Pharmaceutical Industry and Pharmacokinetics/Pharmacodynamics PRNs' Focus Session—Pharmacometrics in Drug Development and Research
Activity No. 0217-0000-11-094-L04-P (Knowledge-Based Activity)

Tuesday, October 18
1:15 p.m.–3:15 p.m.
Convention Center: Rooms 315 & 316

Moderator: Chee M. Ng, Pharm.D., Ph.D., FCP
Research Assistant Professor of Pediatrics, Children Hospital of Philadelphia; Director, CUDA Research Center for Drug Development, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Agenda

1:15 p.m.	Methodology and Techniques for Population Pharmacokinetic and Pharmacodynamic Analysis *Joan M. Korth-Bradley, Pharm.D., Ph.D., FCCP, FCP* Senior Director, Clinical Pharmacokinetics, Pfizer, Inc., Collegeville, Pennsylvania
1:35 p.m.	Role of Quantitative Clinical Pharmacology in Guiding Drug Development and Regulatory Decisions *Nitin Mehrotra, Ph.D.* Visiting Associate, Division of Pharmacometrics, Office of Clinical Pharmacology, U.S. Food and Drug Administration, Washington, D.C.
2:15 p.m.	Incorporating Population PK Studies into Clinical Research and Practice *Paul R. Hutson, Pharm.D.* Associate Professor of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin
3:00 p.m.	Question and Answer

Faculty Conflict of Interest Disclosures

Paul R. Hutson: employee of Midwest Pharmcokinetic Consulting, LLC.; serves as consultant/member of advisory board for Projections Research, Inc., Centocor, Genzyme, Mithridion, and Ameritox.
Joan M. Korth-Bradley: employee of Pfizer; owns Pfizer stock.
Nitin Mehrotra: no conflicts to disclose.

Learning Objectives

1. Understand the methodology and techniques for population data analysis.
2. Explain the use of pharmacometric modeling in drug development and approval.

3. Identify opportunities for practicing pharmacists to conduct population pharmacokinetics/pharmacodynamic research.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

Pharmacometrics in Drug Development and Research

18 October 2011

Methodology and Techniques for Population Pharmacokinetic and Pharmacodynamic Analysis

JM Korth-Bradley, PharmD, PhD, FCCP, FCP
Senior Director
Clinical Pharmacology, Pfizer, Inc.

Conflicts of Interest

I work for Pfizer Inc. and hold shares in the company. The opinions presented are my own and not intended to represent those of my employer.

The case studies involved do not advocate for use of products, but are used only as examples of pharmacokinetic/pharmacodynamics issues.

Presentation Objectives

- To provide an overview of methodology and techniques for population data analysis in drug development
- To set the stage for the other speakers about the use of pharmacometric modeling in drug development

Goal of Population Pharmacokinetics and Pharmacodynmics

- Describe PK and/or PD parameters
  - Central tendency
  - Amount of variability
  - Spare sampling limitations
- Identify characteristics responsible for differences between different groups of patients
- Models developed allow high-quality simulations

How to achieve these goals?

- Two-stage
  - Perform independent studies in two (or more populations) and then test for differences between them
  - Single-dose or multiple-dose
  - 10 to 12 blood samples over 4 to 5 half-lives or dosing interval
- Population analysis
  - Collect enough data to characterize population of interest and covariates of interest

Regulatory Guidances

- General pharmacokinetic directions
- Special populations
  - Pediatric subjects
- Population pharmacokinetics

Study Design Considerations

- GIGO – no amount of detail is too much
- Type of data collected
  - Drug administration (time, amount)
  - Plasma (blood/serum) concentrations (time)
  - Baseline subject information
    - Intrinsic (age, race, sex, size)
    - Extrinsic (concomitant medications, food/fast)
    - Pharmacodynamic/genetic
- Structural model

Study Design Considerations

- Optimal design considerations
- Amount of data
- Variability
- Length of time required for analysis
  - Model development
  - Model application
  - Model validation

Pharmacokinetic Methods

- NONMEM
  - Most commonly used software
  - Developed by UCSF, now ICON
  - Training courses available to start
  - Consultants available to perform analysis as well
- NPEM
- BigNPAG
- ADAPT II

Opportunities for Population Analysis in Drug Development

- Preclinical pharmacokinetics
- Toxicokinetics
- Physiological based pharmacokinetic models

Phase 1 – Healthy Volunteers

- SAD & MAD -> inform phase 2 dosing considerations
- Combine to obtain estimates of parameters for labels

Phase 1 Example

Population Pharmacokinetics of Tigecycline in Healthy Volunteers

S. A. Van Wart, MS, B. B. Cirincione, MA, E. A. Ludwig, PharmD, A. K. Meagher, PharmD, J. M. Korth-Bradley, PharmD, PhD, and J. S. Owen, PhD

Tigecycline, a novel glycylcycline, possesses broad-spectrum antimicrobial activity. A structural population pharmacokinetic model for tigecycline was developed based on data pooled from 5 phase 1 studies. Intravenous tigecycline was administered as single (12.5–300 mg) or multiple (25–100 mg) doses every 12 hours for up to 10 days. Three-compartment models with zero-order input and first-order elimination separately described the single- or multiple-dose full-profile data. Additional models were evaluated using a subset of the phase 1 data mimicking the phase II/III trial sparse-sampling scheme and dosage. A 2-compartment model best described the reduced phase 1 data following single or multiple doses and provided reliably accurate estimates of tigecycline AUC_{0-12}. This modeling supported phase II/III population pharmacokinetic model development to further determine individual patient tigecycline exposures for safety and efficacy analyses.

