Bridging Drug Efficacy and Safety to the Obese: Considerations and Scientific Approaches
November 9th, 2022

How a Systems Approach May Help Drug Development Cater for Better Dose Adjustment in Obese Patients

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Declaration of Conflict of Interest

As the Director of CAPKR (Centre for Applied Pharmacokinetics Research my research is sponsored by a group of pharmaceutical companies (currently AbbVie, Amgen, Eli Lily, EMD Serono, Genentech, GSK, J&J, Servier, Takeda) in addition to grants from non-for-profit organizations, governments and research councils.

As the Chief Scientific Officer and SVP of R&D at Certara, I have been involved in overseeing the development of software tools which are used by a large group of pharmaceutical companies during drug discovery and development; particularly in the area of physiologically-based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP).

Disclaimer

This presentation is prepared in my personal capacity as a scientist engaged with clinical pharmacology and pharmaceutical science for over 30 years. The opinions expressed herein are my own and do not reflect the views, policies, and strategies of any of the organisations I am affiliated with.
Reality of Special Populations in Clinic

100 Years Old
Problem
Known within Modern Medicine.

Sir William Osler (1849-1919)
Professor of Medicine Oxford, England

“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no individuals react alike and behave alike under the abnormal conditions which we know as disease”

Issues with Current Drug Development

- Regulators,
- Professional Associations, and
- Patient Advocacy Groups

Are asking for more diversity in the clinical drug trials.

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry

FDA Guidance for Industry

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Clinical/Medical
November 2020
April 2022
On the Verge of Impossibility: Caring for All Permutations of Comorbidities Influencing the Fate of Drugs
Simulated postsurgical/presurgical AUC ratio over a range of selected drugs at LOW, MED, and HIGH therapeutic doses: Simvastatin Immediate Release (IR), Omeprazole Enteric Coated (EC), Diclofenac EC, Fluconazole IR, and Ciprofloxacin IR for:
(a) Roux-en-Y gastric bypass surgery (RY)
(b) Biliopancreatic Diversion with Duodenal Switch (BDDS)
(c) Jejunoileal Bypass (JI-B)
A Potential Solution to Address the Problem

Focusing on SYSTEMS rather than DRUG


Revers Translation in PBPK and QSP: Going Backwards in Order to Go Forward With Confidence

Amin Rostami-Hodjegan1,2

Combining the ‘bottom up’ and ‘top down’ approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data

Nikolaos Tsimopoulos, Amin Rostami-Hodjegan1,2 & Leon Aarons3

Clarifying Common Philosophical Misconceptions

Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20 years: in-depth analysis of applications, organizations, and platforms

Eman El-Khateeb, Susan Burkhill, Susan Murby, Hanca Amirat, Amin Rostami-Hodjegan, Amais Ahmad

Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program


- **Dose Selection**: 78.9%
- **Clinical Trial Simulation**: 47.7%
- **Mechanistic Safety**: 21.1%
In-Depth Analysis of Patterns in Selection of Different Physiologically-Based Pharmacokinetic Modeling Tools:

Part I - Applications and Rationale Behind the Use of Open Source-Code Software

Part II - Assessment of Model Reusability and Comparison Between Open and Non-Open Source-Code Software

Reusability Concept for Models

A computational model is considered entirely reusable if it may be utilised as a simulation component within other mathematical models, with its physical scope being the sole constraint.

Definitions - Current Analysis by the University of Manchester for PBPK Models Reusability

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Reusability</td>
<td>The reutilisation of (I) the model in its entirety, (II) the systems components, (III) the drug-dependent components, (IV) the modelling strategy, or (V) Leveraging the aforementioned</td>
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<tr>
<td>Partial Reusability</td>
<td>(II), (III), (IV) or (V) above</td>
</tr>
<tr>
<td>Full Reusability</td>
<td>(I) above</td>
</tr>
<tr>
<td>External Reusability</td>
<td>Reusability by researchers outside the organisations affiliated to original model development</td>
</tr>
<tr>
<td>Internal Reusability</td>
<td>Reusability of involving researchers from the same institution involved in the development of original model</td>
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</tbody>
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DDI still dominates the submissions

Virtual Patients to Conduct In Silico Trials

Biosimulation to predict how the attributes of body affect the drug fate in each population:

Possible Applications:

- First-in-Human Dosing
- Drug-Drug Interactions
- Clinical Study Design
- Pediatric Dosing
- Bioequivalence
- Formulation
- Renal Impairment
- Hepatic Impairment
- Reduced Cardiac Output
- Food Effect

