ERRATUM

Erratum: Physiologically-Based Pharmacokinetic Modeling Analysis for Quantitative Prediction of Renal Transporter-Mediated Interactions Between Metformin and Cimetidine

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After publication of our article, the following errors were brought to our attention:

1. incorrect equations used for the calculation of intrinsic metabolic clearance in the liver compartments in the modeling software;
2. typographical errors and character corruptions in the model equations in Supplementary Material S2.

When we corrected the errors related to the calculation of intrinsic metabolic clearance in the liver, the recalculated results were mostly comparable to those included in the original publication. Thus, the overall conclusion remains unchanged.

The first error was the use of incorrect equations for the calculation of intrinsic metabolic clearance in the liver compartments in the modeling software. When converting the equations into the codes for the software platform, Eq. 1 was inadvertently used for intrinsic metabolic clearance (CL_{int,met}) in the liver instead of the correct Eq. 2.

\[ CL_{int,met} = \frac{CL_{h, int, all}}{(1 - \beta_{liver}) * (1 + R_{dif})} * \frac{R_{dif}}{\gamma} \]  
(1)

\[ CL_{int,met} = \frac{CL_{h, int, all}}{(1 - \beta_{liver}) * (1 + R_{dif})} * \left( \frac{R_{dif}}{\gamma} + \frac{e^N}{R_{OCT1, inf/eff}} \right) \]  
(2)

\[ N = z * \Phi * F * R * T \]  
(3)

(CL_{h, int, all}, the intrinsic hepatic clearance; R_{dif}, the passive-to-active influx clearance ratio from plasma to hepatocyte; \gamma, passive influx-to-efflux clearance ratio; R_{OCT1, inf/eff}, OCT1-mediated influx-to-efflux ratio; z, \Phi, F, R and T, the valence, the membrane potential, Faraday’s constant, the gas constant, and the absolute temperature, respectively).

The passive efflux, OCT1-mediated efflux and intrinsic metabolic clearance play a role in the hepatic elimination of metformin. The correct equation (Eq. 2) considers the impact of membrane potential on passive efflux and OCT1-mediated efflux in the calculation of intrinsic metabolic clearance. By inadvertently using the Eq. 1 instead of Eq. 2, the impact of membrane potential on OCT1-mediated efflux was omitted in the initial calculations. We apologize for our oversight. Upon recalculation, the contribution of hepatic clearance to the total clearance increased from 15% to 23% (renal clearance decreased from 85% to 77%). We corrected these errors and recalculated the results, as briefly described below.

Because the contribution of hepatic and renal clearance to the total clearance changed with the use of the correct equations, the values for the optimized parameters (k_{a}, k_{trans}, and R_{MATE,dir}) for metformin physiologically-based pharmacokinetic (PBPK) model also changed. The results of drug-drug interaction (DDI) simulation were mostly comparable before and after the correction.

Cimetidine in vivo K_i value for multidrug and toxin extrusion (MATEs) was estimated by fitting to clinical DDI data with k_{a}, k_{trans} and R_{MATE,dir} fixed to their optimized values at varying \beta_{kidney} values. Estimated in vivo K_i values from the recalculation ranged from 0.25 to 1.2 μM instead of initially reported values 0.23 to 1.7 μM (Table 3) and DDI simulation with estimated in vivo K_i values reproduced the observed fold-changes in area under the curve (AUC), renal clearance (CLR), and peak plasma concentration (C_{max}) (Figure 3, Table 3). Upon recalculation, the estimated in vivo K_i values for MATEs was within the range of in vitro K_i value at \beta_{kidney} value of 0.1 instead of 0.1 and 0.3.

In the sensitivity analysis of K_i value of cimetidine for MATEs, the extent of plasma AUC, CLR, and/or proximal tubule AUC changes were comparable before and after the correction. The observed fold-changes in the plasma AUC or CLR were...
reproduced using the $K_i$ values for MATEs near and within the range of those obtained in vitro when the $\beta$ kidney value of 0.1, 0.3, or 0.5, but not 0.8 (Figure 4). Thus, the overall conclusion is the same as the original publication.

These differences do not change the conclusion that DDI between metformin and cimetidine is likely mediated by the inhibition of MATEs by cimetidine, rather than by the inhibition of OCT2.

The second error was typographical errors and character corruptions in the model equations in Supplementary Material S2. These errors were made inadvertently when equations were copied and reformatted from the simulation software. These errors make it difficult for readers to reproduce our results and utilize our model. We apologize for this oversight and not catching typographical errors in the early proof. The corrected details are listed below.

These errors do not change the conclusion of our paper that DDI between metformin and cimetidine is likely mediated by the inhibition of MATEs by cimetidine, rather than by the inhibition of OCT2.

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**Cited by**
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Taskar K.S. et al., Physiologically-based pharmacokinetic models for evaluating membrane transporter mediated drug–drug interactions: current capabilities, case studies, future opportunities, and recommendations. *Clin Pharmacol Ther.* **107**, 1082–1115 (2019). https://doi.org/10.1002/cpt.1693.