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.

$$CL_{int,met} = \frac{CL_{h,int,all}}{\left(1 - \beta_{liver}\right) * \left(1 + R_{dif}\right)} * \frac{R_{dif}}{\gamma} \tag{1}$$

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

$$N = \frac{z * \Phi * F}{R * T} \tag{3}$$

($CL_{h,int,all}$, the intrinsic hepatic clearance; R_{dif}, the passive-to-active influx clearance ratio from plasma to hepatocyte; γ, passive influx-to-efflux clearance ratio; $R_{OCT1,inf/eff}$, OCT1-mediated influx-to-efflux ratio; z, Φ, 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 $R_{MATE/dif}$) for metformin physiologically-based pharmacokinetic (PBPK) model also changed. The results of drug-drug interaction (DDI) simulation were mostly comparable between 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 $R_{MATE/dif}$ fixed to their optimized values at varying β_{kidney} values. Estimated *in vivo* K_i values from the recalculation ranged from 0.25 to 1.2 $^\mu$M instead of initially reported values 0.23 to 1.7 $^\mu$M (**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 β_{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 β_{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.

Page and line	Where it reads	The sentence should read
p. 1 line 5	For "$-k_{in}*V_{plasma}*C_{plasma}$)"	Read "$-k_{in}*V_{plasma}*C_{plasma}$"
p. 1 line 10	For "$k_{out}*V_{erythro}*C_{erythro}$)"	Read "$k_{out}*V_{erythro}*C_{erythro}$"
p. 1 line 13, 15 and p. 13 line 7	For "dtC_{muscle}"	Read "dC_{muscle}"
p. 2 line 2, 4 and p. 13 line 8	For "dtC_{skin}"	Read "dC_{skin}"
p. 2 line 5, 7 and p. 13 line 9	For "$dtC_{adipose}$"	Read "$dC_{adipose}$"
p. 3 line 8	For "$k_{out}*(V_{EH,e}/5)*C_{EH,e,I}+ fh * (PS_{dif,eff} / 5) * C_{HC,i} - (V_{max\_met\_OCT1}$"	Read "$k_{out}*(V_{EH,e}/5)*C_{EH,e,i} + fh * (PS_{dif,eff} / 5) * C_{HC,i} - V_{max\_met\_OCT1}$"
p. 3 line 12	For "$(V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} +C_{EH,p,i})$"	Read "$V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}))$"
p. 3 line 14	For "$(C_{erythro} - C_{EH,e,i})$"	Read "$((C_{erythro} - C_{EH,e,i}); (i=1)$ or $(C_{EH,e,(i-1)} - C_{EH,e,i}); (i=2-5))$"
p. 4 line 4	For "$(V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) – C_{HC,i}$"	Read "$V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) – C_{HC,i}$"
p. 4 line 6	For "$fh*CL_{int,met} * C_{HC,i}$"	Read "$fh*(CL_{int,met} /5)* C_{HC,i}$"
p. 4 line 13	For "$Q_{GFR}*(fu*C_{G,p} - C_{G,u}))$"	Read "$Q_{GFR}*(fu*C_{G,p} - C_{G,u})$"
p. 5 line 16	For "$Q_{r,e,i}*C_{PT,e,(i-1)} + k_{in}*(V_{PT,p}/3)*C_{PT,p,i} – Q_{r,e,2}*C_{PT,e,i}$"	Read "$Q_{r,e,i}*C_{PT,e,(i-1)} + k_{in}*(V_{PT,p}/3)*C_{PT,p,i} – Q_{r,e,i}*C_{PT,e,i}$"
