M1030-02-09

Integration of Gut Microbiome Metabolism in a PBBM-PBPK Model: its impact on the Sulfasalazine absorption

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PURPOSE

- Inflammatory bowel disease (IBD) is a recurrent or continuous inflammation of the bowel that affects 1.4 million patients in the United States.
- The two main forms of IBD are Crohn's disease and ulcerative colitis.
- IBD's first in-line treatments are sulfasalazine and its metabolite 5-aminosalicylic acid (5-ASA, also called mesalamine). 5-ASA is produced by the gut microbiome present in the colon lumen (Figure 1).
- Development of generic drug products for IBD is based on pharmacodynamic endpoint studies as the local concentration at the site of action cannot be sampled in humans and may not be reflected in plasma exposure.
- Physiologically based pharmacokinetic (PBPK) models can provide insight into drug partitioning into the gut wall.
- PBPK may support the development and regulatory assessment of GI locally acting new and generic drug products.

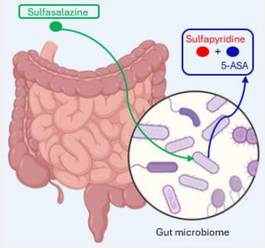

Figure 1: sulfasalazine biotransformation in the colon lumen

OBJECTIVE

- To develop a PBPK model for 5-ASA in healthy subjects.
- To predict sulfasalazine & 5-ASA systemic exposure following sulfasalazine oral (PO) administration in healthy subjects.

METHODS

- All simulations were performed using GastroPlus® version 9.8.2 (Simulation Plus Inc., Lancaster, CA, USA).
- The extended Advanced Compartmental Absorption and Transit (ACAT™) model was used to build all PBPK models (beta version of extended ACAT model, including transverse colon, descending colon, sigmoid colon, and rectum).
- Physicochemical, biopharmaceutical, and clearance parameters were obtained from the literature; or predicted from sulfasalazine & 5-ASA chemical structure using the ADMET Predictor® module v.10.4.
- Development and validation of the PBPK models were done following the workflow presented in Figure 2.
- Models were deemed acceptable if calculated fold errors for both Cmax and AUC_{0-t} ratios were within two folds for each study.

Development and validation of a PBPK model for 5-ASA using 2 IV and 1 PO clinical studies[1,2,3]

Connection of both 5-ASA and sulfasalazine PBPK models[4] + fit of gut microbiome non-linear clearance parameters (Vmax and Km)

Validation of the PBPK model connecting 5-ASA and sulfasalazine using 1 PO clinical study[5]

Figure 2: sulfasalazine & 5-ASA PBPK models development and validation workflow

RESULTS

5-ASA

- PK metrics (Cmax and AUC_{0-t}) for 5-ASA were predicted within two-fold for each study used to develop and validate its PBPK model (Figure 3).
- The 5-ASA PBPK model was used to simulate the concentration at its site of action *i.e*, in the different layers of the colonic segments (mucosa, submucosa, and muscularis propria) (Figure 3E additionally shows 5-ASA concentrations in the ascending colon segment).

Table 1: Ratios of 5-ASA PK parameters for IV & PO simulations

Simulation	PK parameters	Observed (O)	Predicted (P)	P/O
IV bolus – 100mg dose	AUCt (ng.h/mL)	2852	3681	1.29
IV bolus – 250mg dose	AUCt (ng.h/mL)	6447	9403	1.46
IV infusion – 500mg dose	Cmax (ng/mL)	5.039E-4	3.632E-4	0.72
	AUCt (ng.h/mL)	2.301E-4	1.92E-4	0.83
Suspension– 1g dose	Cmax (µg/mL)	13.28	11.48	0.86
	AUCt (µg.h/mL)	29.59	24.27	0.82

