Supplemental text

Hybrid parameters defined in the liver model

Hybrid parameters such as $CL_{h,int,all}$, R_{dif}, β_{liver}, and γ_h were used for the liver model and defined in the following eqs. (1)-(5)

$$CL_{h,int,all} = PS_{h,inf} * \beta_{liver} = PS_{h,inf} * \frac{CL_{int,met}}{PS_{h,eff}+CL_{int,met}} \quad (1)$$

$$PS_{h,inf} = PS_{OCT1,inf} + PS_{h,dif,inf} \quad (2)$$

$$PS_{h,eff} = PS_{OCT1,eff} + PS_{h,dif,eff} \quad (3)$$

$$\gamma_h = \frac{PS_{h,dif,inf}}{PS_{h,dif,eff}} \quad (4)$$

$$R_{dif} = \frac{PS_{h,dif,inf}}{PS_{oct1,inf}} \quad (5)$$

($CL_{h,int,all}$, the intrinsic hepatic clearance; $PS_{h,inf}$, the intrinsic hepatic uptake clearance; $PS_{h,eff}$, the intrinsic hepatic efflux clearance from the hepatocyte to the blood vessel; $CL_{int,met}$, the intrinsic hepatic metabolic clearance; $PS_{h,dif,inf}$, the intrinsic passive influx clearance from the blood vessel to the hepatocyte; and $PS_{h,dif,eff}$, the intrinsic passive efflux clearance from the hepatocyte to the blood vessel)

β_{liver} was fixed to 0.5 since the fitting results were similar with β_{liver} of 0.2, 0.5 and 0.8 (data not shown). $fbCL_{h,int,all}$ was calculated using eq. (6) and the hepatic availability (F_h) in the equation was calculated using the clinical data after the intravenous administration of 250 mg metformin (Tucker *et al.,* 1981):

$$f_b CL_{h,int,all} = 5 \cdot Q_h \left(\frac{1}{\frac{1}{F_h^5}} - 1 \right) \quad (6)$$

Metformin (pKa of 12.3) exists mainly in an ionized form at physiological pHs and γ_h is defined as shown in eq.(7) using the Nernst equation [1].

$$\gamma_h = \frac{PS_{h,dif,inf}}{PS_{h,dif,eff}} = \frac{f_{o,union} + \lambda * f_{o,ion}}{f_{i,union} + e^N * \lambda f_{i,ion}} \approx \frac{1}{e^N} = 4.46 \quad (7)$$

where $f_{o,union}$ and $f_{o,ion}$ are the fractions of the unionized and ionized forms in the extracellular compartments, respectively; $f_{i,union}$ and $f_{i,ion}$ are the fractions of the unionized and ionized forms in cells, and λ is the ratio of the passive diffusion for the ionized form to that for the unionized form.

Development of the cimetidine PBPK model

The cimetidine PBPK model was developed by implementing the following modifications to the PBPK model of metformin (Figure 1B). For the intestinal absorption process, the transit compartment was removed and three intestine compartments were combined into one with the addition of a parameter representing the time delay of intestinal absorption (T_{lag}). The erythrocyte and plasma compartments were combined into one blood compartment.

Reference for supplemental text

1. Yoshikado T, Toshimoto K, Nakada T, Ikejiri K, Kusuhara H, Maeda K, Sugiyama Y (2017) Comparison of Methods for Estimating Unbound Intracellular-to-Medium Concentration Ratios in Rat and Human Hepatocytes Using Statins. *Drug. Metab. Dispos.* **45:** 779-789.