil®, blood samples were collected at 72, 73, and 74.5 hr, and the concentration of paeoniflorin in these samples was measured using LC-MS/MS. Modeling was conducted with ADAPT II using one-compartment with 1st absorption model, and Monte Carlo simulation of 1,000 subjects was performed.

Results

In SHT-autoclaved group, there is no difference between before and after administration of Zoletil®. In SHT164 group, after administration of Zoletil®, Ke was decreased from 1.09 ± 0.18 to 0.51 ± 0.36 and Ka was increased from 1.09 ± 0.18 to 10.21 ± 0.60 significantly ($p<0.001$).

Conclusions

Tiletamine-zolazepam may affect absorption rate of drugs based on the result of other study where they have an effect on elevating mean arterial blood pressure, so it should be considered when using anesthetic.

Methodology- Modeling approaches

PM4-12

Pharmacokinetic Comparison of 2 Formulations of Anastrozole (1 mg) in Healthy Korean Male Volunteers

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Objectives

Anastrozole is an aromatase inhibitor used to treat advanced breast cancer in postmenopausal women. A generic 1-mg tablet of anastrozole was recently developed. We evaluated the comparative bioavailability of the test and reference formulations in healthy male adult volunteers.

Methods

This single-dose, randomized, double-blind, 2-way crossover trial was conducted in the Clinical Trial Center at the Asan Medical Center (Seoul, Korea). A total of 24 healthy male Korean volunteers were enrolled. Subjects were randomized to receive 1 mg of the test or reference formulation, and pharmacokinetic (PK) parameters were measured. After a 3-week washout period, the other formulation was administered, and PK parameters were measured again. Cmax and AUClast were determined from blood samples obtained at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, and 216 hours after drug administration. The formulations were considered bioequivalent if the 90% CIs of the geometric mean ratios of test-to-reference formulations for AUClast and Cmax were within the bioequivalence limits of 0.8–1.25. Nonlinear mixed-effectmodeling and Monte Carlo simulations for both formulations were also conducted, and the results were used to characterize and compare the PK properties.

Results

Both formulations were best described by a 2-compartment disposition model with lag phase. The 90% CIs of the geometric mean ratios of test formulation to reference formulation were 0.96–1.08 for Cmax and 0.93–1.0 for AUClast. The visual predictive check plot (95% prediction interval for the plasma concentration-time profile using the PK model of the reference drug) showed that the PK model for the reference formulation reliably predicted the actual plasma concentrations of the test formulation, which suggests the similarity of the PK properties between the 2 formulations. The Monte Carlo simulation yielded very similar concentration profiles for the 2 formulations in the therapeutic dosing regimen (90% prediction interval for the plasma concentration-time profile using the PK model of the reference drug).

Conclusions

The test and reference formulations had similar PK parameters and similar plasma concentration-time profiles. The test formulation of anastrozole met the Korean regulatory criteria (AUC and Cmax) for assuming bioequivalence.

References

This abstract was presented in the PAGE 2012 meeting on the date of 6 June 2012.

Methodology- Modeling approaches

PM4-13

Representing Eliminating Organs In Physiological Pharmacokinetic Models

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Objectives

Physiologically based pharmacokinetic (PBPK) models in the literature show differences in methods for coding eliminating organs with regard to the concentration that is linked to the clearance term. The clearance term can be linked to either the arterial drug concentration (Cart), the organ venous drug concentration (Cven) or the tissue drug concentration (Ctis). We examined each of these alternatives for a match between the organ clearance of a drug [the product of organ blood flow (Q) and drug extraction ratio (E)] and the systemic clearance of the drug (as determined from AUC). Extraction ratio must be calculated correctly if the venous concentrations merging from the organ (and hence returning to the systemic circulation) are in turn calculated correctly.

Methods

Algebraic steady-state solutions for models with one compartment elimination kinetics and venous equilibrium were solved for cases where clearance was linked to Cart, Cven or Ctis. The algebraic calculations were confirmed by simulation. The simulations were also used to estimate the approximate magnitude of the error that could be expected by mis-specifying the equation for an eliminating organ. Equations for correcting errors in CL from model mis-specification were derived.

Results

A clearance term linked to Cart was the only one of the three alternatives that produced a match between the organ clearance of a drug and the systemic drug clearance. By simulation, when the arterial concentrations were a square wave input of 1 mg/L into an organ with CL of 1 L/min and Q of 2 L/min, clearance linked to Cart gave the correct steady-state extraction ratio of 0.5 (CL/Q = 1/2). For a Cven link the extraction ratio was 66% of the correct value, while for a Ctis link the extraction ratio was 120% of the correct value.

Conclusions

A clearance term linked to arterial concentration in an eliminating organ is the only one of the three alternatives that produceda match between the organ clearance of a drug and the systemic clearance of the drug. Algebraic equations can be used for correcting CL values in the alternative situations provided the blood flow can be estimated.

Methodology- Modeling approaches

PM4-14 **Population Pharmacokinetics of Oral Sumatriptan in Healthy Korean Adults: Application to the Formulation Comparison**
This abstract was presented at Population Approach Group Europe meeting, 5-8 June, 2012.

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Objectives

Sumatriptan is a selective agonist at vascular 5-hydroxytryptamin (5-HT) 1B/1D receptor subtype, which has proved to be effective and safe for the treatment of migraine attacks. It frequently displays a particular absorption profile with multiple peaks of plasma concentration. Few reports on the pharmacokinetics (PK) properties of sumatriptan in Korean population have been identified. In this study, wesought to develop a population PK model for sumatriptan in healthy Korean male subjects and to compare the PK characteristics to those in other populations. In addition, we applied the methodology to the comparison of two different oral formulations (which were bioequivalent) to investigate whether both formulations show identical PK profile.

Methods

A randomized, two-period, crossover bioequivalence study was performed in 26 healthy Korean male subjects. All subjects were received either the test or reference formulation as a single 50-mg oral dose of sumatriptan succinate with a 1-week washout period. Blood samples were collected at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after dosing. Plasma sumatriptan concentrations were analyzed using UPLC/MS/MS. A population PK analysis was performed using plasma concentration data from both formulations through NONMEM (Ver. 7.2).

Results

A one-compartment disposition model described the best fit to a total of 676 concentrations. The best structure of PK model explaining the time-concentration profile was identical in both oral sumatriptan formulations. Because absorption kinetics patterns showed double peak, parallel first-order absorption was chosen and transit compartment model were recruited for the rapid absorption pathway before the first peak plasma concentration. There were no significant covariates affecting PK parameters. The final structural model was validated through the visual predictive check (VPC) and bootstrap with no serious model misspecification.

Conclusions

A population PK model was developed and reasonable parameters were obtained from the data of healthy Korean male subjects.

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Methodology- Modeling approaches

PM4-15 — Early Exploration of Optimal Dosing Regimens of a D2 Antagonist via Modeling and Simulation Analysis in a D2 Receptor Occupancy Study

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Objectives

Dopamine (D2) receptor blockade is the main mechanism of action of many antipsychotic agents. This study evaluated the potential usage of D2 receptor occupancy (D2RO) measured by positron emission tomography (PET) using [18F]fallypride, together with modeling and simulation methodology in early clinical stage of antipsychotic agent development.

Methods

In this randomized, parallel group study, eight healthy male volunteers received an oral doses of 0.5 (n=3), 1 (n=2), or 3 mg (n=3) of haloperidol once daily for 7 days. PET's were scanned prior to haloperidol, and on days 8, 12, with serial pharmacokinetic sampling on day 7. Pharmacokinetics and binding potential (BP) to D2 receptor in putamen and caudate nucleus by time on haloperidol were analyzed, and Monte-Carlo simulation for the profiles of D2RO by time on various dosing regimens of haloperidol was conducted using NONMEM in order to find the optimal dosing regimens.

Results

One-compartment model with a saturable binding compartment, and inhibitory Emax model in the effect compartment were the best pharmacokinetic and pharmacodynamics model. The plasma haloperidol concentrations at half-maximal inhibition were 0.791 and 0.650 ng/ml, in putamen and caudate nucleus, respectively. Simulation clearly showed the relationship between D2RO and dose, and suggested the optimal therapeutic dosing regimen successfully.

Conclusions

This study demonstrated that the relatively sparse D2RO measurements after multiple administrations of D2 antagonist in steady state pharmacodynamic study design could provide the information on the possible treatment effect, and also could recommend the optimal dosing regimens for later clinical studies by modeling and simulation analysis.

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Methodology- Modeling approaches

PM4-16

A Frequency-Domain Based Analysis Linking Schedule and Toxicity of Anticancer Therapeutics

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Objectives

Neutropenia is a common side effect of cytotoxic and targeted antineoplastic agents, as neutrophils are derived from a rapidly dividing, drug-sensitive progenitor pool. Since neutropenia is also a reflection of drug effect and pharmacologic activity in the peripheral compartment, mathematical modeling of neutropenia has been useful for simulating anticancer schedules in the clinic, and can capture the time course of treatment as well as the variability observed in the population.

