**Table S1.** Various parameters used in the metformin PBPK model and reported *in vitro* Km values for transporters of metformin

Parameters used in the metformin PBPK model

| Parameter (unit) | Value | Reference |
|---|---|---|
| *Physicochemical* | | |
| pKa | 12.3 | 1 |
| logP | -1.25 | 1 |
| *Absorption-related* | | |
| FaFg* | | |
| 250 mg | 0.84 | 2, 3 |
| 1,500 mg | 0.57 | 3 |
| *Distribution-related* | | |
| $f_{u,met}$ | 1 | 4 |
| $K_{p,adipose}$ | 0.27 | 4 |
| $K_{p,muscle}$ | 2.09 | 4 |
| $K_{p,skin}$ | 1.46 | 4 |
| $k_{in,RBC}$ (/h) | 0.006 | 5 |
| $k_{out,RBC}$ (/h) | 0.02 | 5 |
| *Liver-related* | | |
| membrane potential (mV) | - 40 | 6 |
| $CL_{int,all}$ (L/h) | 10.7** | 3 |
| $R_{dif}$ | 0.186 | 7 |
| $\beta_{liver}$ | 0.5 (fixed)** | - |
| $R_{OCT1,\ inf/eff}$ | 1.32 | 8 |
| *Kidney-related* | | |
| $P_d$ (m/h) | $1.8*10^{-5}$ | 9 |
| $R_{OCT2,inf/eff}$ | 1.32 | 8 |

*in vitro* Km (μM) values for metformin

| Transporter | geometric mean | range | Reference |
|---|---|---|---|
| OCT1 | 1,470 | 1,470 | 10 |
| OCT2 | 1,178 | 810-1,465 | 10, 11, 12 |
| MATEs | 740 | 283-1,980 | 13, 14, 15 |

$k_a$, absorption rate constant; $k_{trans}$, transit rate constant; FaFg, intestinal availability; $f_{u,met}$, unbound metformin fraction in plasma; $K_{p,adipose}$, adipose/plasma concentration ratio; $K_{p,muscle}$, muscle/plasma centration ratio; $K_{p,skin}$, skin/plasma concentration ratio; $k_{in,RBC}$, plasma-to-erythrocyte partitioning rate constant; $k_{out,RBC}$, erythrocyte-to-plasma partitioning rate constant; CLint,all, overall hepatic intrinsic clearance ; $R_{dif}$, passive-to-active clearance ratio; $R_{OCT1,inf/eff}$, OCT1 influx-to-efflux clearance ratio; $CL_{met}$, hepatic metabolic clearance; $P_d$, permeability value; $R_{OCT2,inf/eff}$, OCT2 influx-to-efflux clearance ratio
*: FaFg was back calculated from bioavailability. Total clearance and hepatic availability was calculated using non-renal clearance in 250 mg i.v. dose study as hepatic clearance assuming non-renal clearance is independent from dose.
**: $CL_{int,all}$ was calculated from the reported clinical data,[3] and used as fixed. The $\beta_{liver}$ value was initially set at three different values (0.2, 0.5, and 0.8) in order to obtain the fitted values of $R_{MATE/dif,}$ $k_a$, and $k_{trans}$. However, the optimized values and goodness of the fitting were similar regardless of the $\beta_{liver}$ value. Thus, the $\beta_{liver}$ value was set to be 0.5 in subsequent simulations.

Reference in Table S1


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