Reusability for 25 Virtual Patient Populations & >100 Compound Files
Areas of Significant Impact: PBPK-IVIVE Approach

Clinical Trial Waivers  Extrapolation to Special Populations  Reduction in Study Patients

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-022-01169-4

SYSTEMATIC REVIEW

Altered Bioavailability and Pharmacokinetics in Crohn's Disease: Capturing Systems Parameters for PBPK to Assist with Predicting the Fate of Orally Administered Drugs

Sarah Alrubia1,2, Jialin Mao3, Yuan Chen5, Jill Barbel1, Amin Rostami-Hodjegan1,4,6

(1) Integration of Existing Data;
(2) Creation Non-Existent Data

Hepatic DMET

Intestinal DMET

Blood/Vascular System

Levels of e1-AGP

Levels of Albumin

Mesenteric Blood Flow

Relative Exposure (CDI/Healthy volunteers)

Gastrointestinal Motility

Gastric Emptying Time ↑

Intestinal Transit Time ↓

Intestinal pH

Small Intestine pH ±

Large Intestine pH ±

Gut Morphology

Gut wall thickness ±

Villus length ±

Epithelial cells shedding ±
Model Verification/Credibility Requires Multiple Drugs & Formulations

Same Changes in Physiology: Varying Impact on Different Drugs (Midazolam [MDZ] vs Budesonide [BDS])

What Does Validation Mean in This Context? e.g. DDI & RI

Effect of ketoconazole on the pharmacokinetics and safety of telithromycin and clarithromycin in older subjects with renal impairment

J. Shi¹, S. Chapel¹, G. Montay², P. Hardy², J.S. Barrett¹, D. Sica³, S.K. Swan³, R. Noveck⁴, B. Leroy¹ and V.O. Bhargava⁴

Renal Impairment (Clinical Study)

Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug-drug-disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice

Joseph A. Griffin⁵, Ping Zhao⁵, Julie Bullock⁶, Brian P. Booth⁶, Min Lu⁶, Kathy Robie-Suh⁶, Eva Gil Berglund⁴, K. Sandy Pang⁵, A. Sikir Rahman⁵, Lei Zhang⁸, Lawrence J. Lesko° and Shiew-Mei Huang°
Ten Years Later and with the Help of RWDA (Real World Data Analysis)

896,728 mild to mod RI
595,185 (66%) RI + Rx
67,835 (7.0%) RI & Rx
56725 (6.3%) RI +Pgp/CYP3A INH + Rx
20,957 (2.3%) RI had drug-induced bleed (DIB)
3,496/67,835 (5.2%) RI+Rx had DIB
3.171/3.496 (91%) RI +Pgp/CYP3A INH +Rx had DIB

Source:
SQL extracts from EHR from HIPAA-compliant anonymized individual-patient-level data from 117 U.S. institutions in the Cerner-Oracle RWD dataset for the 5 year period (1/2017−12/2021).

Analysis:
Fishers exact test

Conclusion:
Mild/Mod RI + Pgp/CYP3A INH +Rx approximately doubles the risk of drug-induced bleeding from 2.8% to 5.6%

Clin Pharmacokinet 2011; 50 (12): 809-822

Application of a Systems Approach to the Bottom-Up Assessment of Pharmacokinetics in Obese Patients
Expected Variations in Clearance

Cyrus Ghebali,1 Trevor N. Johnson,1 Mohsen Jannabi,1 Lisa M. Almond,1 Aurel Constant Allibi,1 Karen Rowlundi-Yoo,1 Masoud Jame1 and Amin Rostami-Hodjegan12

Cardiac output vs BMI

The National Institute of Health defines obesity as having too much body fat. It’s been described as the fastest growing public health challenge for the U.S. As the prevalence of obesity has increased, so have related health care costs.

Obesity: Key ‘Known’ Physiological Changes Then

Ghobadi et al., 2011

GI Physiological Differences in Obesity Known Since Then

Gastric Emptying: 
\[ T_{1/2} \] Is Shorter in Obese

Small Intestine in Obese:
- Higher Contractility
- Shorter Transit Time
- Lower Median pH

Effect of obesity on gastrointestinal transit, pressure and pH using a wireless motility capsule

**Trends: Bariatric Surgery**

A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution

Adam S. Darwich1, Devendra Pede2, Basil J. Ammor2,5, Masoud Jamei1, Darren M. Ashcroft* and Amin Rostami-Hodjegan*3,5

**ORIGINAL ARTICLE**

**Evaluation of an In Silico PBPK Post-Bariatric Surgery Model through Simulating Oral Drug Bioavailability of Atorvastatin and Cyclosporine**

AS Darwich1, D Pede2, K Rowland-Yeo2, M Jamei1, A Åsberg3, H Christensen4, DM Ashcroft* and A Rostami-Hodjegan*5,3

**Conduct of in Silico Bariatric Surgery**

**Not Just Anatomy: Bariatric Surgery induces villi elongation in rats**

(Mendieta, et al. 2012)
Exposure/Dose Ratio ↓ after JI-Bypass: Cyclosporine

[Graph showing the relationship between exposure and dose]

(Chenhsu et al. 2006)

Predicted ↑ AUC for MDZ but ... De-Supression of CL Post-Surgery?