Keywords: *Tigecycline; pharmacokinetics; phase 1*
Journal of Clinical Pharmacology. 2007;47:727-737

Example -

- Data
  - 5 phase 1 studies
  - 2333 concentrations collected in 174 subjects
- Dose
  - 12.5 to 300
- Analysis
  - NONMEM V5, Level 1.1, FOCE
  - 3 compartment model for single dose
  - 2 compartment model for multiple dose
  - No covariates investigated

Two-stage Example

The Comparability of Etanercept Pharmacokinetics in Healthy Japanese and American Subjects

Shinichi Kawai, MD, PhD, Hisayuki Sekino, MD, PhD, Noriaki Yamashita, PhD, Shinichi Tsuchiwaki, MS, Hongji Liu, PhD, and Joan M. Korth-Bradley, PharmD, PhD

Thirty Japanese (J) and 32 American (A) healthy subjects received single doses of etanercept by subcutaneous injection, in 3 separate trials. Serum samples were collected for 480 hours after dosing. Concentrations were determined using enzyme-linked immunosorbent assay methods. Pharmacokinetic parameters were calculated using both noncompartmental and compartmental methods. Etanercept was slowly absorbed, with mean ± SD time to maximum serum concentration of 47 ± 15 hours (J) and 51 ± 20 hours (A). The maximum serum concentration and area under the concentration time curve increased for doses 10 mg, 25 mg, and 50 mg, in a linear relationship. Etanercept was slowly eliminated, with observed mean ± SD half life of 80 ± 26 hours (J) and 75 ± 15 hours (A) and mean ± SD apparent clearance of 144 ± 65 mL/h (J) and 132 ± 74 mL/h (A). Very low concentrations of etanercept were observed in the urine samples collected in the Japanese subjects. All adverse reactions observed resolved without issue, and none required discontinuation from the study.

Keywords: *Etanercept; Japanese; pharmacokinetics; TNFR; rheumatoid arthritis*
Journal of Clinical Pharmacology. 2006;46:418-423

Two-stage Example

- Data
  - 30 Japanese(study 1), 32 American (studies 2, 3)
- Dose
  - 10, 25, 50 mg (J) and 10, 25 mg (A)
- Analysis
  - Noncompartmental analysis of each individual
  - ANOVA to evaluate different populations
  - Dose proportional and no difference due to race detected

Phase 2 and 3 Example

ANTIMICROB. AGENTS CHEMOTHER., Nov. 2006, p. 3701–3707 Vol. 50, No. 11

Population Pharmacokinetics of Tigecycline in Patients with Complicated Intra-Abdominal or Skin and Skin Structure Infections

S. A. Van Wart[1]* J. S. Owen,[1,2] E. A. Ludwig,[1] A. K. Meagher,[1] J. M. Korth-Bradley,[1] and R. B. Cirincione[3]

Covington Corporation, Buffalo, New York[1]; Auburn University, Auburn, Alabama[2]; and Wyeth Research, Collegeville, Pennsylvania[3]

Received 25 December 2006/Returned for modification 26 March 2006/Accepted 29 August 2006

Tigecycline, a first-in-class expanded glycylcycline antimicrobial agent, has demonstrated efficacy in the treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal (cIAI) infections. A population pharmacokinetic (PK) model for tigecycline was developed for patients with cSSSI or cIAI enrolled in two phase 2 clinical trials, and the influence of selected demographic factors and clinical laboratory measures was investigated. Tigecycline was administered as an intravenous loading dose followed by a 0.5- or 1-h infusion every 12 h for up to 14 days. Blood samples were collected the day before or the day of hospital discharge for the determination of serum tigecycline concentrations. Patient covariates were evaluated using stepwise forward ($\alpha = 0.05$) and backward ($\alpha = 0.001$) procedures. The predictive performance of the model was assessed separately using pooled data from either two phase 3 studies for patients with cSSSI or two phase 3 studies for patients with cIAI. A two-compartment model with zero-order input and first-order elimination adequately described the steady-state tigecycline concentration-time data. Tigecycline clearance was shown to increase with increasing weight, increasing creatinine clearance, and male gender ($P < 0.001$). The final model provided a relatively unbiased fit to each data set. Individual predicted values of the area under the concentration-time curve from 0 to 12 h (AUC_{0-12}) were generally unbiased (median prediction error, −1.68% to −3.79%) and were ideally precise (median absolute prediction error, <4%) when compared across data sets. The population PK model provided the basis to obtain individual estimates of steady-state AUC_{0-12} in later exposure-response analyses of tigecycline safety and efficacy in patients with cSSSI or cIAI.

Phase 2 and 3 Example

- Data
  - 169 subjects from 6 studies, 631 concentrations
- Doses
  - 100 mg then 50 mg every 12 hours (0.5 and 1 hr)
  - 50 mg then 25 mg every 12 hours (1 hr infusion)
- Analysis
  - NONMEM V5, level 1.1, FOCE
  - 2 compartment model
  - Weight, CrCL, male -> increased CL

Phase 3 Example

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5100–5106 Vol. 54, No. 12

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Tigecycline Population Pharmacokinetics in Patients with Community- or Hospital-Acquired Pneumonia

Christopher M. Rubino, Alan Forrest, Sujata M. Bhavnani, Gary Dukart, Angel Cooper, Joan Korth-Bradley, and Paul G. Ambrose

Institute for Clinical Pharmacodynamics, Latham, New York; School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo, New York; and Wyeth Research, Philadelphia, Pennsylvania