Methods

Several well-characterized mathematical models exist to describe the kinetics of neutropenia in the clinical setting. Here, we utilize these models to develop a fundamental, first-principles understanding of the the relationship between dose schedule and neutropenia, framed in terms of pharmacokinetic (PK) parameters such as Area Under the Curve (AUC) or peak plasma concentration (Cmax). We simulate the effect of treatment schedules with different dosing frequency on absolute neutrophil count (ANC) in a population for a variety of drugs. While each cytotoxic agent induces different degrees of neutropenia, the underlying dynamics of stem cell differentiation provide a common set of principles for the prediction of neutropenia.

Results

We find that for equal dosing density, short bursts of high doses induce a nadir that is lower than constant low levels of dosing. The same relationship is found to hold for the probability of inducing grade 4 neutropenia, with short bursts of high doses being more effective at inducing neutropenia. While this finding runs counter to the conventional view of widely spaced high doses for minimization of neutropenia, clinical evidence to support this view can be found in the published literature with several antineoplastic agents. Based on first-principles, we derive PK measures that correlate with the induction of neutropenia, and demonstrate a strong relationship with neutropenia across a range of treatment schedules.

Conclusions

The results presented here represent a first attempt at deriving a fundamental understanding of the underlying pharmacokinetic drivers of neutropenia, and provide insights that can be leveraged in a translational setting in schedule selection. This novel approach is applicable to any toxicologic endpoint allowing one to link schedule and pharmacological effect of anticancer therapeutics.

Methodology- Modeling approaches

PM4-17 A Semi-mechanistic Integrated Glucose-Insulin-Glucagon Model to Assess Glycemic Response following Meals in Subjects with Type 2 Diabetes (T2DM)

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Objectives
Semi-mechanistic modeling includes selected physiological processes in an attempt to reduce complexity and yet preserve the informative and predictive ability of the model [1]. A previously established model [2-5] was extended to include glucagon in order to describe the effect of glucose, insulin, and glucagon on glucose homeostasis.

Methods
Data collected prior to drug treatment (baseline) and from placebo cohorts were pooled together from subjects with T2DM from two Phase 1 clinical studies. Sampling for glucose, insulin, and glucagon occurred after standardized meals at breakfast, lunch, dinner, and bedtime. Carbohydrate and protein amounts were input into the model to assess the effect of meals on glucose dynamics. The glucose and insulin scheme used in this analysis was based on the model developed by Jauslin et al. and Silber et al. [2-5]. Basal glucagon secretion, the inhibitory influence of glucose and insulin, and the stimulatory influence of ingested exogenous protein on glucagon secretion were combined in a differential equation to describe glucagon dynamics. A stimulatory effect on hepatic glucose production was captured by a factor comprised of the composite effect of contemporaneous glucose, insulin, and glucagon concentrations. Certain physiologically related parameters were fixed to previously published values in order to reduce the computational intensity of the model or to compensate for missing information in the dataset. The "expectation maximization" method known as Monte Carlo Importance Sampling assisted by Mode A Posteriori (IMPMAP) and ADVAN13 were used to execute the model in NONMEM 7.2 [6]. Model selection was based on goodness-of-fit plots, the plausibility of the physiological system, and the objective function value. The predictive performance of the model was assessed by applying a visual predictive check [7].

Results
Diagnostic plots, predictive check figures, and representative individual profiles indicated that observed data were described adequately by an integrated glucose-insulin-glucagon model.

Conclusions
By linking to PK models, the integrated glucose-insulin-glucagon model could be customized to aid in the characterization of the mechanism of action of a drug, to quantify a dose-response relationship, to evaluate the effects of combination drug therapy, or to support the development of drugs that directly affect glucagon secretion.

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Methodology- Model evaluation

PM5-1 Residual-based Bootstrap Methods for Estimating Uncertainty of Parameters in Nonlinear Mixed-Effects Models with Heteroscedastic Error

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Objectives

Bootstrap methods are used for estimating uncertainty of parameters in multi-level or linear mixed-effects models with homoscedastic error [1-2]. Residual-based bootstrap methods which resample both random effects and residuals are an alternative approach to case bootstrap, which resamples the individuals [3]. However, most PKPD applications use the case bootstrap, for which software is available [4-5]. We propose to investigate the residual bootstrap for nonlinear mixed-effect models (NLMEM) with heteroscedastic error.

Methods

We implemented nonparametric and parametric residual bootstrap [6-7], as well as the case bootstrap, in R 2.14. The performance of the three bootstraps was assessed by a simulation study based on clinical trials of aflibercept, an anti-VEGF drug, in cancer patients. We assumed that the PK of aflibercept follows a two-compartment infusion model with 1st order elimination. A frequent sampling design (30 subjects and 9 samples per subject) with fist-order or Michaelis-Menten (MM) elimination and a sparse sampling design (70 subjects and 4 samples per subject) with first-order elimination were investigated using 100 replicates and 1000 bootstrap samples per replicate for each bootstrap method. Each bootstrap dataset was fit with Monolix 4.1. The bootstrap approaches were compared with respect to bias of parameters, standard errors (SE) and coverage rate of the 95% confidence intervals. They were also compared to the asymptotic approach.

Results

The bootstrap and the asymptotic approaches provided similar estimates of SE and coverage rate in designs with first-order elimination. In the frequent sampling design with MM elimination, the bootstrap approaches provided better estimates of SE and better coverage rate for several parameters than the asymptotic approach, especially for Km (parameter with highest nonlinearity).

Conclusions

The nonparametric residual bootstrap works as well as the case bootstrap for all designs in NLMEM with heteroscedasticity. The parametric residual bootstrap works slightly better than others but may not be as robust to distributional misspecifications. Bootstrap methods provide a better description of uncertainty for nonlinear parameters compared to the asymptotic approach, however they do not improve the estimation of uncertainty for linear parameters, even in the sparse design tested here.

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Methodology- Model evaluation

PM5-2

Further Investigations of the Weighted Residuals in NONMEM 7

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Objectives

Improving the calculations of the weighted residuals has proven to be of high importance; especially if the model is highly nonlinear in the random effects [1, 2]. Various new and published methods for calculating the weighted residuals have been implemented in NONMEM 7 [3]. Previously these methods have been investigated under the assumption that the population parameters (PP) used to simulate where at the maximum likelihood (ML) estimates [4]. In that work the CWRES and NPDEs were shown to perform best. This work aims to investigate if estimating the ML-PP will improve the statistical properties of the weighted residuals.

Methods

A sigmoidal Emax-model (gamma=4.5) was used to investigate the different residuals [1]. Emax and EC50 both had between subject variability (BSV) corresponding to ~71%CV. The study design was rich; 200 individuals with 25 observations each. Five different scenarios were investigated 1) Additive residual variability (RV), 2) proportional RV, 3) exponential RV, 4) exponential BSV on the proportional RV, 5) Between occasion variability on Emax with an additive RV. The residuals investigated were: NWRES and WRESI (first order residuals without or with interaction), CWRES and CWRESI (First order conditional residuals without or with interaction), ECWRES and EWRES (Monte Carlo calculated weighted residuals without and with interaction), NPDE (Normalised Prediction Distribution Errors). All the residuals were calculated for 100 simulated data sets. Hypothesis tests for mean 0, variance 1 and normality were calculated.

Results

The CWRES and NPDE again seem to outperform the other residuals, with a slight advantage for NPDEs, especially for model 4). As expected the NWRES and WRESI did not perform well in any of the investigated cases.

Conclusions

These results show, together with [4], that statistical tests with NPDEs are more sensitive to the ML estimate than CWRES which implies that NPDEs can be used as a diagnostics for ML-PP estimates or consequently that CWRES will perform better if the estimates are not at the precise ML-PP estimates (mainly for the variance equal 1 test). This may be because of the ability of empirical bayes estimates (used in CWRES) in the population model to correct for slight bias in the PP.

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Methodology- Model evaluation

PM5-3

A New Model for Diurnal Blood Pressure Profiling And its Application in the Evaluation of Ambulatory Blood Pressure

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Objectives

To develop a new model for 24 hour ambulatory blood pressure measurements (ABPM) that can be applied in the evaluation of the smoothness of antihypertensive effect.

Methods

Eight different data sets were prepared from four studies to accommodate different modeling strategies. 24 hour ABPM profiles (42 to 65 measurements per profile) of 232 patients were obtained during the placebo run-in phase. Sine and cosine models were evaluated to describe the circadian rhythm in blood pressure. After that, the best model was selected to fit the data obtained after 8 weeks during the treatment of 4 different antihypertensive drugs. The range parameter in the model can be used to reflect the smoothness of antihypertensive effect.

Results

When compared with the common cosine model, the sine model is relatively simple and with a higher successful fitting rate of the data. Moreover, the range parameter P1 in the sine model can quantitative the smoothness of antihypertensive effect much more accurately and be more accord with professional judgment.

Conclusions

The sine model could be popularized or at least provide methodological reference in the ABPM study.

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PM5-4 External Validation of a New Dosing Scheme of Busulfan in Conditioning Therapy for Hematopoietic Cell Transplantation Regimen

This abstract was partially presented as an oral presentation at the 17th Annual Congress of the Korean Society for Clinical Pharmacology and Therapeutics in Seoul, South Korea (Nov. 14, 2008).