The Pharmacokinetics of the CYP3A Substrate Midazolam in Morbidly Obese Patients Before and One Year After Bariatric Surgery

Margrit J. Brill, Anne van Rangen, Eric P. van Dongen, Bert van Ramshorst, Eric J. Hazebroek, Adam S. Darwich, Armin Rostami-Hodjegan, Catherine A. Knibbe
Estimates MDZ CL of 19 Obese Adolescents (red triangles represent orthopedic surgery patients, green triangles represent bariatric/laparoscopic surgery patients, black triangles represent other patients, i.e. tonsillectomy) vs BW. CL MDZ CL are reported for 20 morbidly obese patients (black dots) and 18 of these 1 year after bariatric surgery (grey dots, with dotted lines for corresponding values and healthy volunteer studies (grey squares). Black lines represent population mean estimates.

**LETTER TO THE EDITOR** 2018

Author’s Reply to Reith: “Higher Midazolam Clearance in Obese Adolescents Compared with Morbidly Obese Adults”

Anne van Rongen1, Johannes N. van den Anker2,3,4, Catherine A. J. Knibbe5,6

Suppression of CYP3A Activity as a Result of Prolonged Inflammation and Prolonged Obesity in Adults (as opposed to Adolescents)
‘Liquid Biopsy’ for ADME: Abundance & Activity

Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters

Brahim Achour1,3,4, Zuhida M. Al-Majed1b, Agnieszka Grybos-Gajniak1, Kristi Lee1, Peter Kilford1, Min Zhang1, David Knights1, Jill Barber1, Jeffrey Schagman1 and Amin Rostami-Hodjegan1,6

Liquid Biopsy for Patient Characterization in Cardiovascular Disease: Verification against Markers of Cytochrome P450 and P-Glycoprotein Activities

Brahim Achour1,2,3, Pauline Goselin1,2,3, Jean Terrier1,2,3, Yvonne Gloor1,2,3, Zuhida M. Al-Majed1b, Thomas M. Pollock1,2,3, Youcef Dakh2,3, Amin Rostami-Hodjegan1,6 and Jean-Luc Renz1,4

- In addition to several other enzymes, transporters and PD targets.

MR = metabolic ratio;
LB = liquid biopsy;
RPM = reads per million
Liquid Biopsy: Quantitative Grade for Virtual Twins

Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters

Traditional cancer diagnostic tests

Is the disease marker expressed?
- No
- Yes

Proposed liquid biopsy use

- High expression
- Medium expression
- Low expression

‘Liquid Biopsy’
A Game Changer for Handling Variability

Going Forward: PD Variability using Liquid Biopsy

- Can we address PD variability using liquid biopsy?
- 362 PD targets in plasma (23 as protein in liver), enzymes/receptors involved in inflammation, cancer, immune response and cirrhosis
- Established correlations for several PD targets: biomarkers of change in response to drugs & disease progression

The Link Between Pharmacodynamics and Physiologically Based Pharmacokinetic Models

V Perera¹, MA Elmeliegy¹, G Rao¹ and A Forrest¹

Response to “The Link Between Pharmacodynamics and Physiologically Based Pharmacokinetic Models”

A Rostami-Hodjegan¹,²

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 93 NUMBER 2 | FEBRUARY 2013
Correlations with Tissue Expression

**PD/Disease Targets**

- 362 PD targets in plasma:
  - **81 FDA-approved drug targets**
  - 202 with established link with disease
  - **Examples:** EGFR (drug target of anti-cancer TKIs and mABs); DPP4 (target of the anti-diabetics glitins); GPT (marker of liver function); LGALS4 (cancer prognosis marker)

**Hepatic & Renal FcRn Expression in Overweight/Obese Donors > Donors with Normal BMI**
Conclusion:

➢ Systems Approach Can Help with (*a priori*) Dose Adjustment in Obesity.
➢ However, Systems Data Are Required to Build Robust Population Models and Apply to Large Sets of Verification Cases.

Thanks for Listening

Questions?