GLP-1-Induced Delays in GI Motility and Their Effects on Co-Administered Drug Absorption: A PBPK Analysis

Levi Hooper, PharmD; Shuhan Liu, PhD; Manjunath P. Pai, PharmD

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

SCAN ME

INTRODUCTION

Background

- Since the FDA's approval of glucagon-like peptide-1 (GLP-1) receptor agonists as a treatment for obesity, their use has surged across the United States amid rising obesity rates.
- GLP-1 agonists do not typically cause drug-drug interactions through cytochrome or transporter mechanisms.
- However, their impact on gastrointestinal (GI) motility could alter the pharmacokinetics of concurrent, orally administered medications in patients with obesity.

Objective

- To investigate the potential pharmacokinetic interactions between GLP-1-induced GI motility delays and commonly used co-medications, utilizing physiological-based pharmacokinetic (PBPK) modeling and simulation.

METHODS

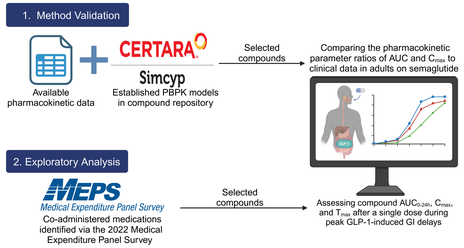

Figure 1. Study Schema

PBPK Modeling & Simulation

- **Software**: Certara's Simcyp® Simulator V23
- **Model Adjustments**: GLP-1-associated delays in gastric emptying and small intestine motility were incorporated by modifying model GI mean residence time parameters, using capsule endoscopy measurements in patients taking liraglutide.[1]
- **Simulations**: Performed on a virtual cohort of obese adults (n=100)

Method Validation

- **Compounds**: Atorvastatin, metformin, metoprolol, ethinyl estradiol, and digoxin (selected based on available PK data and established PBPK models)[2]
- **Analysis**: Compare the pharmacokinetic parameter ratios of AUC and C_{max} to clinical data in adults on semaglutide.

Exploratory Analysis

- **Compounds**: Rosuvastatin, valsartan, rivaroxaban, bupropion, and dabigatran (selected based on 2022 Medical Expenditure Panel Survey)
- **Analysis**: Assess compound $AUC_{0\text{-}24h}$, C_{max}, and T_{max} after a single dose during peak GLP-1-induced GI delays.

RESULTS

Co-administered Medication	AUC ratio	C_{max} ratio
Atorvastatin		
Simulated (90% CI)	1.00 (0.92-1.07)	0.76 (0.64-0.88)
Observed (95% CI)	1.01 (0.95-1.08)	0.66 (0.45-0.86)
Metformin		
Simulated (90% CI)	1.01 (0.92-1.10)	1.01 (0.92-1.11)
Observed (95% CI)	1.03 (0.97-1.08)	0.93 (0.86-0.99)
Metoprolol		
Simulated (90% CI)	0.89 (0.52-1.25)	0.96 (0.84-1.07)
Observed (95% CI)	1.19 (1.11-1.28)	1.32 (1.20-1.45)
Ethinylestradiol		
Simulated (90% CI)	1.02 (0.91-1.12)	1.00 (0.81-1.18)
Observed	1.07 (1.05-1.10)	1.02 (0.99-1.07)
Digoxin		
Simulated (90% CI)	1.04 (0.82-1.26)	0.86 (0.70-1.02)
Observed (95% CI)	1.01 (0.98-1.06)	0.95 (0.88-1.02)

Table 1. Predicted and observed AUC and C_{max} ratios for oral medications co-administered with Semaglutide

- The Simcyp® Simulator V23 effectively predicted the pharmacokinetic exposure ratios of the selected assessment compounds, with most predictions aligning within the 95% confidence interval of the observed semaglutide data **(Table 1)**.
- In the exploratory analysis of medications identified from the 2022 MEPS, the model predicted that peak GLP-1 delays increased the $AUC_{0\text{-}24h}$ for rosuvastatin, valsartan, and dabigatran by 65-, 82-, and 132%, respectively **(Figure 2)**. Additionally, these medications showed delayed T_{max} and, to a lesser extent, increased C_{max}.

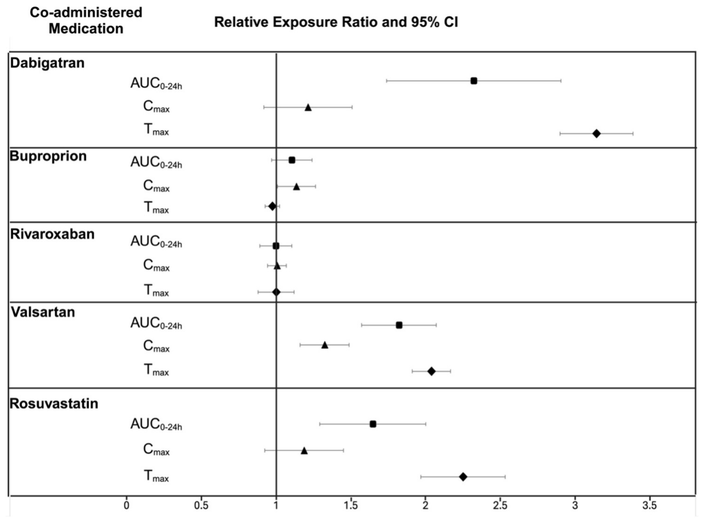

Figure 2. Predicted relative exposure ratio and 95% CI for commonly co-administered medications identified in MEPS 2022 survey data during peak GLP-1 effect on GI motility.