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Objectives

This study aimed to evaluate a new dosing scheme of busulfan as hematopoietic cell transplantation regimen based on the population pharmacokinetic model using the method of external validation.

Methods

Thirty-seven adult patients received busulfan intravenously based on one of the conventional or new doing scheme randomly at the first day of conditioning therapy for hematopoietic cell transplantation. Although the conventional method requires the actual body weight (ABW) and ideal body weight (IBW), the new dosing scheme is based on ABW. The required new daily dose was $23 \times ABW^{0.5}$ mg when the target area under the concentration versus time curve (AUC_{Target}) was 5924 $\mu M \cdot min^{1-2)}$. Blood samples were taken at randomly selected two time points among 3.5, 5, 6, 7 or 22 hour after administration of busulfan. The predictability of concentration was evaluated using the standardized prediction error on observation (SPEY), standardized prediction error on observation with simulation (SPEYS) and conditional weighted residual (CWRES). The predicted pharmacokinetic parameters were tested by the standardized prediction error on hyperparameter (SPEH) and standardized prediction error on hyperparameter with simulation (SPEHS). The applicability of the new dosing regimen was evaluated by the predicted AUC (AUC_{PRED}) and its relative standard error (RSE) as compared with the conventional regimen.

Results

The bias and imprecision of the predicted busulfan concentrations were 3.73 % and 32.37 %. SPEY and CWRES were not able to support the assumption of the population model but the result of Kolmogorov-Smirnov test in SPEYS supported the assumption of normality. There were the differences in pharmacokinetic parameter using the metric of SPEH between the learning and external validation dataset. But the result of SPEHS indicated no differences between two dataset. The mean and RSE of AUC_{PRED} with the new dosing scheme were 6046.3 $\mu M \cdot min$ and 14.0%. With the conventional regimen, the mean and RSE of AUC_{PRED} were 5580.7 $\mu M \cdot min$ and 21.6%.

Conclusions

This study demonstrates the external validity of the new dosing scheme of busulfan in conditioning therapy for hematopoietic cell transplantation based on the population pharmacokinetic model.

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Methodology- Model evaluation

PM5-5   Population Pharmacokinetic Analysis of Risperidone and 9-Hydroxyrisperidone with Genetic Polymorphisms of CYP2D6 and ABCB1

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Objectives

This study estimated the population pharmacokinetics of risperidone (1) and its active metabolite, 9-hydroxyrisperidone (2), according to genetic polymorphisms in the metabolizing enzyme (CYP2D6) (3) and transporter (ABCB1) genes (4) in healthy subjects.

Methods

Eighty healthy subjects who received a single oral dose of 2 mg risperidone participated in this study. However, eight subjects with rare genotype variants in CYP2D6 alleles were excluded from the final model built in this study. We conducted the population pharmacokinetic analysis of risperidone and 9-hydroxyrisperidone using a nonlinear mixed effects modeling (NONMEM) method (5) and explored the possible influence of genetic polymorphisms in CYP2D6 alleles and ABCB1 (2677G>T/A and 3435C>T) on the population pharmacokinetics of risperidone and 9-hydroxyrisperidone.

Results

A two-compartment model with a first-order absorption and lag time fitted well to serum concentration-time curve for risperidone. 9-hydroxyrisperidone was well described by a one-compartment model as an extension of the parent drug (risperidone) model with first-order elimination and absorption partially from the depot. Significant covariates for risperidone clearance were genetic polymorphisms of CYP2D6*10, including CYP2D6*1/*10 (27.5% decrease) and CYP2D6*10/*10 (63.8% decrease). There was significant difference in the absorption rate constant (ka) of risperidone among the CYP2D6*10 genotype groups. In addition, combined ABCB1 3435C>T and CYP2D6*10 genotypes had a significant (P<0.01) effect on the fraction of metabolite absorbed from the depot. The population pharmacokinetic model of risperidone and 9-hydroxyrisperidone including the genetic polymorphisms of CYP2D6*10 and ABCB1 3435C>T as covariates was successfully constructed (6).

Conclusions

The estimated contribution of genetic polymorphisms in CYP2D6*10 and ABCB1 3435C>T to population pharmacokinetics of risperidone and 9-hydroxyrisperidone suggests the interplay of CYP2D6 and ABCB1 on the pharmacokinetics of risperidone and 9-hydroxyrisperidone according to genetic polymorphisms.

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Methodology- Model evaluation

PM5-6

Extended NPDE Diagnostics for the Between-Subject Variability and Residual Error Model

(encore presentation from PAGE2012:
http://www.page-meeting.org/default.asp?abstract=2538)

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Objectives

To evaluate the ability of EBE-npde and IWRES-npde to diagnose model misspecification.

Methods

For diagnosis of misspecification of the between-subject (BSV) and residual error (RE) models, summaries of empirical Bayes estimates (EBE) and individual weighted residuals (IWRES) are commonly employed. However, these diagnostics are very sensitive to η- and ε-shrinkage.[1] As extension and improvement to the above diagnostics, we propose to construct npdes[2] for EBE and IWRES (instead of or in addition to DV-npdes). These new npde-diagnostics would have two main advantages:a) the decomposition of the DV-npde diagnostic to the BSV model (EBE-npde), and the RE model (IWRES-npde) b) the proposed npde diagnostics would not be subjective to shrinkageCalculation of the proposed npdes requires iterated re-estimation of EBEs (but not population parameter values) based on simulated data. Algorithms for this were implemented in PsN (versions 3.5.3 and up).[3] A previously developed model for a PK dataset (prazosin, n=65, 11 obs.) was used. Several misspecifications in the BSV model and the RE model were implemented and evaluated, as well as models without misspecification. DV-npde, EBEs, IWRES-npde, EBE-npde and IWRES-npde were then calculated for the base model. The analysis was repeated at varying levels of shrinkage. Several diagnostic plots based on the new npde diagnostics were evaluated for their diagnostic ability.

Results

EBE-npdes were able to detect misspecification at low and high levels of η-shrinkage, which could not be detected using diagnostic plots of EBE or DV-npde, and were also informative in diagnosing appropriateness of covariance structure. IWRES-npde were equal or more sensitive to detect misspecification in the RE model than IWRES, at both high and low levels of ε-shrinkage.

Conclusions

EBE-npde and IWRES-npde offer valuable diagnostic tools, with improved diagnostic power in the case of shrinkage. These new npde diagnostics also allow decomposition of the DV-npde diagnostic to the BSV and RE level.

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Methodology- Model evaluation

PM5-7   Dealing with BQL Data in Normalised Prediction Distribution Errors: A New Version of the Npde Library for R

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Objectives
Over thelast few years, several new approaches including VPC (Visual Predictive Check) [1], prediction discrepancies (pd) [2] and normalised prediction distribution errors (npde) [3] have been proposed to evaluate nonlinear mixed effect models. We created a R library to facilitate the computation of pd and npde using simulations under the model [4]. We propose a new version of this library with methods to handle data below the limit of quantification (BQL) [5] and new diagnostic graphs [6].

Methods
BQL data occur in many PK/PD applications, but are generally omitted from diagnostic graphs, introducing biases. Here, we propose to impute the pd for a BQL observation by sampling in $U(0,pLOQ)$ where pLOQ is the model-predicted probability of being BQL. To compute the npde, censored observations are first imputed from the imputed pd, using the predictive distribution function obtained by simulations, then npde are computed for the completed dataset [3]. New graphical diagnostics include a graph of the empirical cumulative distribution function of pd and npde, and prediction intervals can be added to each graph. Tests can be performed to compare the distribution of the npde relative to the expected standard normal distribution. In addition, graphs and tests to help selecting covariate models have been added [7].These extensions were implemented in a new version of the npde library. We used S4 classes from R to provide an easier user-interface to the many new graphs, while remaining mostly compatible with the previous version. Exceptions are that computing the pd in addition to the npde is now a default option.

Results
We illustrate the new library on data simulated using the design of the COPHAR3-ANRS 134 trial. In the trial, viral loads were measured for 6 months in 34 naïve HIV-infected patients after initiation of a tri-therapy, and up to 50% of data were BQL. Ignoring BQL data results in biased and uninformative diagnostic plots, which are much improved when pd are imputed. Adding prediction intervals is very useful to

highlight departures from the model.

Conclusions
Version 2 of the npde library implements new methods to handle BQL data, and new graphs including prediction intervals for distributions.

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Methodology- Model evaluation

PM5-8

Why a Decrease in Between Subject Variability May not Occur When Adding a New Covariate?

(PAGANZ 2012)

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Objectives

Population pharmacokinetic-pharmacodynamic (PK-PD) analyses include models for heterogeneity between subjects (between subject variance - BSV). The total BSV is the sum of the random (BSVR) and predictable component (BSVP). The BSVP (BSVbase − BSVRcovariate) is explained by covariates (patient characteristics e.g. weight). The aim here is to explore the hypothesis that a decrease in BSV may notalways occur when adding a significantly correlated covariate. We explored situations where BSVR may not decrease when a significant covariate is added and whether different statistical models for the covariate effect may eliminate this issue.