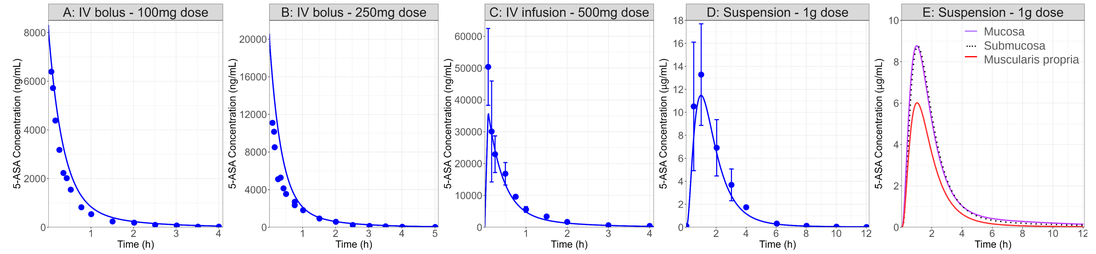

Figure 3: Observed (points) and simulated 5-ASA plasma (blue line) and colon layers (red, black and purple line) concentration-time courses in healthy subjects following a single IV (A, B, C) or oral (D, E) administration of 5-ASA

Sulfasalazine + 5-ASA

Table 2: Ratios of sulfasalazine PK parameters following its PO administration

Simulation	PK parameters	Observed (O)	Predicted (P)	P/O
Suspension– 1g dose	Cmax (µg/mL)	7.538	7.625	1.01
	AUCt (µg.h/mL)	68.64	95.57	1.39
Tablet – 2g dose	Cmax (µg/mL)	12.96	12.75	0.98
	AUCt (µg.h/mL)	125.1	149.5	1.20

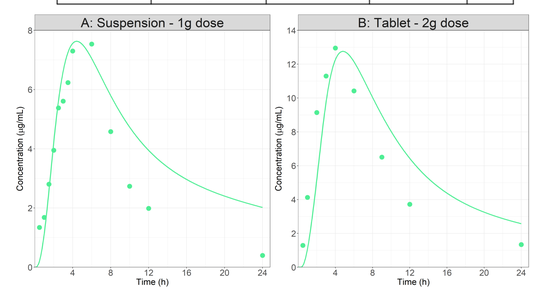

Figure 4: Observed (points) and simulated (green lines) sulfasalazine plasma concentration-time courses in healthy subjects following a single oral administration of sulfasalazine

Table 3: Ratios of 5-ASA PK parameters following sulfasalazine PO administration

Simulation	PK parameters	Observed (O)	Predicted (P)	P/O
Tablet – 2g dose	Cmax (ng/mL)	146	78.43	0.54
	AUCt (ng.h/mL)	2031	2051	1.01
Tablet – 4g dose	Cmax (ng/mL)	95.35	82.01	0.86
	AUCt (ng.h/mL)	1572	2391	1.52

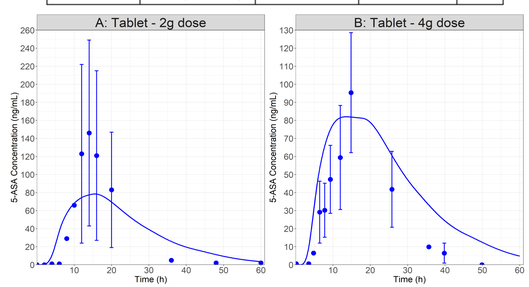

Figure 5: Observed (points) and simulated (blue lines) 5-ASA plasma concentration-time courses in healthy subjects following a single oral administration of sulfasalazine

CONCLUSION

- Implementation of the microbiome metabolism in the sulfasalazine PBPK model allows for both the prediction of its low absorption and the 5-ASA appearance through metabolism by colonic bacteria in healthy subjects.
- This successful implementation of the microbiome effect on drug absorption is an important step toward the ability of the PBPK model to predict drug PK in IBD patients
- It is expected that PBPK models will significantly support the development and regulatory assessment of new and generic drug products for IBD patients.
- This case study also demonstrates how PBPK models can predict drugs' systemic exposure following oral administration of prodrugs metabolized by colonic bacteria.

FUNDING/GRANT

This project is funded by the U.S. Food and Drug Administration: grant number: 1U01FD007660.

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