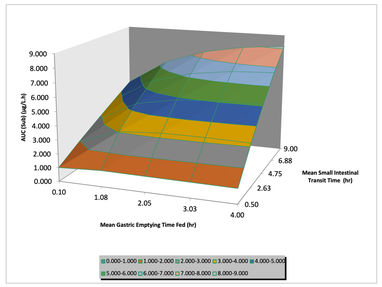

Figure 3. The effect of GLP-1-associated delays in gastric emptying and small intestine motility on dabigatran exposure

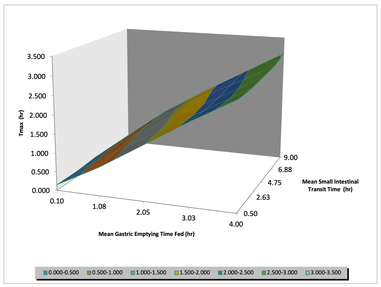

Figure 5. The effect of GLP-1-associated delays in gastric emptying and small intestine motility on dabigatran T_{max}

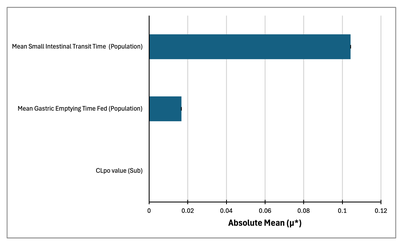

Figure 4. Morris method global sensitivity analysis of gastric emptying and small intestine motility inputs on the fraction of dabigatran absorbed (Fa)

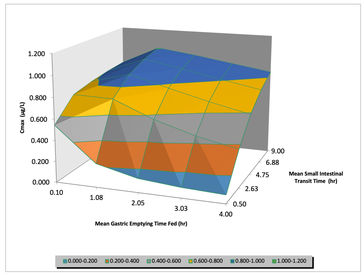

Figure 6. The effect of GLP-1-associated delays in gastric emptying and small intestine motility on dabigatran C_{max}

Sensitivity analyses were conducted for dabigatran to evaluate the influence of GI input parameter's on the predicted PK profiles.

- **$AUC_{0\text{-}24h}$**
  - Increased AUC due to longer small intestinal transit time, enhancing absorption **(Figure 3)**.
  - Global sensitivity analysis reveled minimal effect of gastric emptying time on absorption compared to mean small intestinal transit time **(Figure 4)**.
- **T_{max}**
  - Increased T_{max} caused by prolonged gastric emptying **(Figure 5)**.
- **C_{max}**
  - Sensitivity analyses showed that while C_{max} was less affected overall, it depends on gastric emptying time. Prolonged emptying time leads to a decrease in C_{max} **(Figure 6)**.

CONCLUSION

Analysis Overview

- Out of the 10 drugs analyzed, 7 showed no clinically significant pharmacokinetic (PK) changes. However, our findings suggest that GLP-1-induced delays in GI motility can alter drug exposure metrics like AUC, C_{max}, and T_{max}.

Key Findings

- **Dabigatran:** A significant increase in AUC was observed for dabigatran, indicating potential safety risks due to GLP-1-induced delays in GI motility. This increase was linked to prolonged small intestine transit time, as confirmed by sensitivity analyses.
  - This change may result in a clinically significant risk of bleeding due to the anticoagulant's narrow therapeutic index.

Implications

- **Predictive Value of PBPK Models:** This study demonstrates the critical role of PBPK modeling in predicting drug-drug interactions, particularly for medications with a narrow therapeutic index, such as dabigatran.
- **Clinical Relevance:** PBPK models play a crucial role in enhancing drug safety and efficacy. Understanding these interactions is essential to optimize drug therapy, especially with the increasing use of novel biologics.

Next Steps

- Further validation against clinical data is essential to confirm these findings and ensure the safe co-administration of GLP-1 agonists with other medications.

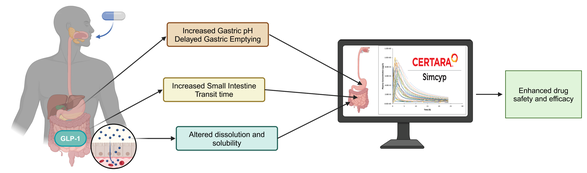

Figure 7. Using PBPK to investigate GLP-1 Drug-drug interactions.

ACKNOWLEDGEMENTS

Funding: Levi Hooper is supported by an NIH T32 (T32TR004371).
Software: Certera® SimCyp Academic license.
COI: The authors have no conflicts of interest to disclose.

References

1. Nakatani Y, Maeda M, Matsumura M, Shimizu R, Banba N, Aso Y, Yasu T, Harasawa H. Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy. Diabetes Metab. 2017 Oct;43(5):430-437. doi: 10.1016/j.diabet.2017.05.009. Epub 2017 Jun 23. PMID: 28648835.
2. Nordisk, N. (2021). WEGOVY (semaglutide) injection. *US Food and Drug Administration*.