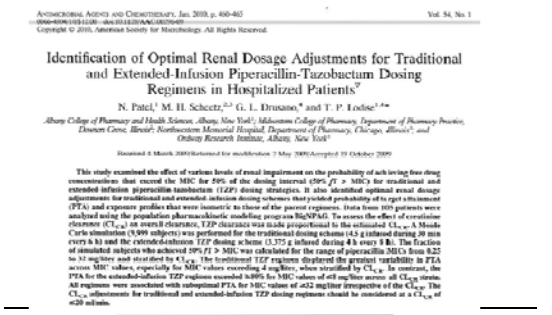
Received 6 October 2009/Returned for modification 25 March 2010/Accepted 26 September 2010

Tigecycline is a new-generation of tetracycline (glycylcyclines) and is active in vitro against bacteria that possess any of the classical genes that confer tetracycline resistance through ribosomal protection or efflux pumps. Herein, tigecycline disposition in patients with community- or hospital-acquired pneumonia was described using a population pharmacokinetic model. Additionally, the influence of covariates, such as body surface area, severity of illness, and clinical laboratory measures, on tigecycline disposition was evaluated. An intravenous loading dose of 100 mg was followed by 50 mg of tigecycline every 12 h. The final population pharmacokinetic model was a two-compartment model with linear elimination and with a relationship between tigecycline clearance and body surface area and creatinine clearance. The model was parameterized using total clearance (CL), the volume of the central compartment, distributional clearance from the central to the peripheral compartment, and volumes of distribution at steady state. Relationships between body surface area and creatinine clearance were identified as significant predictors of interindividual variability on CL. This model will serve as the basis for estimating tigecycline exposure for pharmacokinetic-pharmacodynamic analyses for efficacy and safety among patients with community- or hospital-acquired pneumonia.

Phase Three Example

- Data
  - 412 subjects from 3 studies, 1581 concentrations
- Doses
  - 100 mg then 50 mg every 12 hours
- Analysis
  - MCPEM implements using S-ADAPT using ADAPT II (USC)
  - BSA, CrCL -> increased CL

Pharmacodynamic Example



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2010, p. 460–465 Vol. 54, No. 1

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Identification of Optimal Renal Dosage Adjustments for Traditional and Extended-Infusion Piperacillin-Tazobactam Dosing Regimens in Hospitalized Patients

N. Patel, M. H. Scheetz, G. L. Drusano, and T. P. Lodise

Albany College of Pharmacy and Health Sciences, Albany, New York; Midwestern College of Pharmacy, Department of Pharmacy Practice, Downers Grove, Illinois; Northwestern Memorial Hospital, Department of Pharmacy, Chicago, Illinois; and Ordway Research Institute, Albany, New York

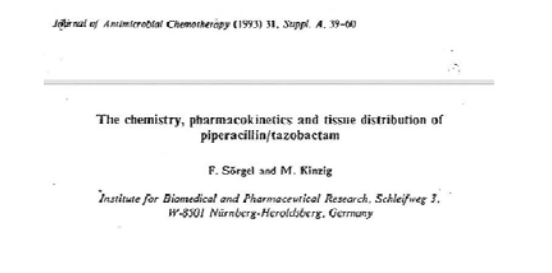
Received 6 March 2009/Returned for modification 7 May 2009/Accepted 10 October 2009

This study examined the effect of various levels of renal impairment on the probability of achieving free drug concentrations that exceed the MIC for 50% of the dosing interval (50% $fT > MIC$) for traditional and extended-infusion piperacillin-tazobactam (TZP) dosing strategies. It also identified optimal renal dosage adjustments for traditional and extended-infusion dosing schemes that yielded probability of target attainment (PTA) and exposure profiles that were isometric to those of the parent regimens. Data from 105 patients were analyzed using the population pharmacokinetic modeling program BigNPAG. To assess the effect of creatinine clearance (CL_{CR}) on overall clearance, TZP clearance was made proportional to the estimated CL_{CR}. A Monte Carlo simulation (5,000 subjects) was performed for the traditional dosing scheme (4.5 g infused during 30 min every 6 h) and the extended-infusion TZP dosing scheme (3.375 g infused during 4 h every 8 h). The fraction of simulated subjects who achieved 50% $fT > MIC$ was calculated for the range of piperacillin MICs from 0.25 to 32 mg/liter and stratified by CL_{CR}. The traditional TZP regimen displayed the greatest variability in PTA across MIC values, especially for MIC values exceeding 4 mg/liter, when stratified by CL_{CR}. In contrast, the PTA for the extended-infusion TZP regimen exceeded 90% for MIC values of ≤8 mg/liter across all CL_{CR} strata. All regimens were associated with suboptimal PTA for MIC values of ≥32 mg/liter irrespective of the CL_{CR}. The CL_{CR} adjustments for traditional and extended-infusion TZP dosing regimens should be considered at a CL_{CR} of ≈20 ml/min.

