Tutorial 1 Introductory PBPK Modeling

The Value of PBPK in Drug Development & Regulation

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Continuous Transepidermal Drug Collection: Basis for Use in Assessing Drug Intake and Pharmacokinetics

Fig. 1. General mammillary model: drug enters the central compartment \( (A_1) \) by any of the indicated routes, and distributes into the collection device \( (A_c) \) and the peripheral compartments \( (A_2 \text{ to } A_l) \). Elimination can occur from either the central compartment or any of the peripheral compartments with rates \( K_E, K_{E2} \ldots K_{E_l} \)

\[
A_c(t) = \int_0^t \left\{ K_{1c} \left( \int A_1 \, dt \right) - K_{c1}A_c \right\} \, dt
\]
Bottom-up vs Top-down Modeling

**Top Down Modeling**
- Derived from PK observations
- Empirical compartmental models
- Population PK-PD

**Bottom Up Modeling**
- Mechanistic
- Genes/proteins/networks
- PBPK-PD unification

Adapted from ppt by Thomas Colatsky, FDA: Application of Mechanistic Modeling to Drug Safety Detection and Management at FDA, ACDRS May 7, 2010

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Affiliations

• **CDDS** ([http://cdds.ucsf.edu](http://cdds.ucsf.edu))

• **NDA Partners** LLC ([www.ndapartners.com](http://www.ndapartners.com))

• **SimCyp** SAB ([www.silmcyp.com](http://www.silmcyp.com))
Next 20 minutes

• A little history

• Progress

• Future
Heros of PBPK

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Torsten Theorel
1937

*Adapted from Rowland, SimCyp Workshop, SF 08
Bischoff & Dedrick
1968

Thiopental Pharmacokinetics
By K. B. Bischoff* and R. L. Dedrick

A mathematical pharmacokinetic model, including flow limitations, lipid solubility, protein binding, and metabolism, is used to make accurate predictions of the distribution of thiopental in four body regions. Tissue binding is correlated by means...
Evolution of PBPK Body Model *

‘Minimammal’ model
Bischoff & Brown, 1966

Full model

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Physiologically Based Pharmacokinetics in Drug Development and Regulatory Science: A Workshop Report (Georgetown University, Washington, DC, May 29-30, 2002)
Submitted: October 3, 2003; Accepted: December 30, 2003; Published: February 10, 2004
Malcolm Rowland,¹ Luc Balant,² and Carl Peck³

• Conference Goals:
  – Examples & potential utilities
  – Methodologies & issues

• Findings:
  – Few DD&R examples
    • Most examples in environmental toxicology
  – Potential Utilities
    • Drug candidate selection, preclinical prediction of human PK & metabolism, teratogenicity risk, lactation
• Findings:
  – Key methodologies available
    • PBPK models, estimation & simulation techniques
  – Then-current Issues
    • Software general but user unfriendly
    • Incomplete physiological & anatomical databases
    • Education, managerial & cultural barriers
Nine Years Later

Where are we?

• Increasingly substantial uptake
  – Industry (large pharma) FDA, EMEA

• Methodologies
  – More & more capable software
  – Expanded databases & software capabilities

• More progress needed
  – Education, managerial & cultural barriers
Nine Years Later
Where are we?

• Demonstrated & potential capabilities
  – Prediction of human PK & metabolism
    • CYP enzymes, transporters influences
    • Drug-drug & disease interactions
    • Site of drug administration & formulation influences
    • Candidate selection
    • Animal rule & EUA (bioterrorism, military)
  – Regulatory review & policy development
    • Pregnancy, Teratogenicity, Lactation
    • Pediatric drug development
    • Generic drug bioequivalence policy
PBPK-based Regulatory Guidance & Policy Development

• Generic Drugs:
  – Biowaivers for BCS Class II, III drugs, fed studies & products exhibiting multiple peaks
  – Locally acting GI drugs & skin/lung site of administration
  – Methods for characterizing complex products
  – Improved drug release profile criteria, Improved IVIC
  – Prediction of alcohol induced dose-dumping
  – Mechanism based formulation development
  – Non-small molecule products: liposomes, nanotechnology, multiple-component mixtures

• New Drugs:
  – Pregnancy & Lactation Guidances
  – Multiple drug interactions
  – DDI guidance – Ketoconazole regimen @ CYP3A4 inhibition
Quantitative Evaluation of Pharmacokinetic Inhibition of CYP3A Substrates by Ketoconazole: A Simulation Study

Ping Zhao, PhD, Isabelle Ragueneau-Majlessi, MD, Lei Zhang, PhD, John M. Strong, PhD, Kellie S. Reynolds, PharmD, Rene H. Levy, PhD, Kenneth E. Thummel, PhD, and Shiew-Mei Huang, PhD

The US Food and Drug Administration draft drug interaction guidance recommends that 400 mg ketoconazole (KTZ) be administered once daily for several days (QD400) for maximal CYP3A inhibition. Some investigators suggest that a single dose of 400 mg (SD400) KTZ is sufficient given its short half-life ($t_{1/2} \approx 3-5$ hr). To determine the impact of KTZ regimens on CYP3A inhibition, we simulated AUC fold-change (AUCR) in the presence of SD400, QD400, or 200 mg twice-daily (BID200) KTZ for theoretical CYP3A substrates. Ratios of AUCR ($\text{AUCR}_{\text{QD400}}/\text{AUCR}_{\text{SD400}}$ and $\text{AUCR}_{\text{BID200}}/\text{AUCR}_{\text{SD400}}$) increase with increasing bioavailability and increasing substrate $t_{1/2}$. The SD400 KTZ regimen may provide maximal inhibition only for a subset of substrates (ie, low bioavailability and short $t_{1/2}$). For substrates with $t_{1/2}$ longer than that of KTZ, multiple KTZ dosing is critical and BID200 appears to provide greater inhibition than QD400. Also, timing of KTZ administration should be optimized to allow maximal presystemic enzyme inhibition prior to substrate administration.

