

Application of Pharmacometrics in Pregnancy

Kevin M. Krudys, Ph.D.

Team Leader, Division of Pharmacometrics

Office of Clinical Pharmacology

Center for Drug Evaluation and Research

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Disclosures and Acknowledgements

- Disclosures
 - The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.
- Contributors to the ideas presented today
 - Members of the Division of Pharmacometrics & Office of Clinical Pharmacology
 - Previous collaboration at the University of Washington

Goal: Appropriate Dosing During Pregnancy

- Understanding of PK and PD data in pregnancy is important when:
 1. The drug is known or anticipated to be prescribed in or used by pregnant women (especially 2nd and 3rd trimesters)
 2. Use is expected to be rare, but the consequences of inappropriate doses are great (e.g., narrow therapeutic range drugs)
 3. Pregnancy is likely to alter significantly the PK (or PD) of a drug

Challenges: Deriving Dosing in Pregnancy

- Parallels to pediatric drug development
 - Considered an “orphan” population with respect to drug development
 - Ethical considerations when conducting studies
 - Limits to blood sampling
 - Recruitment challenges
 - Expected changes in pharmacokinetics
- Questions include:
 - Is the exposure-response relationship expected to change during pregnancy?
 - What is the dose during pregnancy to achieve a target concentration?

Application of Pharmacometrics: Efficient Design and Analysis of Studies

- Leveraging prior knowledge
 - Pharmacology, physiology, drug-specific properties
- Design
 - Optimal sample size, blood samples
 - Dose selection
 - Trial execution
- Analysis
 - Impact of covariates (e.g., gestation) on pharmacokinetics
 - Simulation of dosing regimens



Pharmacometric Tools

Population pharmacokinetics

Physiologically based pharmacokinetic modeling

Optimal design

Clinical trial simulation

PK-PD analysis

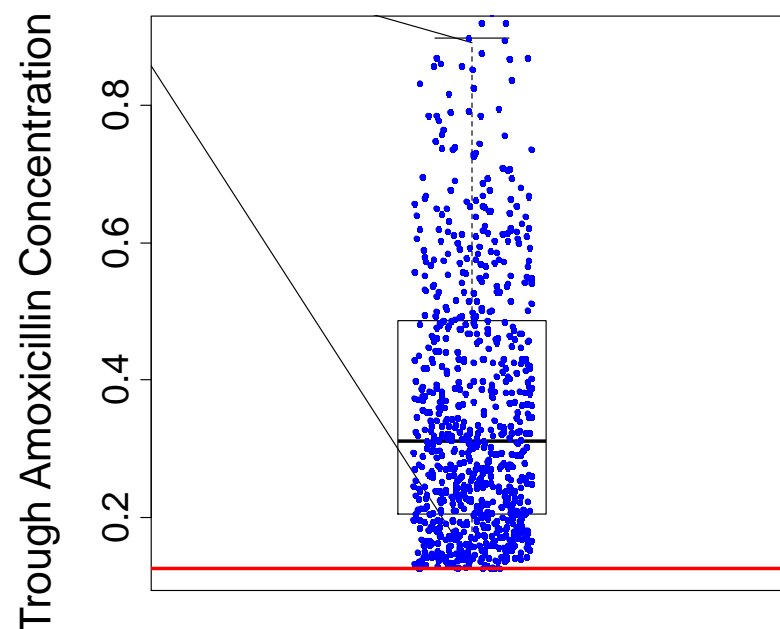
Case Study: Dosing of Amoxicillin in Pregnant Women for Post-Exposure Inhalation Anthrax

Non-Labeled Dosing of Amoxicillin for Post-Exposure Inhalation Anthrax

- Dosing for pregnant women in the event of an intentional release of or accidental exposure to penicillin-susceptible strains of *B. anthracis*
- Amoxicillin may be considered when other antibacterial drugs are not as safe to use
- Dosing recommendations are based on the following:
 1. Maintain plasma concentrations above an MIC of 0.125 mcg/mL
 2. Dosing intervals of less than 8 hours are not practical
 3. Consistent dosing recommendations regardless of pregnancy status
 4. Same dosing frequency in adult and pediatric patients

Approach to Amoxicillin Dosing Recommendations

- Pharmacokinetic data in adults, children and pregnant women (2nd trimester, 3rd trimester and postpartum) were obtained from various drug applications and literature*
- A population pharmacokinetic approach was used to characterize the concentration time-course of amoxicillin
 - Such an approach can be used to simulate dosing regimens that may not have been studied previously
- Simulations were performed at different dose levels (e.g, 500 mg and 1000 mg) and frequencies (e.g., 8, 6 and 4 hours)



Amoxicillin Dosing Recommendations: Pregnancy

Adult Recommended Dose: 1000 mg every 8 hours

Pregnancy Status	Trough (mcg/mL) Median [5th to 95th]	Time Above MIC 0.125 mcg/mL)		
		100% of dosing interval	75% to 100% of dosing interval	< 75% of dosing interval
2nd Trimester	0.20 [0.06 – 0.53]	77%	23%	0%
3rd Trimester	0.29 [0.10 – 0.71]	90%	10%	0%
Postpartum	0.29 [0.12 – 0.75]	93%	7%	0%
Non-Pregnant Adults	0.50 [0.16 – 1.36]	98%	2%	0%