Methods

Simulations were performed using MATLAB (2011a) and estimation using NONMEM (ver 7.2) with FOCE-INTER using a simple intravenous bolus PK model. The BSV was assumed to follow log-normal distribution for parameters. Initially, we show that BSVR is not decreased with the addition of a significant covariate via a simple simulation. Then, five scenarios with correlation from 0 - 100% between the covariate (Z) and CL were evaluated. Each simulated scenario was replicated 100 times and estimated by a base model (i.e. no covariate) and six covariate model parameterisations which

included not nested - slope only (NNCM), nested - slope and intercept (NCM), and two types of interaction models (additive & exponential) for each of NNCM and NCM respectively.

Results

In the case of 0% correlation, NNCM showed a negative BSVP whereas NCM showed a calculated BSVP of zero. NNCM resulted in negative BSVP (BSVR > BSV) with 50% correlation and needed a minimum of 75% correlation to show a positive BSVP. NCM showed positive but downwardly biased BSVP with 25% correlation. Use of a covariate-eta interaction term for both types of covariate models resulted in marginal improvement in BSVP. Under perfect positive correlation, all models perform equally with covariate-eta interaction models showing the same BSVP.

Conclusions

It was found that the misspecification resulting from NNCM appears to inflate BSVR with negative predictions of BSVP. The effect of this misspecification is not evident with NCM except at low correlation (<50%). The use of covariate-eta interaction models could be useful as a diagnostic in such situations to expect a decrease in BSVR.

Methodology- Model evaluation

PM5-9

Time Measurement Error in Population Pharmacokinetic Studies

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Objectives

Observational population pharmacokinetic (PK) data collectedfrom routine clinical practice is a potential rich source of valuable information. In contrast to PK data collected from a clinical trial or a well-controlled environment, the analysis of observational population PK data poses several statistical challenges, among them measurement error in variables in PK models. In observational PK studies, time information for blood sample draw or drug administration is often missing or inaccurately recorded, and hence the nominal time by design is used for the true timein the PK modeling. The goal of this study was to investigate the effects of measurement errors in times at blood draw or drug administration in population PK models and to propose a measurement error correction method.

Methods

We conducted systemic simulations studies with a variety of scenarios. We used simple PK models to explain key concepts in measurement error within PK modeling setting. Especially, the relationships between bias and the types of measurement error were explored, and a measurement error correction method was developed. We further investigated the consequences of time measurement error using more complicated population PK data mimicking data collected from real observational PK studies, and applied the measurement error correction method.

Results

Unlike linear models, we found that both classical error and Berkson error models could result in substantial bias. The bias could be especially serious for population PK data with sparse sampling. We provided predicted bias in PK parameter estimates and their bias correction by the measurement error correction method under different types of measurement error models, degrees of measurement errors, and PK models.

Conclusions

When non-ignorable measurement errors are to be expected in time records, the analysis should be performed carefully and need to use a measurement error correction method.

Methodology- New tools

PM6-1   The Visual Run Record: Visualization of the Model Development History

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Objectives

Implement a software tool that produces a visualization of the hierarchical model development history.

Methods

Pharmacometric model development most often progresses in a hierarchical fashion, using the likelihood ratio test to assess significance of improved fit between nested models. An appropriate visualization of the model hierarchy will help the modeler gain a better overview of the model development history, and will aid in communicating it to others. Although several software keep track of model hierarchy (e.g. PsN run record, Pirana, [1-2]), currently no tool is available that visualizes the model hierarchy in an effective and convenient manner. An algorithm was implemented in Perl, which extracts model hierarchy data from the PsN run record. The algorithm produces Javascript code compatible with the Data-Driven Documents Javascript library (d3.js, [3]), and creates a dendrogram that visualizes the hierarchy between models. The visualization can be generated as an SVG image in any modern internet browser. Several options were implemented that allow customization of the visualization, and both dynamic and static images can be created. The algorithm to produce these plots is implemented in Pirana, and will be released as an open source stand-alone Perl script as well.

Results

Using the algorithm, Visual run records (VRR) could be generated from Pirana, or from the stand-alone script. In the VRRs, the hierarchy of models is immediately visible, and using the dynamic collapsible dendrograms, non-relevant model threads can be hidden from the visualization. The dynamic images also allow the display of additional model information when focusing on specific nodes. Coloring and size of nodes aids in visualizing the improvement / worsening of model fit, and whether the model has children or not. When a final model is specified, the modeling path can be made visible, thereby easily identifying key runs. The VRR can be implemented as a horizontal or radial tree, the latter of which may be useful when the tree structure is very large.

Conclusions

The visual run record presents an effective and convenient approach to visualize the model development history.

References

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[3] http://d3js.org/

Methodology- New tools

PM6-2   Application of the Berkeley Madonna software to Nonlinear Mixed-Effects Models – Possibilities and Limitations

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Objectives

The Berkeley Madonna software is widely used within and outside of the field of pharmacometric research. It has been suggested as a useful tool for visualization of pharmacometric models and to "facilitates effective communication, enhanced quantitative decision making, and thus increases the impact of pharmacometrics in drug development" [1]. However the possibilities with respect to application of random effects have largely been neglected and hence it has not reached its full potential. This study aims to highlight possibilities and limitations with Berkeley Madonna in application to simulations with nonlinear mixed-effects model.

Methods

Berkeley Madonna was applied for simulations with a range of PK and PKPD models, ranging across PBPK models, drug-metabolite models, time-to-event models, and Markov models [2-5]. Simulations were utilized for various purposes such as investigating alternative dosing regimens, extrapolations to other settings, finding a suitable starting model and reasonable initial parameter estimates, illustrating covariate relationships and communicating modeling results in general.

Results

A wide range of models were successfully implemented in Berkeley Madonna including features such as multiple layers of random effects (residual variability and variability between: occasions, subjects, and studies), conditional design (i.e. dose adjustments), mixture probabilities etc. One major limitation was identified with respect to straightforward implementations of random-effects correlations. With regards to visualization of model output the functionalities for batch runs and sliders for adjusting parameter estimates was found to be particular useful in communications of modeling results. The possibilities for summarizing model output across individuals/studies were limited to mean and standard deviation (on log- or normal-scale). For summary of results with non-parametric metrics such as different percentiles, data needs to be exported and processed in another software (e.g. R).Berkeley Madonna simulations of 10,000 subjects were compared to that from NONMEM for all above models and resulted in highly similar median and 90% prediction interval. The computational time for the simulations were reduced up to a 100-fold compared to NONMEM, likely due to a more efficient integration routine.

Conclusions

Berkeley Madonna is an inexpensive software with a wide range of applications for increasing the utility of nonlinear mixed-effects models.

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A Bayesian Solution to the Inverse Problem of Patient Compliance and Its Role to Reveal the Underlying Drug Intake and Disposition Relationship

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Objectives

Poor adherence to a drug prescription has a significant impact on efficacy and safety of a planned therapy. The relationship between drug intake and drug disposition can only be partially obtained through the forward influence investigation of the former on the latter. The so-called "inverse problem", which is concerned with the issue of retracing the patient compliance scenario using limited clinical knowledge, provides a platform to give insights into this complex issue.

Methods

Based on the reported Pop-PK model of a specific drug where the PK parameters and associated variability were well determined, imatinib in this work, we were able to simulate a whole range of drug concentration values at a given sampling point in once daily multidose regimens. All possible drug compliance profiles were mimicked for a population of patients. We developed a Bayesian decision rule to determine the associated compliance profile prior to a given sampling value. The success of this method allowed us to design a heatmap-style image that provides an intuitive and interactive way to evaluate the relationship between drug input and drug disposition along with their consequences on PK profile.

Results

The adopted approach allows, for thefirst time, to quantitatively acquire knowledge about the compliance patterns having a causal effect on a given PK. Moreover, using a simulation approach, we were able to evaluate the evolution of success rate of the retracing process in terms of the considered time period before sampling as well as the model-inherited variability. Moreover, our invented visual representation clearly presented the heterogeneity of different sampling concentrations for susceptible drug compliance profiles.

Conclusions

This work allows, from a probability viewpoint, to propose a solution for this inverse problem of compliance determination. And for the first time, we provide a direct visualization of complex relationship of drug input and disposition such that these two currently separated topics can be studied in the same framework.

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Methodology- New tools

PM6-4

Miscellaneous Modeling and Simulations by Using Napp

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Objectives

Napp (Numeric Analysis Program for Pharmacokinetics) is a general-purpose application for modeling and simulation developed by the author, and has been used in various studies (ref 1-4). The most prominent feature is easiness in making, modifying and combining new models of various mathematical expressions including ordinary equations, differential equations, Laplace-transformed equations and partial differential equations. It also features moment analysis, nonlinear least squares fitting, extended nonlinear least squares fitting (for population analysis), random data generation, convolution and deconvolution. In this presentation, some of representative modeling analyses are demonstrated.

Methods

Napp was originally developed in 1992 on NeXT workstation and has been updated constantly. The newest version is downloadable from our website (under reconstruction) or provided by arequest. It works under Japanese and English environments in Mac OS-X (later than 10.6). Detailed English manual is under preparation.