Keywords: Ketoconazole; pharmacokinetics; CYP3A inhibition; drug interaction; dosing regimen; bioavailability; half-life; FDA guidance

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From the Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration (Dr Zhao, Dr Zhang, Dr Reynolds, Dr Huang)

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# Submissions with PBPK Simulations

<table>
<thead>
<tr>
<th>Phase (software)</th>
<th>Submission</th>
<th>Recommendation/remarks</th>
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| 3 (SimCYP)       | - Metabolized by multiple CYPs  
- DDI with oral formulation available  
- Simulation showed less degree of CYP3A inhibition after i.v. | Under review: CYP contribution was calculated using data from one pathway only |
| 3 (Sponsor’s mechanistic/ PK-Sim) | - Multiple CYPs and renal elimination  
- Dedicated DDI and organ impairment data available a. Simulate CYP3A inhibition in renal impairment  
b. Simulate dosing in Pediatrics  
- Substrate with fm_CYP3A4<0.2  
- Negative DDI after 200 mg ketoconazole QD in vivo and simulations  
- Seek waiver of 400 mg ketoconazole QD study | Study in renal impaired patients taking CYP3A/Pgp inhibitor needed: Enzyme inhibition and renal impairment may not be independent  
Under review: Pediatrics  
Agreed |
| Pre-IND (SimCYP Gastroplus) | - Substrate of multiple CYPs  
- CYP2C9 predominant, CL is much lower in PM  
- Exclude CYP2C9 PM in first-in-man trial  
- Support the absence of non-CYP | Agreed |
FDA Lactation Guidance

- Although nonclinical models (e.g., mechanistic, in vitro, animal, physicochemical-based, and physiological-based PK (PBPK)) have demonstrated limited success in predicting the amount of drug in breast milk and in predicting infant exposures to drug in breast milk (Oo, Transport of Cimetidine, 1995; Oo, Alprazolam Transfer, 1995) the applicability of nonclinical predictive models is still under investigation. Because of this, data obtained from clinical lactation studies would enable testing of the predictive value of these nonclinical models. The incorporation of the additional information obtained from clinical lactation studies into nonclinical models would strengthen the association between predicted and observed exposures and optimally improve the predictability of such approaches.
EMEA Workshop on Modeling in Paediatric Medicines

• $5^+$/26 presentations on PBPK
• SimCyp, PKSim, GastroPlus, MoBi (MatLab)
• Utilities
  – Predicting PK, Metabolism
    • Midazolam, gabapentin
  – Understanding developmental influences on PK
Example
Teratogenic Risk of Tretinoin

• ~90’s: unregulated topical tretinoin for ‘wrinkles

• Tretinoin
  ~ 40x teratogenic as thalidomide
  ~10% systemically absorbed
  ?? Risk of fetal exposure & birth defects in to-be-marketed product (Renova, J&J)

• FDA requested PBPK simulation to assess risk of fetal exposure

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A physiologically based pharmacokinetic model for retinoic acid.

The predominance of the glucuronide pathway in human tretinoin metabolism, leading to detoxification, plays a major role in the calculation of the lower internal tretinoin dose in the PBPK model. The model predicts that topical exposure to tretinoin results in an internal exposure that is four to five orders of magnitude lower than a minimally teratogenic dose.
The data obtained in the clinical studies, and those discussed in the nonclinical pharmacokinetic section were used to develop a physiologically based pharmacokinetic model. The model was used to estimate maternal and fetal plasma concentrations of tretinoin and its metabolites in a theoretical abuse situation, i.e., after excessive application to face, lower arms, chest and neck and assuming exaggerated absorption of 10%. This model demonstrated that the systemic concentrations of tretinoin and potentially toxic metabolites achieved under such conditions remained several orders of magnitude below endogenous concentration and minimally teratogenic dose of retinoic acid.
Conclusions & Future

• PBPK is being employed more frequently in DD&R
  – Under-utilized
  – Powerful potential in multiple DDI’s, pediatrics, pregnancy

• Needed advances
  – PBPK-PD
  – Trial simulation

• Vision – continuous PBPK model throughout DD for understanding, trial design, labeling

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END
Fig. 2. Arthur Guyton’s computer model of the cardiovascular system. This was the first large-scale computer model that integrated many factors influencing the peripheral circulation, the heart, the endocrine systems, the autonomic nervous system, the kidneys, and body fluids. (Reprinted, with permission, from the *Annual Review of Physiology*, Volume 34 copyright 1972 (*Am J Physiol Regul Integr Comp Physiol* 287: R1009-R1011, 2004)}