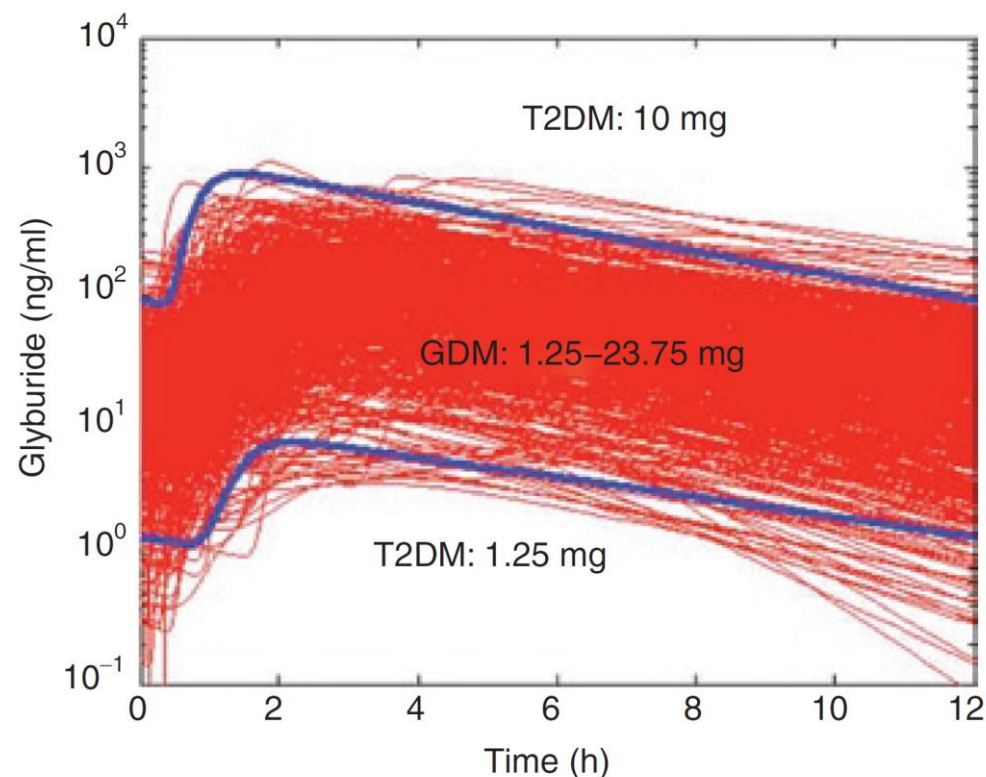
Case Study: PK/PD of Glyburide in Gestational Diabetes

Glyburide Use in Pregnancy

- Prevalence of gestational diabetes mellitus (GDM) is as high as 9.2% and poor glucose control can lead to adverse neonatal outcomes
- Glyburide dose (1.25 mg/day to 20 mg/day) in GDM is consistent with dosing in non-pregnant women with type 2 diabetes
- Little was known about potential effect of pregnancy on glyburide PK
- Objectives of study
 - Assess steady state PK of glyburide in women with GDM (n=40) and non-pregnant women with type 2 diabetes (n=26)
 - Assess model-derived markers of insulin sensitivity and beta cell function in GDM, type 2 diabetes and healthy pregnant women (n=40)

Glyburide Concentrations ~50% Lower in Pregnancy

- Increased clearance of glyburide possibly due to induction of CYP2C9 and CYP3A4
- Monte Carlo simulations were useful to identify doses in pregnant women that would match exposure to non-pregnant women with type 2 diabetes



Beta Cell Function (Corrected for Insulin Sensitivity) Lower in GDM than Healthy Women

- Model-based PD analyses were used to derive indices of beta cell function and insulin sensitivity from glucose, insulin and c-peptide data from a meal tolerance test