Pharmacodynamic Example

- Data
  - Model development – 105 patients, 873 samples
  - Validation – 12 patients, 90 samples
- Dose
  - 2,3,4 PIP + 0.25, 0.375, 0.5 TAZ over 30 minutes every 8 hours
- Analysis
  - BigNPAG (Leary et al), ADAPT II (USC)
  - Simulation to assess target attainment

Review Paper Example



Journal of Antimicrobial Chemotherapy (1993) 31, *Suppl. A*, 39–60

The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam

F. Sörgel and M. Kinzig

Institute for Biomedical and Pharmaceutical Research, Schleifweg 3, W-8501 Nürnberg-Heroldsberg, Germany

Review Paper Example

- 36 references cited
- Studies presented in tables
- No statistical summary of individual studies
- Overall ADME and pharmacodynamic evaluation

Conclusions

- Two stage and NONMEM are most commonly used methods to describe population pharmacokinetics
- Other software is available to perform population analyses
- Population models are useful in drug development

Incorporating Population PK Studies into Clinical Research and Practice

Paul Hutson, Pharm.D., BCOP
Associate Professor
University of Wisconsin School of Pharmacy
Associate Member
UW Paul P Carbone Cancer Center

Conflicts of Interest

- Principal / Owner of Midwest Pharmacokinetic Consulting, LLC
- PK Modeling consulting within past 12 months for:
  - Projections Research
  - Pfizer
  - Centocor
  - Genzyme
  - Mithridion
- No association/conflict with TDMS or EPIC

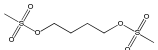
Learning Objectives

- Identify commercially available computer programs that provide empiric and Bayesian adaptive dosing recommendations.
- List three drugs that have been shown to be more accurately dosed using population pharmacokinetic parameters other than creatinine clearance and/or weight.
- Describe barriers to integrating population PK-based therapeutic drug management into an electronic medical record (EMR).
- Describe 3 justifications for integrating/linking Bayesian TDM into the EMR.
- Describe issues that should require human interpretation and approval of EMR-based TDM recommendations.

Presentation Outline

- Examples of Applied PopPK clinical research
  - Sampling design (Times and Numbers)
  - Strength in Numbers (Patients and Sites)
  - Pharmacodynamic Correlates
- Applying PopPK to the EMR in clinical practice
  - Which assay and target concentration or AUC?
  - How quickly is adaptive dose modification needed?
  - Which PopPK model will be used?
  - How is it linked to the Electronic Medical Record?

Busulfan



Bleyzac N, et al. BMT 2001; 28: 743-51

- Alkyl alkane sulfonate used for BMT conditioning treatment
  - Orally administered (eg., Q6h x 16 doses (4 d))
  - AUC_{6h} target is 5 – 7 mg*h/L
    - Substantial interpatient PK variability
  - Veno-occlusive disease (VOD) leads to hepatic failure and is a major problem with busulfan
    - Incidence is 20 – 30%
    - Mortality is 3 – 67% in varying studies

Busulfan

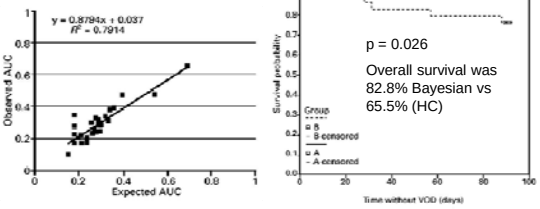
Bleyzac N, et al. BMT 2001; 28: 743-51

- N = 29 pediatric subjects
  - N=29 matched, historical controls
- Adaptive PK dosing
  - Test dose with 3 blood samples drawn based on D-optimality (1, 2.5, 5 hr)
  - USCPACK NPEM Bayesian program used to estimate subject's busulfan CL and determine dose for target AUC_{6h} = 6
  - Evaluation of AUC_{6h} daily with 2 samples

Busulfan

Bleyzac N, et al. BMT 2001; 28: 743-51

NPEM Bayesian methods allowed better AUC control, resulting in lower incidence of VOD and no difference in engraftment w.r.t. historical controls



p = 0.026

Overall survival was 82.8% Bayesian vs 65.5% (HC)

Pentobarbital Sedation

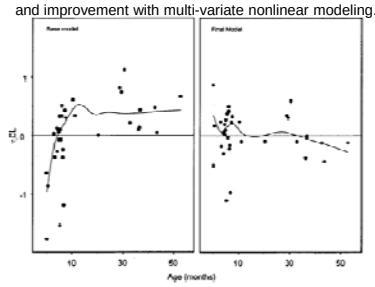
Zuppa AF, et al. J Pediatr 2011; 159: 414-9

- Pentobarbital used for pediatric sedation for post-op and some procedures
  - Substantial inter-patient variability
- MAP-Bayesian modeling performed (N=35)
  - PK samples drawn after bolus and at
    - 30, 60, 120 minutes
    - 4-6, 12-18, 18-24, 36-48, 56-72 hours after the bolus
  - NONMEM used to determine structural and covariate model
    - Age added to CL up to 12 months

Pentobarbital Sedation

Zuppa AF, et al. J Pediatr 2011; 159: 414-9

Rapid age-related maturation of pentobarbital clearance, and improvement with multi-variate nonlinear modeling.



Mycophenolate

- Immunosuppressant used to block de novo synthesis of guanosine by inhibition of IMPD
  - Administered as mycophenolate mofetil ester
  - De-esterified in intestine and liver to MPAcid
  - MPA is primarily glucuronidated to MPAG
  - Extensively bound to albumin (97-99%)
  - Extensive, variable enterohepatic recirculation
  - Usually TDM is based upon multiple linear regression from samples at 0, 0.5, and 2 hours

Multilinear Regression

Hampered by discrete sampling time points
Focuses on Clearance (AUC)
- Low variability of distribution volume assumed
- Limited ability to include covariates

