A physiological approach to predicting pharmacokinetics in chronic kidney disease

Paul Malik, Cindy Yeung, Shams Ismaeil, Urooj Advani, Sebastian Djie and Andrea Edginton

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

Background

The current approach to approximating the pharmacokinetics of drugs in patients with chronic kidney disease (CKD) only accounts for changes in the estimated glomerular filtration rate. However, CKD is a systemic and multi-faceted disease that alters many body systems.

Objective

To develop and evaluate a **whole-body** mechanistic approach to predicting pharmacokinetics in patients with CKD

Chronic Kidney Disease

- Defined as a reduction in estimated renal function by at least 50% for longer than 3 months
- Multifactorial disease that is often comorbid with hypertension, diabetes and autoimmune disorders
- Progressive exponential decline in renal function until patients require dialysis to remove uremic solutes
- Doses of drugs that are renally eliminated must be modified to avoid toxicity in patients with renal impairment

Stage	Description [a]	eGFR (mL/min/1.73m^2) based on the Cockcroft-Gault equation
1	Control (normal) GFR	≥90
2	Mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	End-stage renal disease (ESRD)	<15

[a] Stages of renal impairment are based on K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation in 2002

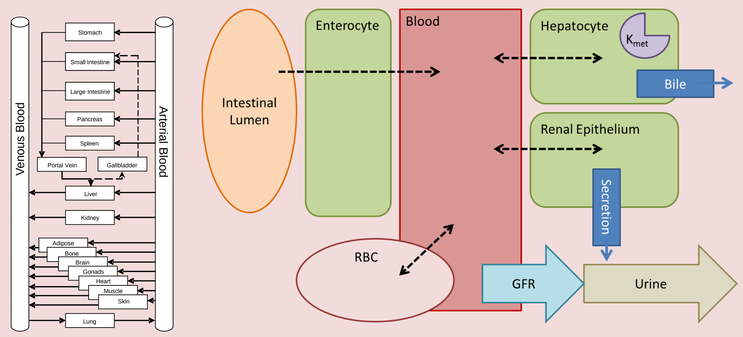
1. Build PBPK Model for Healthy Subjects

Drug Properties:
Lipophilicity
Molecular Weight
Water Solubility
Acid-Base Status
Protein Binding

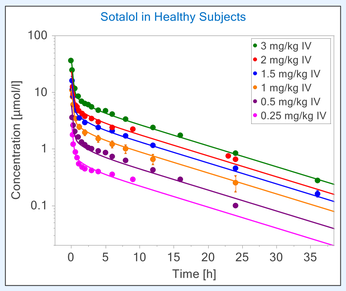
Physiology:
Organ Volume
Blood Flow
Body Composition
Hematocrit
GFR
GI Physiology

Clinical PK Data:
- Concentration-Time Profile
- Fraction Excreted to Urine

Physiologically-based Pharmacokinetic Model



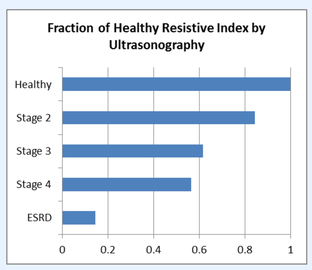
Optimize Uncertain Parameters:
- Assess Sensitivity
- Confirm Identifiability
- Monte-Carlo Estimation



