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Does the well-stirred model assess the intestinal first-pass effect well?

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Abstract

The pre-systemic intestinal extraction ratio (E_g) has been estimated by an equation based on the well-stirred model, which does not have a term of membrane transport. In this report, we have identified the application limitations of the well-stirred model equation to assess the pre-systemic intestinal extraction ratio. The E_g of metoprolol (CYP2D6 substrate) was assessed by three methods. Intrinsic clearances for metoprolol metabolism in hepatic and gastrointestinal microsomes were from a published report. Method 1 (model-independent method): the E_g of 0.228 was obtained according to the equation, $F = F_f \times (1 - E_g) \times F_h$, where F, F_f and F_h were the bioavailability, the fraction entering the intestinal tissue and the hepatic availability, respectively. Method 2: the E_g of 0.0071 was calculated according to the well-stirred model equation, and was much lower than the value of 0.228. Method 3: the E_g of 0.213 was obtained by the transport-metabolism-flow (TMF) model equation, and was much closer to the value of 0.228 obtained by the model-independent method than the E_g of 0.0071 calculated by the well-stirred model equation. Therefore, we propose that the factor of membrane transport process be incorporated into the pharmacokinetic model for the assessment of the pre-systemic intestinal extraction ratio.

Introduction

The liver has been targeted as a primary organ for pre-systemic (first-pass) drug metabolism or bioavailability in the body. However, intestinal metabolism also influences the bioavailability of orally administered drugs (Rowland & Tozer 1995). The impact of intestinal metabolism on the absorption (or pre-systemic intestinal extraction ratio) is determined by the balance of membrane transport clearance and metabolic clearance (Mizuma et al 1996; Wacher et al 1998), as orally administered drugs must pass through the intestinal tissue to enter the systemic circulation. However, the pre-systemic intestinal extraction ratio has been estimated by an equation based on the well-stirred model (Klippert et al 1982; Koster et al 1985; Mistry & Houston 1987; Chiba et al 1997; Thummel et al 1997), which does not have a term of membrane transport. In this report, we have identified the application limitations of the equation to assess the pre-systemic intestinal extraction ratio, and propose to incorporate the factor of membrane transport process into the pharmacokinetic model.

Intestinal vs hepatic extraction ratio, and pre-systemic vs systemic metabolism

The bioavailability of orally administered drugs (F) is determined by the fraction entering the intestinal tissue (F_f), which is the fraction neither lost in the faeces nor decomposed in the lumen, the fraction escaping destruction within the walls of the gastrointestinal tract (F_g), and the fraction escaping liver extraction (F_h) (Rowland & Tozer 1995):

$$\begin{aligned} F &= F_f \times F_g \times F_h \\ &= F_f \times (1 - E_g) \times (1 - E_h) \end{aligned} \quad (1)$$

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where E_g and E_h are the gastrointestinal extraction ratio and hepatic extraction ratio, respectively. E_g and E_h were calculated by equations 2 and 3 based on the well-stirred model (Gibaldi & Perrier 1982):

$$E_g = (CL_{int,g} \times fu)/(Q_g + CL_{int,g} \times fu) \quad (2)$$

$$E_h = (CL_{int,h} \times fu)/(Q_h + CL_{int,h} \times fu) \quad (3)$$

where Q_g and Q_h are the blood-flow rate of the gastrointestine and liver, respectively. $CL_{int,g}$ and $CL_{int,h}$ are the intrinsic metabolic clearance of gastrointestine and liver, respectively, and fu is the unbound drug fraction in the plasma. However, it should be noted that equations 2 and 3 are essentially the same expression for the first-pass effect. However, it is puzzling to use equation 2 to estimate the intestinal first-pass effect, because the pathway of orally administered drugs through the gastrointestine (pre-systemic pathway) is different from that of intravenously administered drugs (systemic pathway), although the pathway of orally administered drugs through the liver is the same as that of intravenously administered drugs (Mizuma 2002). Drugs metabolized in the liver are carried by blood flow, but drugs metabolized in the gastrointestine are not. Therefore, we should reconsider how to assess E_g and be aware of the difference.