Sampling times (h)	Model equation	r^2	rRMSE (%)
0, 0.66, 2	$8.64 + 5.13 \cdot C_0 + 0.62 \cdot C_{0.66} + 2.84 \cdot C_2$	0.70	14
0, 0.33, 2	$10.69 + 4.90 \cdot C_0 + 0.56 \cdot C_{0.33} + 3.33 \cdot C_2$	0.73	26
0, 1.25, 2	$10.09 + 6.39 \cdot C_0 + 1.03 \cdot C_{1.25} + 1.96 \cdot C_2$	0.73	27
0, 0.66, 1.25	$10.29 + 5.17 \cdot C_0 + 0.44 \cdot C_{0.66} + 1.26 \cdot C_{1.25}$	0.70	33
0, 0.33, 1.25	$8.35 + 7.04 \cdot C_0 + 0.54 \cdot C_{0.33} + 1.71 \cdot C_{1.25}$	0.69	35
0.33, 0.66, 2	$7.86 + 0.56 \cdot C_{0.33} + 0.58 \cdot C_{0.66} + 3.95 \cdot C_2$	0.67	36
0.33, 1.25, 2	$7.29 + 0.89 \cdot C_{0.33} + 0.90 \cdot C_{1.25} + 3.50 \cdot C_2$	0.62	41
0.66, 1.25, 2	$10.95 + 0.703 \cdot C_{0.66} + 0.17 \cdot C_{1.25} + 3.5 \cdot C_2$	0.62	41
0, 2	$15.53 + 5.84 \cdot C_0 + 2.98 \cdot C_2$	0.67	47
0, 1.25	$12.8 + 7.70 \cdot C_0 + 1.57 \cdot C_{1.25}$	0.64	48

Musuamba FT, et al. Clin PK 2009; 48: 746-58

Mycophenolate

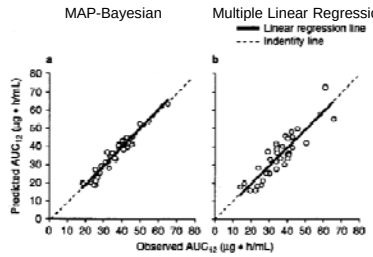
Musuamba FT, et al. Clin PK 2009; 48: 746-58

- N=40 stable adult renal allograft patients
  - Full PK profiles for MPA and MPAG were performed at baseline and at 60 and 270 days after switching from cyclosporin to sirulimus
    - MMF dosed at 1gm BID PO, then 0.75gm BID PO
    - NONMEM used to perform NLME modeling
    - N=27 training set; N=13 validation set

Mycophenolate

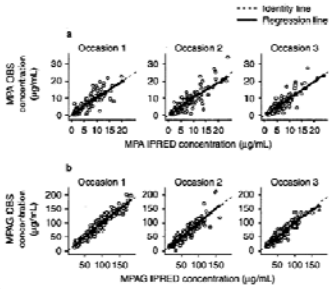
Musuamba FT, et al. Clin PK 2009; 48: 746-58

Bayesian method incorporating AST, ALT, GFR, and concurrent sirolimus dramatically improved the variability in predicting MPA clearance and AUC



Mycophenolate

Musuamba FT, et al. Clin PK 2009; 48: 746-58



Mycophenolate

Musuamba FT, et al. Clin PK 2009; 48: 746-58

Clearance Prediction Method	r^2	rRMSE	MRPE
Multiple Linear Regression	0.79	14%	0.9%
MAP-Bayesian	0.96	0.52%	19%

Equal # of samples drawn and assayed.

What is the benefit of better accuracy vs more a complex computational platform? Is the overall cost to the system decreased or increased?

Adaptive Retroviral Dosing

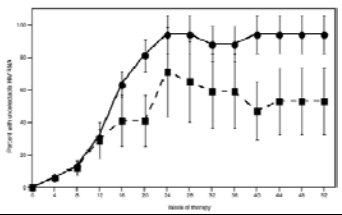
Fletcher CV, et al. 2002; 16: 551-60.

- N=40 adults with HIV (RNA>5000/ml)
  - Prospective, randomized, open-label trial
  - Zidovudine, lamivudine, indinavir
  - 1:1 randomization to conventional treatment vs concentration-controlled arms
  - 8 hr sampling after an observed dose (10 draws)
    - ADAPT II used for MAP-Bayesian estimation of individual patient PK
  - Need for dose increases common:
    - Zidovudine 44%, lamivudine 31%, indinavir 81%

Adaptive Retroviral Dosing

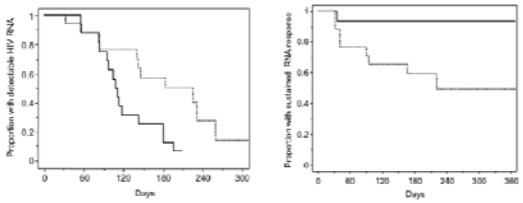
Fletcher CV, et al. 2002; 16: 551-60.

The time to achieve undetectable HIV RNA concentrations was reduced in patients with adaptive Bayesian antiretroviral control



Adaptive Retroviral Dosing

Fletcher CV, et al. 2002; 16: 551-60.