Results

Although Napp can be applied to conventional compartment analyses and physiologically-based pharmacokinetics, some unique models have also been constructed on it. Translocation model is a physiological absorption model based on a concept of trans-locatable flexible absorption site which is composed of the intestinal lumen, associating enterocytes and blood flows. It considers contributions of dissolution, permeability, metabolism and blood flows in the overall absorption process. Mutable covariate model is basically a conventional two-compartment model, but daily fluctuations of renal clearance can be considered quantitatively with it (ref. 4). Zone absorption model is a Laplace transformed model which interpolates zero-order absorption and 1st-order absorption continuously. Nonlinear dispersion model is one of the most satisfactory physiological hepatic models expressed by a partial differential equation (ref. 1), and its application to disease models has also been explored recently to consider variable delays in responses. Napp fits to analyses of various drug-drug-interactions since it can combine multiple models and calculate them simultaneously.

Conclusions

Usefulness of Napp in miscellaneous modeling and simulations is demonstrated especially in exploratory modeling and for educational purposes because of its flexibility, reliability and low cost.

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PM6-5 A Population Pharmacokinetics Based Approach for the Selection of Optimal Drug Regimens - The Case Study of Dovitinib

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Objectives

Many drugs, while possessing a narrow therapeutic window, exhibit significant pharmacokinetics (PK) and pharmacodynamics (PD) variability. Optimised dose and time schedules help decrease the risk of therapeutic failure and/or toxicity. Current methods for individual dose adaptation require the use of detailed individual information which can be difficult to obtain and put excessive burden on patients. A practical and effective method to assist the selection of optimal drug regimen represents an interesting alternative that can bring great benefit for target patients. In this work, we proposed a Pop-PK based computational strategy for dose adaptation, which we have concretized in a readily usable algorithm for renal cancer patients treated with dovitinib, an anti-angiogenic drug.

Methods

A one compartment Pop-PK model of dovitinib with first order absorption and non-linear elimination was used [1] for a dose amount of 400 mg/day. The performance of regimens was evaluated according to the likelihood of different therapeutic indicators (TR) that we proposed, such as the average time that the drug concentrations remains within the therapeutic window or the probability that a patient is considered a responder. Other clinically meaningful indicators can also be used.

Results

Preliminary results indicate that the QID regimen is superior to QD, which is the current adopted regimen in clinical trials. Our suggested optimal regimen has a dose of 100 mg QID, which should be taken at 7, 13 and 17 hours after the first dose. In terms of therapeutic indicators, this QID regimen reaches an average of 9.6 hours for dovitinib concentrations to remain in the therapeutic window, and a response probability of 37%. Compared to QD regimen, this is an improvement of 18% for the first therapeutic indicator and 19% for the second one.

Conclusions

This computational method provides an efficient and quantitative way for the selection of optimal dosage schedules that can be used to reduce therapeutic failure and/or toxicity for a target patient population.

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Methodology- PBPK

PM7-1   Estimation of Optimal Dosages for Patients Receiving Continuous Renal Replacement Therapy: A Proposal for the Description of Pharmacokinetic Data in Product Labeling

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Objectives

Drug dosages for patients receiving renal replacement therapies (CRRT) such as HD and CHDF are not described in the product labeling usually. CRRT is frequently carried out especially in critical ill patients and removes antibiotics and other drugs to significant extents, and hence, dosage setting is difficult. Empiric dosages are applied for these patientsin clinical settings and it often results in therapeutic failure. Therefore, it is important to provide enough information to enable the rational dosage setting for these patients based on pharmacokinetic theory. We tried to estimate the drug clearance of CRRT by in vitro experiment and compared with the observed data.

Methods

First, for estimation of drug clearance by CRRT, in vitro experiments were conducted using 5% human albumin solution containing antibiotics (amikacin, vancomycin and teicoplanin) as artificial plasma (reference 1). Series of artificial plasma and dialysate were corrected for measurement of drug concentrations. CRRT clearances were considered based on its relationship between the flow rate of dialysate (QD) and plasma unbound fraction (fU) of drugs. Next, CRRT clearance was investigated in vitro in sixteen critically ill patients receiving CRRT to verify the in vitro experiment. Because protein bound drug cannot permeate through dialysis membrane in the

CRRT apparatus, and QD is slower than blood flow rate (QB), drug clearance by CRRT was calculated as a product of QD and fU in this study. CRRT clearances were calculated based on individual CRRT conditions and were compared with observed clearances in the 16 critically ill patients receiving CRRT.

Results

The observed clearances of antibiotics agreed well with the theoretical values within 0.67 to 1.5-fold for 15 of 16 patients, and the simulated time-concentration profiles of antibiotics in each patient were in good concordance with observed concentration. This study indicated that clearance and time-concentration profiles of drugs including antibiotics during CRRT were satisfactorily predictable from CRRT conditions and reported pharmacokinetic data.

Conclusions

Product labelingwould be very informative if predicted dose settings for patients receiving CRRT are described appropriately by applying the present method. These data would facilitate the dosage optimization in clinical situation and increase the usability of drugs.

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PM7-2 PBPK/PD Approach to Discern Potential Sex and Ehnic Differences in the Time Course of QT Prolongation following Quinidine Administration: Caucasian vs Korean Healthy Populations

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Objectives

A randomised, double-blind, cross over study in 24 Korean and 13 Caucasian subjects was conducted by Shin et al. (2006) to assess the time course of QT prolongation following an intravenous infusion of quinidine [1]. The objective of the current work was to conduct a virtual clinical trial replicating the above study but using prior systems and drug information to drive the expected QT prolongation within a physiologically based pharmacokinetic (PBPK) model linked with pharmacodynamics (PD).

Methods

Data representing the mean plasma concentration profiles of quinidine and mean QT profiles in male and female Caucasian and Korean populations were extracted from Shin et al. (2006). A PKPD analysis was conducted using the PBPK/PD models and Caucasian and Japanese population libraries within Simcyp (the latter as a surrogate for Korean population). The PK profiles for male and female Caucasian and Korean (/Japanese) were simulated using a minimal PBPK model with single adjusting compartment (SAC) and compared with the observed PK profiles. The rate constants in (kin) and out (kout) of the SAC and volume of SAC (Vsac) parameters were estimated using the parameter estimation module in Simcyp. PBPK/PD profiles were simulated in the 4 groups using the Simulator and an Emax model with additive baseline. The parameters in the PD model were taken from Shin et al. (2006). Both PK and PD models were evaluated using a visual predictive check.

Results

A minimal PBPK model with a SAC compartment provided a good fit to the PK data. Neither sex nor ethnicity influenced the PK of quinidine. The (AUC(0-∞)) and area under the response curve (AUCR) were in agreement with the values reported by Shin et al (2006). The observed PK and PD data fell within the 95th percentile range of simulated values.

Conclusions

Simulations indicated that Caucasian males were most susceptible to QT prolongation following quinidine and Korean females the least. Combining PBPK/PD modelling with prior systems and drug data allowed successful prediction of observed clinical data but also suggested that the source of variable susceptibility does not relate to pharmacokinetics.

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Methodology- PBPK

PM7-3

PBPK Model for the Anticancer Drug Vivia009 and Its Main Metabolite Administered as a New Delivery System in Rats

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Objectives

Vivia009 is a patented new drug indication that targets B cell population overproliferation in leukemic patients. In orderto prevent side effects and to increase drug efficacy in the lymph nodes, a microparticle (MP) has been developed and its pharmacokinetic properties studied. The aim of this project was to develop an integrated PBPK model capable to describe simultaneously the biodistribution of Vivia009 and its main metabolite, after the free drug's administration or MP.

Methods

Fifty-one rats divided in two groups were treated with 0.75 mg/kg of either free drug or MP given as a bolus. At time points 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 6 and 24 hours, three animals were sacrificed. Samples of plasma, axillary lymph node, brain, spleen and bone marrow were collected to measure Vivia009 and its metabolite concentrations. Data regarding blood flows and tissue volumes were taken from literature (1-4). Modelling and simulations were performed with NONMEM version VII using the naïve pool data approach.

Results

An initial PBPK model was built for the free drug's administration: a permeability surface factor was estimated for lymph node, and distinction between vascular and intracellular compartments was required for the case of spleen. Additional model parameters estimated during the fitting were drug clearance (CL), metabolite clearance (CLM), apparent fraction of drug metabolised (Fm), and tissue to plasma partition coefficients (Kp). The latter ones were also calculated using the ratio between AUCtissue/AUCblood (5) resulting similar to the model estimates. A second PBPK model was developed for the MP's administration (6): lymph flow was included in the model (7), as well as extracellular compartments for the MP distribution within tissues. Both models were linked through the in vivo release constant (KREL) of the MP.

Conclusions

Based on the results of the modelling exercise, 45% of the MP's dose was released before the bolus administration behaving as a free drug. CL, CLM and Fm increased 2, 1.3 and 1.3 times respectively, when the drug was administered as a MP. Modelling results will be used to scale to first dose in humans and to predict biodistribution of similar new delivery systems.

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PM7-4 Prediction of a Tissue to Plasma Partition Coefficient in Rats Using Volume of Distribution

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Objectives

Physiologically based pharmacokinetic (PBPK) modeling is used for the purposes of ADME prediction and interspecies and intraspecies pharmacokinetic scaling. Tissue to plasma partition coefficients (K_p) characterize tissue drug distribution and are important input parameters. The objective of this work is to develop an empirically derived K_p prediction algorithm using input parameters available in the pre-clinical phase of drug development.