Pre-systemic intestinal extraction ratio of metoprolol

Model-independent assessment

The F and F_f of metoprolol were reported to be 0.38 (Benet et al 1996) and 0.95 (Lennernas et al 1997), respectively. Madani et al (1999) achieved hepatic intrinsic clearance of 1.55 L min^{-1} for metoprolol oxidation metabolism using hepatic microsomes. In this report, an E_h of 0.482 was calculated according to equation 3, where Q_h was 1.5 L min^{-1} and the fu of metoprolol was 0.9 (approximation of the reported value, 0.89) (Benet et al 1996). An E_g of 0.228 was obtained according to equation 1 (Table 1).

Well-stirred model

Madani et al (1999) obtained intestinal intrinsic clearance of 0.002 L min^{-1} for metoprolol oxidation metabolism using intestinal microsomes. In this study, equation 2 gave 0.0071 (0.007 shown in Table 1) for the pre-systemic extraction ratio of metoprolol across the gut mucosa, where Q_g and fu were 0.25 L min^{-1} (approximation of the reported value, 0.248 L min^{-1}) (Hulten et al 1977) and 0.9 (approximation of the reported value, 0.89) (Benet et al 1996), respectively (Table 1). The E_g of 0.0071 was much lower than that of 0.228 described above, indicating that equation 2 based on the well-stirred model was inadequate for the estimation of E_g. The limitation of applicability of equation 2 to the estimation of E_g has been reported by Mistry & Houston (1987).

Transport-metabolism-flow (TMF) model

E_g was estimated according to equation 4 based on the TMF model, which included the transport process of drug across the gastrointestinal tissue (Mizuma 2002):

$$\begin{aligned} E_g &= 1 - F_g \\ &= (CL_{int,g} \times (1 + CL_{s\text{-}i}fu/Q_g))/(CL_{i\text{-}m} \times (1 + CL_{s\text{-}i}fu/Q_g) \\ &\quad + CL_{i\text{-}s} + CL_{int,g} \times (1 + CL_{s\text{-}i}fu/Q_g)) \end{aligned} \quad (4)$$

where $CL_{i\text{-}m}$ is the transport clearance from the intestinal cell to the mucosal side, $CL_{i\text{-}s}$ is the transport clearance from the intestinal cell to the serosal side, $CL_{s\text{-}i}$ is the transport clearance from the serosal side into the intestinal cell, $CL_{int,g}$ is the intrinsic clearance of intestinal metabolism, and Q_g is the blood-flow rate into small intestinal mucosa. Equation 4 clearly showed that the transport rate influenced the impact of intrinsic metabolic clearance on the pre-systemic intestinal extraction ratio.

The relationship between intestinal extraction ratio and intrinsic metabolic clearance was obtained by a simulation study according to equation 4 under the conditions: $CL_{m\text{-}i} = CL_{i\text{-}m} = CL_m$, $CL_{s\text{-}i} = CL_{i\text{-}s} = CL_s$, $CL_s = 2 \times CL_m$, $Q_g = 0.25$ L min^{-1} and fu = 0.9 (Figure 1). When CL_m and CL_s are higher than $CL_{int,g}$ and as high as the intestinal blood flow rate (0.25 L min^{-1}), the influence of the intrinsic metabolic clearance on intestinal extraction ratio in the TMF model is similar to that in the well-stirred model. However, when CL_m and CL_s are nearly equal to $CL_{int,g}$, the impact of intrinsic metabolic clearance on the intestinal extraction ratio becomes remarkable. When $CL_{int,g} = 0.002$ L min^{-1}, $CL_m = 0.0025$ L min^{-1} and $CL_s = 0.005$ L min^{-1} in equation 4, E_g was 0.213 (Table 1). The E_g of 0.213 obtained by the