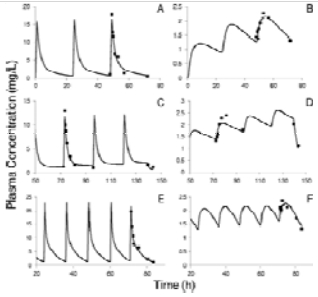


Patients with adaptive control of anti-retroviral concentrations (solid line) had a faster onset of and more durable absence of circulating HIV RNA

Antimicrobial Population PK and PD Modeling

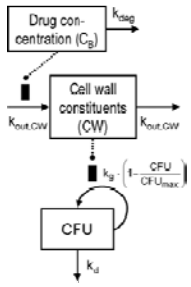
- Antimicrobials provide a convenient method of determining active drug concentrations in *in vitro* and *in vivo* models
- Knowledge or expectation of MIC or MBC, innoculum effect, and PK can guide drug dosing
- Response models can include innoculum effect, resistance *ab initio* or *post facto*,

Representative individual population PK model fits of Colistin Methane-sulfonate (A, C, and E) or formed colistin (B, D, and F) in critically ill patients



Garonzik, S. M. et al. 2011. Antimicrob. Agents Chemother. 55(7):3284-3294

Model for growth and bacterial killing by ceftazidime



CFUmax: Maximum population size

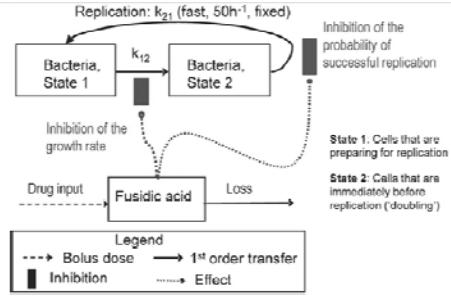
***k*out, CW: 1st order rate constant of the turnover of cell wall constituents**

kg: 1st order growth rate

kd: 1st order natural death rate

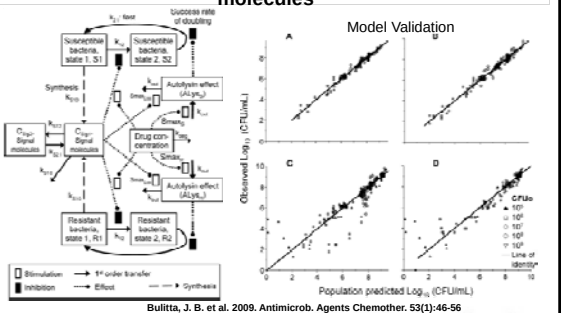
Bulitta, J. B. et al. 2009. Antimicrob. Agents Chemother. 53(1):46-56

Mechanism-based pharmacokinetic-pharmacodynamic model for fusidic acid against methicillin-resistant Staphylococcus aureus.



Tsuji B T et al. Clin Infect Dis. 2011;52:S513-S519

Mechanism-based model for ceftazidime against *P. aeruginosa* that describes the phenotypic tolerance at high initial inocula by cell-to-cell communication via signal molecules



Bulitta, J. B. et al. 2009. Antimicrob. Agents Chemother. 53(1):46-56

Moving Population PK from Clinical Research to Clinical Practice

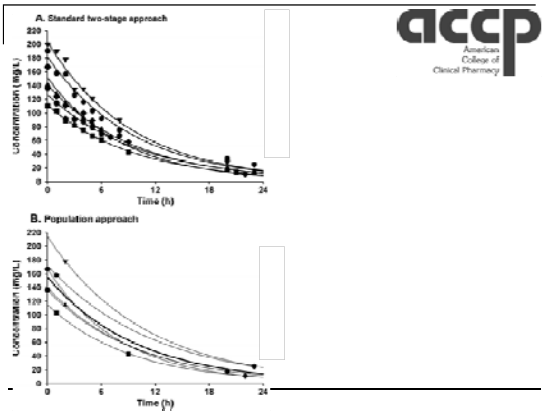
- Sampling
  - Numbers
  - Timing
  - Volume
- Assay
  - Sensitivity
  - Turn-around
- Data Entry
  - Dose, Dose time, and Sampling

Moving Population PK from Clinical Research to Clinical Practice

- User interface
  - Dedicated computer
  - Shared terminal
  - Porting to EMR (Lab, Pharmacy, Nursing, Demog)
- What software to use?
  - Home-grown?
  - Commercial (eg., TDMS)
  - Consortium
  - Transparency and Flexibility

Sampling Numbers and Times (thus Volume)

- Initial identification of population PK and variability with dense sampling is ideal
  - Often in Phase I trials
  - But often limited variability in the subjects
- D-Optimal design can help guide prospective timing of sparse samples (PK and PD)
  - ADAPT-II
  - PFIMOPT
  - WINPOPT

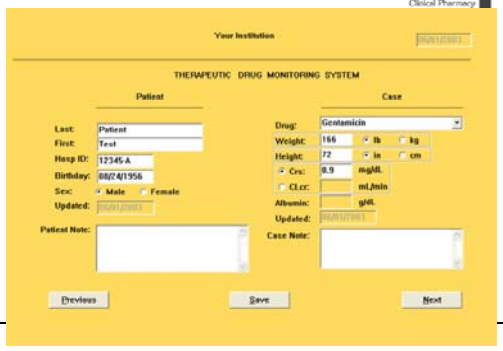


Commercial Systems

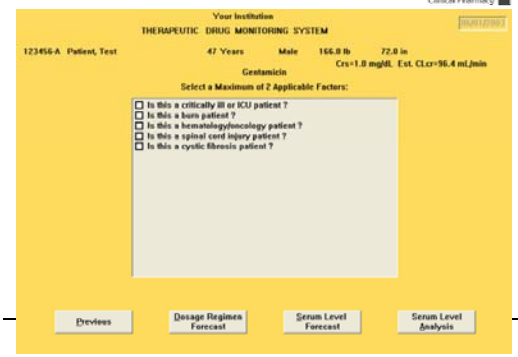
- TDMS provides MAP-Bayesian estimations as well as least squares estimates for more sample-rich patients
  - www.tdms2000.com
- Based upon Shiners program for ADVISE
  - Assumes normal parameter distribution
- Includes all past patient TDM info, but is time weighted
  - More recent samples are weighted more heavily