Methods

A dataset of experimentally-derived K_ps was divided into a development (n = 96 compounds) and test set (n = 20) according to their acidic/basic properties. Based on the development dataset, multiple stepwise regression was used to correlate K_p values with rat volume of distribution at steady state (Vss) along with one or more physicochemical parameters (lipophilicity, degree of ionization, protein binding) to account for inter-organ variability of tissue distribution. K_p prediction equations were developed for 11 tissues: adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, spleen, and skin. The test set was used to evaluate the algorithms, and their relative prediction accuracy was compared to an existing empirically-derived (Janssen *et al.* 2008.) and a mechanistic tissue-composition algorithm (Rodgers *et al.* 2005, Rodgers *et al.* 2006).

Results

Sixty-five percent of predicted K_ps were within two-fold of experimental values which exceeded that of Janssen et al (52%) and Rodgers et al (41%). The presented algorithm resulted in better precision with root mean square error value of 0.42 when compared to Janssen et al. (0.59) and Rodgers et al. (0.66). The relative prediction accuracy of the presented algorithm for a single tissue was determined by calculating the mean of the ratio of predicted to observe K_ps: adipose (0.33), bone (1.40), brain (0.99), gut (1.33), heart (1.19), kidney (1.15), liver (1.19), lung (0.93), muscle (1.14), spleen (0.69), and skin (0.99).

Conclusions

An innovative method is proposed that relies on rat Vss data to estimate K_p values with a physicochemical descriptor as a secondary variable. Because readily available input parameters are used and prediction accuracy is reasonable, this algorithm will enhance both the usability and confidence in PBPK modeling outputs.

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Methodology- PBPK

PM7-5 Prediction of Food-related Changes in Gastric Emptying Function on the Pharmacokinetics of Orally Administered Drugs

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Objectives

The ingestion of food can affect the intestinal absorption of drugs through various physicochemical and physiological mechanisms.[1] One major food-related effect represents its impact on the rate of gastric emptying (GE). In this work, the relationship between the properties of meals and GE rate was characterized to enable the prediction of changes in GE rate on drug absorption.[2, 3]

Methods

In a comprehensive literature search, information about the effect of various meals on GE was collected. Eight mathematical functions were tested for their ability to describe the relevant phases of the experimental GE profiles. The most suitable function was subsequently implemented into the detailed absorption model that is part of the physiologically-based pharmacokinetic (PBPK) software tool PK-Sim®. With the help of this function, the impact of co-administration of meals on the pharmacokinetics of three test substances was predicted for populations of 500 individuals.

Results

About 100 datasets for GE profiles following ingestion of various meals were obtained. The energy content and the fractionof solid components of the meal were found to be the principal factors determining GE rate. The Weibull function was identified to be the most appropriate empirical function to describe the relevant phases of GE. The optimized function was subsequently integrated into the PBPK model. Based on PBPK models established in the fasted state and using the optimized Weibull function, the impact of food ingestion on pharmacokinetics of the three test substances could be predicted well.

Conclusions

The impact ofmeal ingestion on GE rate in humans was analyzed. A comprehensive dataset was successfully transferred into an empirical GE function that can be used to predict the food-related effect of GE on the pharmacokinetics of orally administered drugs. Further food-related physiological changes that are considered to affect the pharmacokinetics of orally administered drugs will be studied soon.

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PM7-6   **Combining Physiology-based Pharmacokinetic Modeling and Markov-Chain-Monte-Carlo Approaches for Analysis of Inter-Individual Variability in Drug Pharmacokinetics**

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Objectives

Interindividual variability in clinical endpoints and occurrence of potentially severe adverse effects may hamper drug development at all phases of (pre-) clinical research. Hence, a comprehensive understanding of the processes governing both pharmacokinetics and pharmacodynamics is of utmost importance. We here apply Bayesian modeling together with physiology-based pharmacokinetic (PBPK) modeling as an analytical tool to investigate inter-individual variability in groups of healthy volunteers and patients [1, 2].

Methods

PBPK models enable a mechanistic investigation of drug distribution and drug action at a mechanistic level of detail based on generic distribution models and extensive collections of physiological parameters. Most notably, the computational models are used to incorporate heterogeneous experimental data ranging from gene expression profiles at the cellular scale to physiological parameters at the whole-body level into one integrative modeling framework. To systematically account for parameter variability, a Bayesian formulation of the original population PBPK model was used to rigorously quantify the probability of a parameter value given the amount of information contained in the measured data. Since these parameter distributions are high-dimensional, Markov-Chain-Monte-Carlo (MCMC) algorithms are used. Moreover, adequate information about the distribution of essential parameters describing drug absorption processes is integrated into the approach.

Results

Considering pravastatin pharmacokinetics, comparison and investigation of the identified parameter distributions to clinical data was used to identify the population pharmacokinetics. In particular transport and metabolization processes were found to be the main sources of variation. Moreover, homogeneous subpopulations could be identified from the clinical results which can be assigned to a polymorphism in the hepatic organ anion transporter OATP1B1 encoding SLCO1B1 [3].

Conclusions

The presented approach of combined PBPK-MCMC systematically characterizes inter-individual variability of physiological parameters and allows the identification of main sources of pharmacokinetic variability. Moreover, clinically relevant homogeneous subpopulations may be mechanistically described. Such integrative approaches may therefore have significant implications for the development of individualized therapeutic strategies with a favorable risk-benefit profile in the future.

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Methodology- PBPK

PM7-7 PBPK Modeling to Predict Drug Interaction of Ketoconazole with Fesoterodine: Accounting for Inhibition of P-gp-mediated Renal Secretion

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Objectives

Fesoterodine fumarate (hereafter referred to as "fesoterodine") is a once-daily oral medication for the treatment of Overactive Bladder (OAB). Fesoterodine is rapidly absorbed in humans and immediately and extensively hydrolyzed by non-specific esterases to the active metabolite 5- hydroxymethyl tolterodine (5-HMT). 5-HMT is then further metabolized via CYP2D6 and CYP3A4[1]. The predicted inhibition of 5-HMT clearance by a physiologically-based pharmacokinetics (PBPK) model including only inhibition of hepatic CYP3A4 after ketoconazole co-administration was underestimated compared with the observed results[2] . This is likely due to inhibition of both CYP3A4 and P-gp by ketoconazole. It is also reported that 5-HMT is a substrate of P-gp *in vitro*[3]and its renal clearance is approximately two-times greater than renal glomerular filtration rate[1]. This suggests the possibility that renal clearance of 5-HMT involves secretion involving P-gp. Therefore, it was considered that in addition to inhibition of CYP3A4, P-gp inhibition by ketoconazole could contribute to 5-HMT exposure increase. To improve model prediction of the effect of ketoconazole on 5-HMT pharmacokinetics, a PBPK model was constructed, incorporating the effects of P-gp inhibition on renal secretion.

Methods

The PBPK model including the contribution of P-gp on renal secretion was constructed using the mean plasma concentration and urinary excretion data of 5-HMT after administration of fesoterodine using Phoenix WinNonlin 6.3. The Ki values of ketoconazole for metabolic CYP3A4 clearance and renal P-gp secretion were estimated. The plasma 5-HMT concentrations with ketoconazole were simulated with/without P-gp contribution and the simulated results were compared with the observed study results.

Results

The estimated Ki of ketoconazole for CYP3A4 and renal P-gp were 0.24 ng/mL and 14 ng/mL, respectively. They were consistent with the reported values of 0.13 − 5 ng/mL for CYP3A4[4] and 12.7 ng/mL for P-gp[5], respectively. The simulated concentration profile co-administered with ketoconazole using the model with P-gp on renal excretion was comparable with the observed profile though the prediction without P-gp contribution was underestimated, especially around the peak.

Conclusions

The results of this PBPK modeling study demonstrated that of the effects on P-gp-mediated renal secretion of 5-HMT significantly contributed to the observed drug interaction of ketoconazole with fesoterodine.

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Methodology- PBPK

PM7-8

A Critical Comparison between CYP1A2 and 3A4 Ontogeny Profiles Used in Pediatric PBPK Models

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Objectives

Pediatric physiologically based pharmacokinetic models (p-PBPK) incorporate algorithms describing the ontogeny of CYPs, however, there are uncertainties regarding their prediction of the observed kinetics of probe compounds. The aim of this study is to compare the performance of three p-PBPK models containing different in vitro derived CPY1A & CYP3A profiles in predicting an in vivo ontogeny derived from the deconvolution of 'top down'clearance (CL) data of Caffeine (CAF)/Theophylline (THEO) as probes for CYP1A2 and iv midazolam (MDZ) as a probe for CYP3A4.

Methods

CYP1A2 and CYP3A ontogeny models [1-3] were used as input to whole organ metabolic CL option of Simcypv11 and population simulations performed to predict CAF, THEO and MDZ CL in 250 neonates, infants, children and adolescents. CL predictions were compared with those from in vivo data expressed as ml/min and allometrically scaled to 70 kg using a 0.75 exponent. A fixed and age changing milligrams of microsomal protein per gram of liver (MPPGL) values were assumed in separate simulations.