p. 6 line 5	For "$Q_{u1}* C_{PT,cell,i}$"	Read "$Q_{ui}* C_{PT,cell,i}$"
p. 6 line 6	For "$Q_{u2}*C_{PT,u,i}$"	Read "$Q_{ui}*C_{PT,u,i}$"
p. 6 line 12	For "$Q_{r,e,5}*C_{DT,e}$"	Read "$Q_{r,e,5}*C_{DT,e}$"
p. 6 line 13	For "$fb*PS_{r,DT,difinf}*C_{dt,p} + fu*PS_{u,DT,difinf}*C_{DT,u} - fc*PS_{r,DT,difeff}*C_{DTt,cell} - fc*PS_{u,DTt,difeff}*C_{DT,cell}$"	Read "$fb*PS_{r,DT,difinf}*C_{DT,p} + PS_{u,DT,difinf}*C_{DT,u} - fc*PS_{r,DT,difeff}*C_{DT,cell} - fc*PS_{u,DT,difeff}*C_{DT,cell}$"
p. 7 line 4	For "МСБбу*вССВбу.ве = Йбкбу65*СВЕбу + лшт*МСБбз*ССВбз – Йкбу66*ССВбу – лщге*МСБбу*ССВбу"	Read "$V_{CD,e} * dC_{CD,e}/dt = Q_{r,e,5}*C_{DT,e} + k_{in}*V_{CD,p}*C_{CD,p} – Q_{r,e,6}*C_{CD,e} – k_{out}*V_{CD,e}*C_{CD,e}$"
p. 11 line 7	For "$CL_{met} = CL_{intall}/(1- \beta_{liver} *Rdif/(1+ R_{dif})/ \gamma_h$,"	Read "$CL_{met} = CL_{intall}/(1- \beta_{liver})/(1+ R_{dif})/ (R_{dif}/\gamma h + e^{Nh}/R_{OCT1,inf/eff})$,"
p. 13 line 3	For "$Q_{r6}*C_{r,6} - Q_h*C_{blod} -Q_{r,p}*C_{plasma}$"	Read "$Q_{r6}*C_{CD} - Q_h*C_{blood} - Q_r*C_{blood}$"
p. 13 line 14	For "$(V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) – C_{HC,I} *e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1}+C_{HC,i}))/5$"	Read "$V_{max\_met\_OCT1}*(C_{EH}/(K_{m\_met\_OCT1} + C_{EH}) – C_{HC}*e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1}+ C_{HC}))$"
p. 14 line 11 top. 15 line 3	For "f_{PT,ion_b}" and "f_{ion_b}"	Read "$f_{r,ion}$"
p. 14 line 12 top. 15 line 7	For "f_{ion_c}"	Read "$f_{c,ion}$"
p. 14 line 12 top. 15 line 7	For "f_{ion_u}"	Read "$f_{u,ion}$"
p. 14 line 11	For "$Q_{r,i}*C_{r,i}$"	Read "$Q_{r,i}*(C_{r,i};(i=1)$ or $C_{PT,r,(i-1)};(i=2,3))$"
p. 15 line 4-5	For "$(f_{ion\_u} * V_{max,MATE}/(K_{m,MATE} + fc *f_{PT,ion\_u} *C_{PT,cell,i})$"	Read "$(f_{c,ion} * V_{max,MATE}/(K_{m,MATE} + fc * f_{c,ion} *C_{PT,cell,i})$"
p. 15 line 6	For "$(V_{PT,u}/3)*dC_{PT,u,i}/dt = Q_{u1}*C_{PT,cell,i} + fc*1/3*(f_{PT,ion\_u} * V_{max,MATE}/(K_{m,MATE} +fc *f_{PT,ion\_u} *C_{PT,cell,i})+PS_{u,PT,difeff}) *C_{PT,cell,i} - fu*1/3*PS_{u,PT,difinf}*C_{PT,u,i} - Q_{u2}*C_{PT,u,i}$"	Read "$(V_{PT,u}/3)*dC_{PT,u,i}/dt = Q_{ui}*(C_G;(i=1)$ or $C_{PT,u,(i-1)};(i=2,3)) + fc*1/3*(f_{c,ion} * V_{max,MATE}/(K_{m,MATE} + fc *f_{c,ion} *C_{PT,cell,i}) + PS_{u,PT,difeff})*C_{PT,cell,i} - 1/3*PS_{u,PT,difinf}*C_{PT,u,i} - Q_{u(i+1)}*C_{PT,u,i}$"
p. 15 line 10	For "$Q_{r4}*C_{PT,3} + f_c*PS_{r,dt,difeff}*C_{DT,cell}$"	Read "$Q_{r4}*C_{PT,r,3} + f_c*PS_{r,DT,difeff}*C_{DT,cell}$"
p. 15 line 16	For "$Q_{r5}*C_{dt,p}$"	Read "$Q_{r5}*C_{DT}$"

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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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.