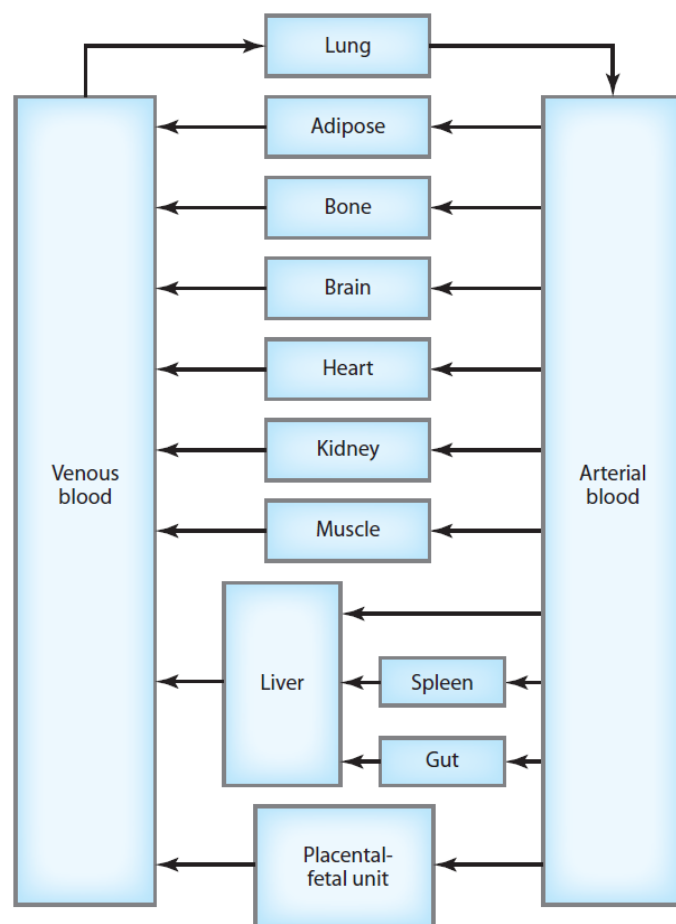
Parameter	GDM	Healthy pregnant
Insulin sensitivity (SI; $10^{-4} \text{ min}^{-1} \text{ per } \mu\text{U/ml}$)	1.2 ± 0.9	5.8 ± 3.9 ($P < 0.0001$)
β -Cell responsivity index (total) (Φ_{total} ; 10^{-9} min^{-1})	140.6 ± 99.9	124.0 ± 53.1 ($P = 0.7$)
β -Cell responsivity index (static) (Φ_s ; 10^{-9} min^{-1})	119.2 ± 87.1	95.4 ± 54.2 ($P = 0.5$)
β -Cell responsivity index (dynamic) (Φ_d ; 10^{-9} min^{-1})	$1,720 \pm 1,319$	$3,120 \pm 1,602$ ($P < 0.0001$)
Disposition index (DI; $10^{-13} \text{ min}^{-2} \text{ per } \mu\text{U/ml}$)	193.1 ± 225.5	698.8 ± 540.7 ($P < 0.0001$)
Peak post-MMTT glucose concentration	167 ± 33	122 ± 16 ($P < 0.0001$)

- Although insulin secretion was enhanced, the effect was not sufficient to overcome degree of insulin resistance

Conclusions: Role of Pharmacometrics

- Simulations were useful to derive doses in pregnant women that would match glyburide exposure to non-pregnant women
- Pharmacodynamic models were used to extract maximal information from meal tolerance test data
- Special considerations for dosing of glyburide in GDM
 - Fetal safety
 - Beta cell function might be fully augmented by glyburide in GDM, suggesting combination therapies targeting other aspects of disease (i.e., insulin sensitivity) may be appropriate

Physiologically Based Pharmacokinetics (PBPK)



- Mechanistic models incorporating drug specific and physiological parameters
- Allow for prediction of different populations/drugs
- Requires rich experimental data and some assumptions
- Can be used to support study design

PBPK Applications: Current Status

	Applications	Status
Drug-drug Interactions	<i>Drug as enzyme substrate</i>	<ul style="list-style-type: none"> Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling
	<i>Drug as enzyme perpetrator</i>	<ul style="list-style-type: none"> Use to confirm the lack of enzyme inhibition Additional evidence needed to confirm predictive performance for positive interactions
	<i>Transporter-based</i>	<ul style="list-style-type: none"> In vitro-in vivo extrapolation not mature Complicated by transporter-enzyme interplay Predictive performance yet to be demonstrated
Specific populations	<i>Organ impairments (hepatic and renal)</i>	<ul style="list-style-type: none"> Predictive performance yet to be improved System component needs an update
	<i>Pediatrics</i>	<ul style="list-style-type: none"> Allometry is reasonable for PK down to 2 years old Less than 2 years old ontogeny and maturation need to be considered
Others with limited experiences	<i>Pregnancy, ethnicity, geriatrics, obesity, disease states</i> <i>Food effect, formulation change, PH effect (including DDIs on gastric PH)</i> <i>Tissue concentration</i>	

High

Light



Low

Heavy

Wagner, CPT-PSP, 2015

PBPK Application: Utility and Future Promise

- Further incorporation of pregnancy-induced physiological and metabolic changes
 - ASCPT 2016 Posters PI-100 & PI-101 (pregnancy-induced OAT changes)
- Verification of model predictions in non-pregnant population before use in pregnancy
- Assessment of sensitivity of model predictions to key parameters
- Incorporation of maternal-fetal kinetics to predict fetal safety

Concluding Remarks

- Modeling and simulation is an important tool to integrate information and improve efficiency of studies in pregnant women
- Must take into account known exposure-response relationships for efficacy and safety as well as the safety of the fetus
- Future progress depends on ability to expand our knowledge of the physiological changes occurring during pregnancy