Results

For CYP1A2, comparison between models and observed CL values showed that all models under-predicted CYP1A2 ontogeny by up to 45% between 100 and 400 weeks PCA. For CYP3A, the Johnson model [3] with an average 5% difference between predicted and observed MDZ CL across the age range was the best ontogeny model giving the most accurate prediction of MDZ CL in neonates and infants. Using a fixed independent MPPGL value of 40 mg/g improved the CL predictions for all drugs.

Conclusions

Optimised ontogeny algorithms based on the development of in vivo CL for specific CYP1A2 and CYP3A4 probes could be used for the prediction of age dependent CL of other drugs where CYP1A2 and CYP3A have substantial role. Further validation of this methodology for other drug metabolising enzymes using specific probe substrates, followed by optimisation of the ontogeny of these enzymes for p-PBPK modelling is warranted.

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Methodology- PBPK

PM7-9   Ethnic Differences in Oral Clearance between East Asian and Western: Metaanalysis of 167 Studies for 26 Substrate Drugs of CYP3A4

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Objectives

This study aimed to investigate significance of ethnic differences in metabolizing clearance of mainly CYP3A4 between East Asian (EA; Japanese, Chinese and Korean) and Western (W) based on literature information.

Methods

Based on a systemic analysis of in vivo drug-drug interactions with inhibitors of CYP3A4 (1), substrate drugs of CYP3A4 were cautiously selected. Pharmacokinetics studies of these drugs were thoroughly searched and screened by severalconditions such as ethnics, formulations, food conditions, assay methods, and the doses in linearity. Ethnic ratios of the oral clearance were calculated based on geometric means of AUC. The clearances were not corrected by the body weight because its difference was not large for pharmacokinetic studies in general. The ethnic differences were analyzed considering inter-individual differences and inter-study differences. Monte-Carlo simulation was extensively used for the statistical analysis since the structure of data was complex and did not fit to conventional ANOVA.

Results

In the present study, 167 studies (62 and 105 studies for EA and W, respectively) of 26   substrate drugs were selected. Studies in EA consist of 53 Japanese, 5 Chinese and 4 Koreanstudies. Overall average of ethnic ratios of oral clearance (EA/W) was 0.93 (95%CI: 0.83~1.03). The ethnic ratios for Japanese/W, Chinese/W and Korea/W were 0.93, 0.93 and 1.07, respectively. The ethnic ratios (EA/W) were varied from 0.65 (Nisoldipine) to1.54 (Eletriptan). However, due to significant inter-study differences, the ethnic ratio of no drug reached statistical significance by Monte-Carlo simulation (p > 0.01). Overall, no significant difference was detected with regard to oral clearance of substrates of CYP3A4 in this analysis based on information from 167 studies with 3656 subjects. Similar analyses for substrates of CYP2C19 and CYP2D6 will also be presented.

Conclusions

The present study demonstrated that metabolizing clearance of the mostimportant enzyme, CYP3A4, in EA is practically the same as that in W, and that inter-study difference should be considered seriously in order to evaluate ethnic difference in pharmacokinetics.

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Other topics

PO-1

Developing Capabilities in Modeling and Simulation to benefit Healthcare in Poorer Countries

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Objectives

The poorer countries (also referred to as emerging or developing countries) have high burdens of communicable diseases, including malaria, HIV and TB while simultaneously dealing with non-communicable diseases like cancer, cardiovascular disease and diabetes. Modeling and Simulation (M&S) methodologies have been shown to be of value to patient care for these healthcare problems. However the scientific capabilities to apply these techniques are not widely available in the poorercountries. The purpose of this communication is to:- Highlight the need for capability development in Pharmacometrics with a focus on poorer countries- Provide examples of specific programs- Highlight the importance of academia-industry collaboration- Share these ideas with a view to solicit other collaborators and partners

Methods

Capability Development programs that we have experience with has 3 major components: - Medium duration (months) on-site research sabbaticals for hands-on training (examples are shown in references 1 and 2)- Short duration (weeks) scientific education via workshops and symposia (hosting institutions and/or examples are shown in 3,4,5)- These education programs are supported with limited infrastructure-building

Results

By both design and consequence, the programs have shown over-arching themes of: scientists engaging in mutual learning; creation of strong collaborative networks from outside and within emerging countries; development of ambassadors of science; building a strong basis of clinical pharmacology in addition to technical modeling skills.The modeling projects have typically sought to understand dosing in target patient groups especially local populations inwhom pharmacokinetic-pharmacodynamic (PKPD) information would not have been collected during the drug development process; development of knowledge of PKPD relationships via integration of in vitro, pre- and clinical data and genetic/genomic information.

Conclusions

Our experience suggests that building scientific capabilities in modeling and simulation in emerging countries has potential to bring value to patient care. The forums for scientific exchange have been successful in bringing together researchers from diverse disciplines (including microbiologists, geneticists, epidemiologists, statisticians, pharmacologists and clinicians) illustrating the cross-disciplinary linkages offered by pharmacometrics. We are committed to continue and expand these programs in the future.

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Other topics

PO-2 **Applications of Population Pharmacokinetics in Drug Labeling in Taiwan-a four-year (2008-2011) Survey of 79 New Drug Applications**

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Objectives

Population pharmacokinetic (PopPK) analyses have become an increasingly important component of New Drug Application (NDA) to support drug approval. The present study intends to investigate the use of PopPK in current drug labeling in Taiwan.

Methods

A retrospective review of data package of NDAs from 2008 to 2011 was reviewed.

Results

A total of 79 NDA submissions were submitted by sponsors from 2008 through 2011. The survey showed that approximately one-half of NDAs (56%) contain PopPK analysis data. A trend toward more PopPK analysis in the NDA submission was observed, with the percentage gradually increasing from 41.2% to 66.7% over the last 4 years. Notably, the application of PopPK analysis for biologicals was account for 83%, which is higher than small molecules (51%). According to the survey results, most of PopPK analysis information was presented in Clinical Pharmacology Section of the labeling. The information included the effects of gender (21 analyses), age (22 analyses), race (18 analyses), drug –drug interactions (3 analyses), disease state (15 analyses), body weight (19 analyses), renal impairment (14 analyses) and hepatic impairment (8 analyses) on the PK parameters. Although PopPK analysis were very helpful in assessing the potential drug interactions, the survey found relatively few analyses had been used to assess clinical drug-drug interactions. Factors such as the actual dose regimens of a coadministered drug and sampling time points were the major issues.

Conclusions

The application of population pharmacokinetics (PopPK) appears increasingly in drug labeling. Modeling and simulation is playing an increasing role in drug review process and is also a very useful tool to support the regulatory decision-making.

Other topics

PO-3

Population Pharmacokinetic Analysis in Bridging Study Evaluation

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Objectives

In accordance with "Double Twelve Announcement" from Taiwan Department of Health, all new drugs, especially new chemical entities, were required to conduct bridging study evaluation (BSE) before new drug application approval. For bridging study evaluation, only additional Asian pharmacokinetic and clinical data successfully assess the ability to extrapolate foreign data from the complete clinical data package to Taiwanese. Taiwan Center for Drug Evaluation has completed approximately 400 BSE cases based on ICH-E5 in the past eleven years. The purpose of this poster is to provide brief review of bridging study evaluation from pharmacokinetics' perspective, the contribution of traditional pharmacokinetic data and population pharmacokinetic analysis (Pop PK) involving Asian population in waiving bridging study evaluation, and regulator's thinking on this issue.

Methods

The submission of population pharmacokinetic analysis in bridging data package increased since 2007. Therefore, a retrospective review of bridging data package of BSE cases from 2007 to 2010 October submitted to Taiwan CDE was conducted. The assessment process of bridging study evaluation was based on ICE-E5 guidance. We defined one drug as one case regardless of the number of BSE submissions. From PK's perspective, the conclusion of BSE will be drawn in three kinds of result: ethnically sensitive, none to minimally ethnically sensitive, can not be determined. But the waiver of BSE would be determined by both pharmacokinetic and clinical section.

Results

The submission % of population pharmacokinetic analysis in BSE was 9.09%,, 10.0%, 25.0%, 26.32%, and 53.33%, respectively, from year 2007 to 2010 October. As compared to BSE cases which only submitted traditional Asian PK data, those cases submitting traditional Asian PK data and Pop PK has higher ratio to confirm the non-ethnic sensitivity and waived (82.61% vs. 77.78%).

Conclusions

Pop PK data is valuable in the bridging study evaluation. The review is still ongoing for further investigation.

Other topics

PO-4

Population Pharmacokinetic Modeling of Midazolam in Healthy Volunteers: Effect of CYP3A Mediated Drug-Drug Interaction

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Objectives

Midazolam is a probe drug for cytochrome P450 (CYP) 3A. The purpose of this study was to develop a population pharmacokinetic(PK) model of midazolam in healthy volunteers to evaluate the effect of CYP3A-mediated drug-interaction.

