Physiologically Based Pharmacokinetic Modeling of Metformin in Children and Adolescents with Obesity: Supplemental Methods

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Adult PBPK Model Description

As described in more detail in the original publication,[1] the adult model describes saturable absorption of metformin via apical membrane transporters plasma membrane monoamine transporter (PMAT) and to a lesser extent organic cation transporter 1 (OCT1) in the small intestine, distribution in the liver via OCT 1, and renal excretion via sequential action of organic cation transporter 2 (OCT 2) and multidrug and toxin extrusion transporter 2 (MATE2) located on the basolateral and apical membrane of the kidney, respectively, as well as passive glomerular filtration.

PK-Sim® calculation of glomerular filtration rate

Simulated pediatric glomerular filtration rate (GFR) was calculated by PK-Sim® as a function of adult GFR and kidney size as follows:

$$GFR_{pediatric} = \frac{GFR_{adult}\ x\ F_{age}}{V_{standard\ kidney}}$$

where $GFR_{pediatric}$ is the simulated pediatric GFR (mL/min), GFR_{adult} is the standard adult GFR, F_{age} is a scaling factor to account for age in children, and $V_{standard\ kidney}$ is a standard adult kidney volume.

Model Evaluation

Sensitivity Analysis

Global sensitivity analysis was performed in PK-Sim® using selected simulations of virtual individuals without and with obesity to explore the relative impact of individual model parameters on simulated outputs. Specifically, input parameters in the model that, when varied by 10%, resulted in ≥10% change in predicted AUC and/or C_{max} were identified.[2] Results from

this analysis were useful for evaluating potential modifications to the adult model when scaling to children without obesity and then extrapolating to a pediatric population with obesity.

Clinical Data and Model Exploration

For the population of children and adolescents with severe obesity, double peaks were observed during the absorptive phase of the concentration-time profile for the majority of patients. Several plausible explanations were proposed by the authors, including the combined effect of the hyperglycemic clamp and lunch, which corresponded to the timing of the second peak; that metformin is a Biopharmaceutics Classification System class III drug; or the result of administering metformin doses in multiple capsules.[3] It is also worth mentioning that the metformin formulation used in that study was prepared and packaged into capsule by the National Institutes of Health; although the dissolution properties were similar to the commercial formulation, the bioavailability and PK may differ. As part of the current work, other potential causes for the double peaks, especially with respect to obesity (and severe obesity), were independently explored along with an exhaustive literature search. Although the double peak phenomenon has been observed for other drugs,[4] the only other report for metformin was in healthy male Chinese volunteers.[5] Furthermore, no connections between the two studies offered alterative explanations. Overall, without evidence to link obesity (or severe obesity) to metformin double peaks, this phenomenon was not accounted for in the pediatric PBPK model.

In addition, although not apparent in the adult model simulations,[1] visual inspection of the pediatric data revealed some potential misspecification in the rate and/or extent of absorption, observed in populations both without and with obesity (**Figures 1 and 2**). This observation may suggest differences in absorption kinetics in pediatric patients compared to adults. To explore

this hypothesis, guided by results obtained from sensitivity analysis, selected input parameters were systematically adjusted to evaluate changes in model output. Specifically, because metformin absorption is transporter-dependent and saturable,[6] parameters describing PMAT kinetics and abundance as well as various intestinal permeabilities were varied. Of the changes explored, inclusion of paracellular permeability in the pediatric model, which was set to 0 in the adult model,[1] resulted in the best visual improvement in predictions in both children without and with obesity. While saturable paracellular absorption of metformin has been previously suggested,[6] more research is needed to verify this finding, especially in pediatrics.

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