Personal Communication:Philip Johnson, PharmD, FASHP. Oct 4, 2011

TDMS



TDMS



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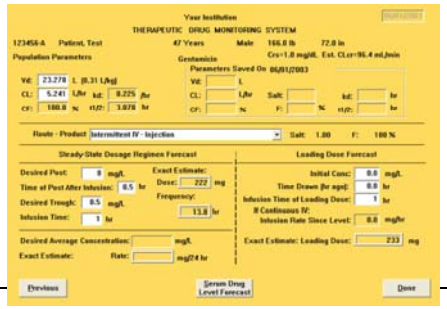

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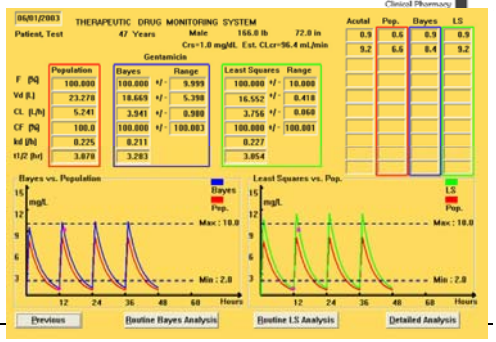

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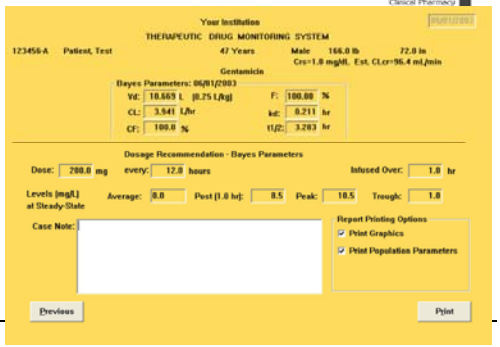
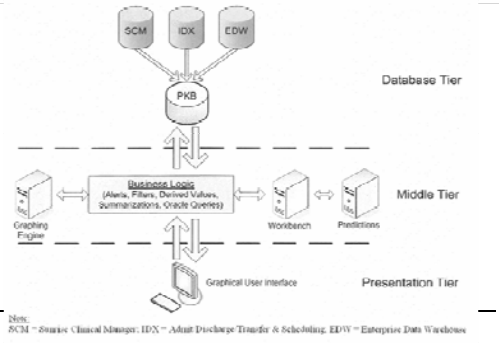
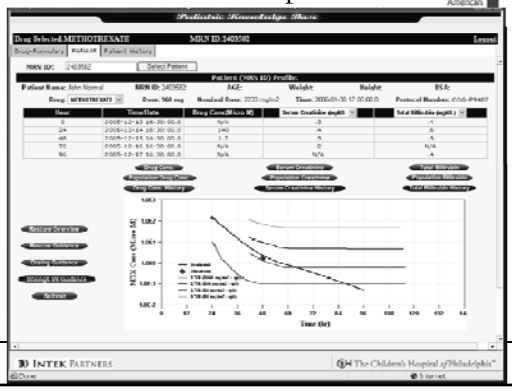


The CHOP TDM Dashboard

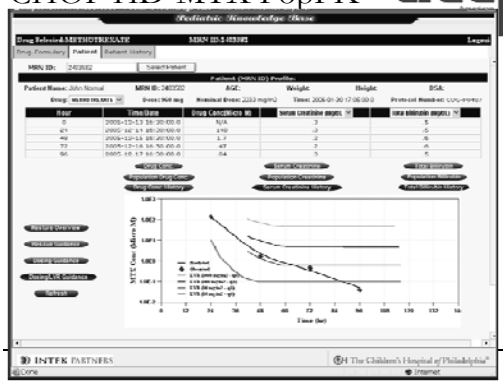
Barrett JS, et al. BMC Med Inform Dec Mak 2008; 8: 6



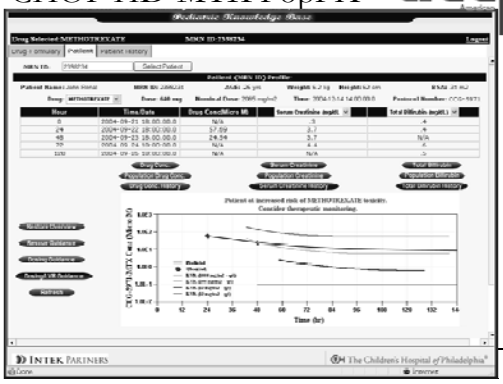
CHOP HD-MTX PopPK



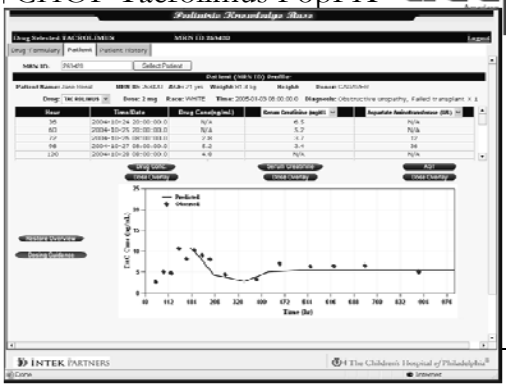
CHOP HD-MTX PopPK



CHOP HD-MTX PopPK



CHOP Tacrolimus PopPK



Who are the EMRs?

Vendor	Total Installations
Meditech	1,185
McKesson Provider Technologies	630
Cerner Corp	560
Siemens Medical Solutions	425
Self-developed	357
CPSI	353
Epic Systems Corp	265
Eclipsys Corp	243
Healthcare Management Systems	237

Live, in-process, or contracted. 2008. Source: HIMSS Analytics

What Data is Needed or Available from the EMR?