OPEN SYSTEMS PHARMACOLOGY

2. Integrate CKD Physiology

Renal Blood Flow ↓

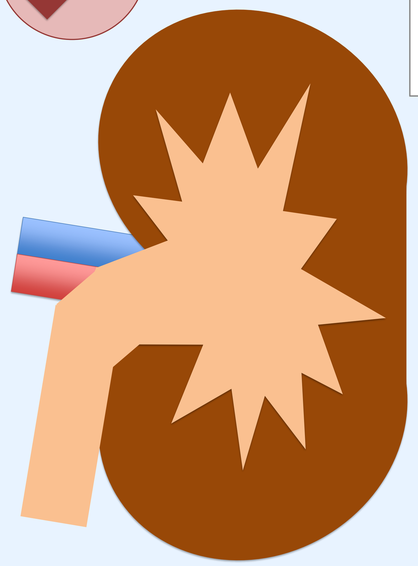


GFR ↓

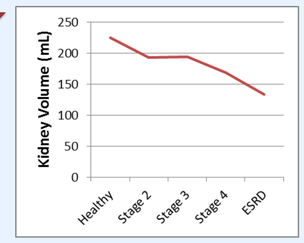
Small Intestine Transit Time ↑

Condition	Transit Time
Healthy	2.1 hours
Stage 4	3.15 hours
ESRD	4.2 hours

Gastric Emptying Time ↑ Increased by 60% in ESRD Patients



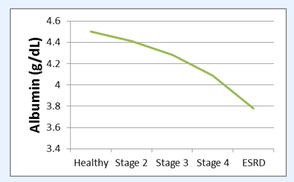
Kidney Volume ↓



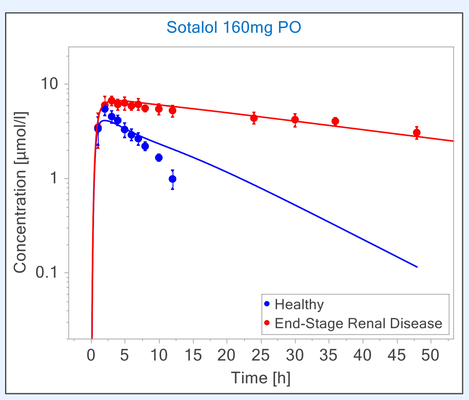
Hematocrit ↓

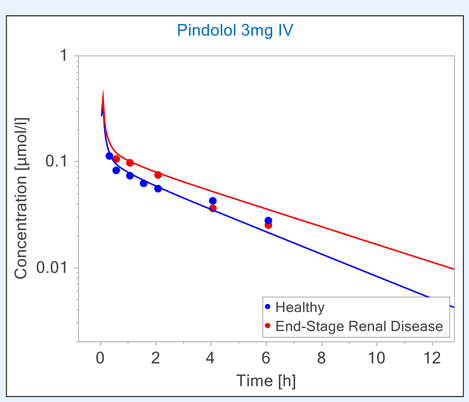
Condition	HCT
Healthy	0.450
Stage 3	0.405
Stage 4	0.367
ESRD	0.281

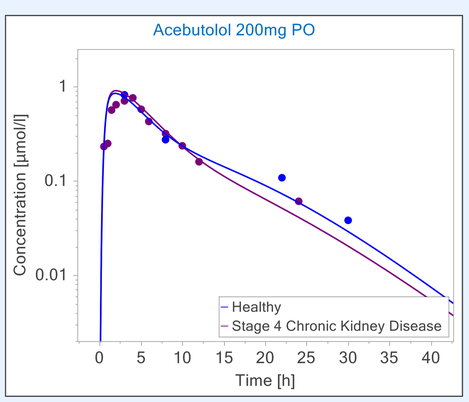
Albumin ↓

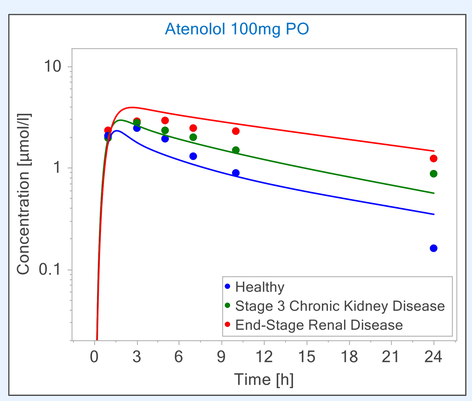


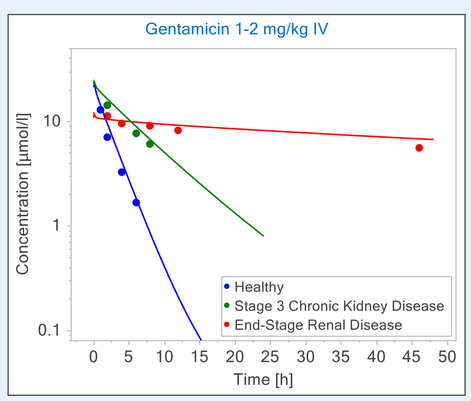
3. Evaluate Predictions

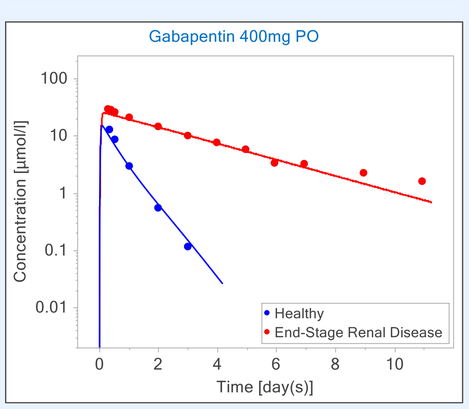


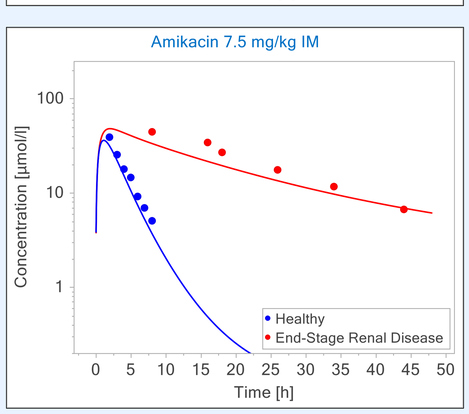


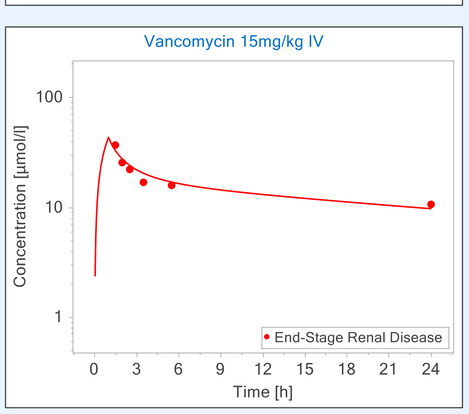












Conclusion

The whole-body mechanistic approach to CKD was successful for predicting the pharmacokinetics of eight drugs that are eliminated by filtration and/or tubular secretion to varying degrees.

Future Directions

- Further qualify the use of PBPK modeling to support clinical trial planning and post-market surveillance for renally-impaired populations
- Consider the effects of CKD on metabolic capacity in the liver