Methods

Twenty four healthy male subjects participated in a 3-treatment, 3-period, crossover study. Each subject received a 1 mg of midazolam in midazolam alone (control phase), 1 mg of midazolam after pretreatment with 400 mg ketoconazole once daily for 4 days (CYP3A inhibited phase), and 2.5 mg of midazolam after pretreatment with 600 mg rifampicin once daily for 10 days (CYP3A induced phase). The population PK analysis was performed using nonlinear mixed effect model (NONMEM®7.2) based on plasma concentrations in healthy volunteers receiving intravenous midazolam. PK model was developed and the first-order conditional estimation with interaction in NONMEM was employed for model run. A three-compartment model with first-order elimination described the PK. The influence of ketoconazole and rifampicin, CYP3A5 genotype, and demographic characteristics on PK parameters was examined. Goodness-of-fit (GOF) diagnostics and visual predictive checks were used to evaluate the adequacy of the model fit and predictions.

Results

Twenty four subjects contributed to 900 midazolam concentrations. Final parameter estimates (%relative standard error, RSE) were as follows; CL = 34.0 L/h (7.68%), Q_2 = 36.4 L/hr (9.48%), Q_3 = 7.40 L/hr (11.7%), V_1 = 70.7 L (3.62%), V_2 = 32.9 L (8.48%), and V_3 = 44.4 L (6.55%). Of the covariates, treatment effect (ketoconazole and rifampicin) and CYP3A5 genotype showed an influence on midazolam PK parameters; Midazolam CL was decreased to 32.5% in CYP3A inhibited phase and increased to 199.9% in CYP3A induced phase compared to control phase. Midazolam CL in CYP3A5*3/*3 genotype was decreased to 89.3% compared to CYP3A5*1/*3 group.

Conclusions

PK model for midazolam with treatment of ketoconazole and rifampicin was developed for healthy volunteers. Population PK modeling with drug-metabolizing enzyme modulatoin may be useful to predict drug-drug interaction quantitatively.

Other topics

PO-5

The Relationship between Drug Clearance and Body Size: Systematic Review and Meta-analysis of the Literature Published from 2000 to 2007

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Objectives

The aim of this study was to explore the use of body size covariates in population pharmacokinetic analyses for describing drug clearance (CL).

Methods

Population pharmacokinetic articles were identified from MEDLINE using defined keywords. A meta-analysis of studies was then performed to determine the average relationship reported between CL and total body weight (TBW). For each study, CL was calculated across the range of TBW for the study population and normalizedto allow comparison between studies. Body surface area (BSA), lean body weight (LBW), and allometric TBW and LBW relationships with exponents of 3/4, 2/3, and estimated values were evaluated to determine the relationship that best described the data overall. Additionally, joint distributions of TBW were compared between studies reporting a 'nonlinear' relationship between CL and TBW (i.e. LBW, BSA and allometric TBW-shaped relationships) and those reporting 'other' relationships (e.g. linear increase in CL with TBW, ideal body weight or height).

Results

A total of 458 out of 2384 articles were included in the analysis, from which 484 pharmacokinetic studies were reviewed. Fifty-six percent of all models for CL included body size as a covariate, with 52% of models including a nonlinear relationship between CL and TBW. No single size descriptor was more successful than others for describing CL. LBW with a fixed exponent of 2/3, i.e. $(LBW/50.45)^{(2/3)}$, or estimated exponent of 0.646, i.e. ~2/3, was found to best describe the average reported relationship between CL and TBW. The success of identifying a nonlinear increase in CL with TBW was found to be higher for those studies that included a wider range of subject TBW.

Conclusions

Although many studies reported a linear relationship between CL and TBW, the average relationship was found to be nonlinear. LBW with an allometric exponent of ~2/3 may be most suitable for describing an increase in CL with body size as it accounts for both body composition and allometric scaling principles concerning differences in metabolic rates across size.

References

Previously published in: McLeay SC, Morrish GA, Kirkpatrick CM, Green B. The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet. 2012 May 1;51(5):319-30.

Poster | **WCoP**

Other topics

PO-6 **The Modified Bland-Altman Method to Measure Agreement with Repeated Measures Data using Random Effects Model**

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Objectives
This study aimed to modify the Bland-Altman method which is used for evaluating agreement between two measurement techniques with repeated measures data through the random effects model.

Methods
The Bland-Altman analysis using a graphical method to plot the difference of two measurement techniques against the mean for each subject is most frequently used to assess agreement between two techniques. However, with repeated measures data, the standard Bland-Altman method ignores the time profiles of repeated measurements by summarizing them as a mean on each subject [1]. Random effects model using statistical package such as SAS (v.9.2) and R 2.14.0 considers correlations between observations from same subject and utilizes all the data.

Results
We compared the modified Bland-Altman methods using random effects model to the standard one using blood and breath alcohol concentrations. The modified plot had 10 times more points so that had more stocks of information including time effects. Furthermore, the modified Bland-Altman method using random effects model took additional explanatory variables such as time and measurement technique into account.

Conclusions
We analyzed agreement of two measurement techniques using the modified Bland-Altman method which utilized all the data and exposed the time profiles of differences between two measurement techniques. In addition, we outlined how our random effects model could account for the dependent nature of the repeated measures data, and additional explanatory variables, to provide reliable estimates of agreement in this setting.

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Other topics

PO-7   # Effect of Dissolved Oxygen in Alcoholic Beverages and Drinking Water on Alcohol Elimination in Humans

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Objectives

Oxygen plays an important role in the metabolism of alcohol. An increased dissolved oxygen level in alcoholic beverages reportedly accelerates the elimination of alcohol. Therefore, we evaluated the effect of dissolved oxygen in alcohol and the supportive effect of oxygenated water on alcohol pharmacokinetics after the excessive consumption of alcohol, i.e., 540 ml of 19.5% (v/v).

Methods

Fifteen healthy males were included in this randomized, 3×3 crossover study. Three combinations were tested: X, normal alcoholic beverage and normal water; Y, oxygenated alcoholic beverage and normal water; Z, oxygenated alcoholic beverage and oxygenated water. Blood alcohol concentrations (BACs) were determined by conversion of breath alcohol concentrations. Four pharmacokinetic parameters (C_{max}, T_{max}, K_{el}, and AUC_{all}) were obtained using non-compartmental analysis and the times to reach 0.05 and 0.03% BAC ($T_{0.05\%}$ and $T_{0.03\%}$) were compared using one-way analysis of variance (ANOVA) and7 Duncan's post-hoc test.

Results

With combination Z, the BAC decreased to 0.05% significantly ($p < 0.05$) faster than with combinations X. Analyzing the pharmacokinetic parameters, the mean K_{el} was significantly higher for combination Z than for combinations X and Y ($p < 0.05$), whereas the mean values of C_{max}, T_{max} and AUC_{all} did not differ significantly among the combinations.

Conclusions

Dissolved oxygen in drinks accelerates the decrease in BAC after consuming a large amount of alcohol. However, the oxygen dissolved in the alcoholic beverage alone did not have sufficient effect in this case. We postulated that highly oxygenated water augments the effect of oxygen in the alcoholic beverage in alcohol elimination. Therefore, it is necessary to investigate the supportive effect of ingesting additional oxygenated water after heavy drinking of normal alcoholic beverages.

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Other topics

PO-8

Establishing Standard Operating Procedures in Population Modeling: an Industry Experience with Population Pharmacokinetic Analysis Guidance

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Objectives

With the increase in the quantity of population pharmacokinetic (Pop PK)analyses submitted to regulatory authorities, the agencies have responded by issuing guidance with a view to improving the consistency and quality of Pop PK analyses [1,2]. Population modeling is an iterative process through "learning" and "confiming" phases of clinical drug development involving years of time [3].Choices made by analysts in building models can appear subjective and are often influenced by the analyst's experience, expertise, and tools used. Within a large organization, developing standardprocedures for analyzing and reporting Pop PK analyses would provide for higher quality more consistently. An industry experience is shared which strives for improved consistency, efficiency and a more systematic approach to model building through the development of a guidance for Pop PK analyses.

Methods

Experts organized within the Clinical Pharmacology community were tasked to develop a guidance on Pop PK analyses. An internal "Wikipedia" page was created to function as a hub for collaboration, collating viewpoints and refining documentation throughout the process. Approximately 3.5 months was required for the development and completion of the guidance.

Results

The guidance consisted of four areas: 1. Considerations prior to conducting a Pop PK analysis; 2. Considerations for base model development; 3. Development of a final model, including covariate model building; and 4. Standardizing graphical/ numerical diagnostics. The "standardized practices" included, but were not limited to, the following: 1) Development of an analysis plan; 2) Thorough data checks in advance of analyses to understand data and eliminate potential errors; 3) Inclusion of structural covariate parameters in the base model to ensure model stability when highly influential covariates are known ; 4) Incorporation of systematic procedures for covariate model building to improve consistency and harmonization across analyses; 5) Sensitivity analyses to check and challenge assumptions; 6) Development of a population modeling analysis report.

Conclusions

The importance and necessity of implementing a systematic, streamlined, and standardized approach to optimize and harmonize the processes which contribute to the Pop PK analysis cannot be overstated. As population modeling is an area of continually evolving science and technology, the guidance will periodically be updated and revised.

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