- Patient-specific information
  - Age, Wgt, Hgt, Sex, Race, Unique Identifier
  - Renal function [Scr]
  - Hepatic function (ALT, GGT, INR, ALB, BILI)
  - Genotype
    - Transporters (ABC, SLC)
    - Enzymes (CYP, UGT, DPD, GST, …)
    - Target Receptors
  - Bacterial MIC/MBC
    - For empiric dosing, MIC likelihoods
  - Concurrent Medications (and times of administration)

Which Bayesian Method or Program Should be Used?

- NONMEM
- S-ADAPT
- NPEM/MM
- Customized and Open-source?
  - GNU as a model
- Customized and open to Members?
  - SIMCYP as a model
- What criteria should be used, and who should decide the platform and algorithms?

Could we Agree on PopPK?

- Although the covariates tested in PopPK models are fairly consistent, their inclusion into the model is not necessarily so
  - Pediatric studies have a larger developmental (age) effect, but may have a small range of Scr
  - Disparate ethnic or regional groups may be less heterogeneous (eg, leaner in developing nations)
  - Dense PK sampling in Phase I studies to seek covariates is usually done in normals or those with decent labs and organ/body performance status

HD MTX PopPK Variability in Covariates

Whose PopPK model should we use?
Should we be constrained to one?

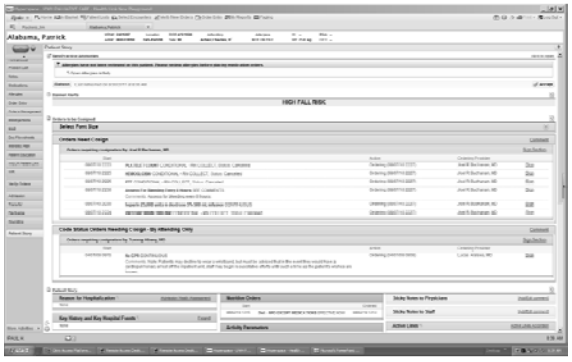
Study	Cohort	CL Covariates	V1 Covariates
Min (2009)	Asian, adult	CLcr (0.31-2.73mg/dl)	Wt (17-115)
Fukuhara (2008)	Asian, adult	CLcr	--- (Wt 29-80)
Aumente (2006)	Euro, peds	Wt (not Scr) (0.3–0.8mg/dl)	Wt
Dupuis (2008)	Euro, adult	ALT, CLcr	Hgt, BSA, Hgb

Central or Decentral?

- Centralized
  - Greater local control over appearance & parameters
    - Less concern with HIPAA
  - Higher workload (maintenance)
    - Customizable PK targets and algorithms
- Decentralized ("The Consortium")
  - PK algorithms and parameters less flexible
    - Less local PopPK expertise required
  - Heuristic adaptation with review of sites
  - Requires standardized porting protocols

Real-time PopPK Advice: Push or Pull?

- CPOE presents challenges – what should be pushed onto their screen?
  - MTX Conc vs Time pop-up on patient access?
    - _ Bayesian extrapolation?
  - MMP or Tacrolimus recommended dose based upon existing TDM values?
    - Incorporation of indices of toxicity?
  - Target Cmax for Aminoglycosides, or Dosing Interval for Beta Lactams?
    - Incorporation of Patient or Historical MIC/MBC data



Real-time PopPK Advice: Push or Pull?

- Interchange between the local clinician interface (many possible forms) and an off-site PopPK Bayesian prediction computer algorithm will create a finite lag.
  - Local Dashboard needs to make the available resources obvious or at least easy to access
  - Delay in the computations cannot be "excessive"
  - A "smart" system would know what the MD should want, and pre-load the information for him/her.

Real-time PopPK Advice: Push …

- HD-MTX Example
  - Sent to Off-site server (active or passive?):
    - Dose and time of MTX infusion
    - Patient covariates (Age, Wt, Ht, Scr, OAT1, OAT3, BCRP, …)
    - Subject's [MTX] and Site's MTX assay statistics
  - Off-site server calculates projected CvsT points
    - Plots and projections returned to local server
    - Estimates would load to Dashboard at clinician EMR access to patient

For Whom is the Bayesian PK System Intended?

- Demonstration studies performed by clinical pharmacologists at tertiary medical centers
  - Is this our target 'audience', or is it the rural physician with limited resources?
  - A Bayesian-based TDM system would in many ways be more 'drug smart' than most physicians regarding the effect of covariates on drug effect
    - 'Just Do It' (Black Box) vs
    - Here's why you should do it differently than normal
      - Educates clinician
      - Provides a double-check on assumptions made

Are Bayesian TDM Systems Cost Justified?

" 'Numbers only' TDM services ...will predominantly generate costs without gaining clinical benefits."

Cochrane EB Database and Medline review

- TDM services were only considered clearly cost-justified for aminoglycosides
  - This assessment for AG pre-dated use of extended interval dosing
- Vancomycin TDM considered cost justified in certain settings
  - Predates new dosing guidelines

Touw DJ, et al. Cost-effectiveness of therapeutic drug monitoring: A systematic review. Ther Drug Monit 2005; 27: 10-17.

Moving Forward…

- Where is the biggest Bang for our Buck?
  - Pediatrics
    - Poor understanding of PK over developmental epochs
    - Dramatic PK changes over relatively short periods
  - Organ transplantation
    - Guides dose modification
    - Clarifies later concerns about PK vs Adherence
  - Oncology
    - HD-MTX
    - Dramatic effects of PM/EM genotypes & phenotypes