Table 1 Assessment of the pre-systemic intestinal extraction ratio of metoprolol

Model	E_g	Conditions
Model-independent assessment	0.228	Equations 1 and 3 $F = 0.38$, $F_f = 0.95$, $E_h = 0.48$, $CL_{int,h} = 1.55$ L min^{-1}, $f_u = 0.9$, $Q_h = 1.5$ L min^{-1}
Well-stirred model	0.007	Equation 2 $CL_{int,g} = 0.002$ L min^{-1}, fu = 0.9, $Q = 0.25$ L min^{-1}
TMF model	0.213	Equation 4 $CL_{int,g} = 0.002$ L min^{-1}, fu = 0.9, $Q = 0.25$ L min^{-1}, $CL_{m\text{-}i} = CL_{i\text{-}m} = CL_m = 0.0025$ L min^{-1}, $CL_{s\text{-}i} = CL_{i\text{-}s} = CL_s = 0.005$ L min^{-1}

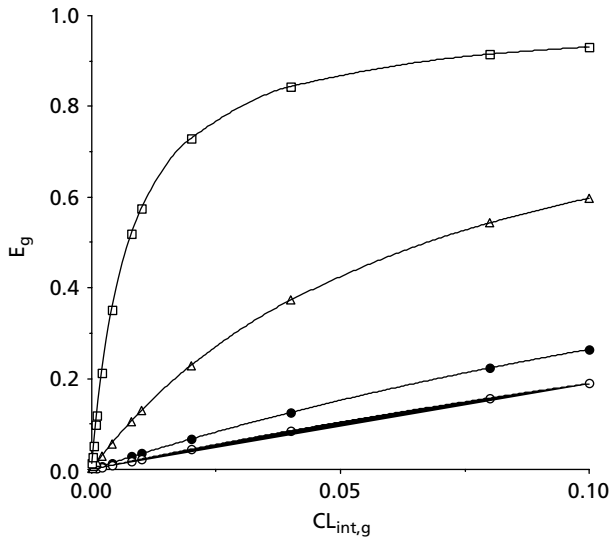

Figure 1 Impact of intestinal transport on the relationship between pre-systemic intestinal extraction ratio (E_g) and intestinal intrinsic clearance. E_g was obtained by a simulation study according to equation 4 in the text. Curves with symbols: closed circle, the well-stirred model; open symbols, the TMF model (circle, $CL_m = 0.25$; triangle, $CL_m = 0.025$; square, $CL_m = 0.0025\,L\,min^{-1}$). $CL_s = 2 \times CL_m$. $Qg = 0.25\,L\,min^{-1}$.

TMF model equation was much closer to the value of 0.228 obtained by the model-independent assessment than to the E_g of 0.0071 calculated by the well-stirred model equation, or to the E_g of 0.0085, which Madani et al (1999) calculated by the well-stirred model equation (fu was assumed to be 1). When CL_m and CL_s are lower than $CL_{int,g}$, the impact of intrinsic metabolic clearance on the intestinal extraction ratio becomes more remarkable. Therefore, although this study used only one set of data, it clearly indicated that the transport process was crucial to the assessment of the intestinal first-pass effect. This is true of drugs, especially with poor transport activity, such as large molecular drugs, which are expected to be future drug candidates.

Moreover, from another viewpoint, we should understand the impact of intestinal metabolism on the intestinal extraction ratio as, even if the intrinsic metabolic clearance of the intestine is lower than that of the liver, the intestinal metabolism has more impact on the organ extraction ratio than the hepatic metabolism. For example, if the intrinsic metabolic clearance in the liver is the same ($0.002\,L\,min^{-1}$) as in the intestine, the hepatic extraction ratio of 0.0012 calculated according to equation 3 is lower than the intestinal extraction ratio of 0.0071 calculated by the well-stirred model equation, equation 2. The impact of the intestinal metabolism on the organ extraction ratio is further emphasized by the TMF model.

In conclusion, pharmacokinetic analysis of the reported data in man showed that the well-stirred model equation would underestimate the intestinal first-pass effect. The pre-systemic intestinal extraction ratio was determined by the balance of the transport activity and the metabolic activity. Therefore, the term of the transport process should be incorporated into the model equation. We should note the impact of intestinal drug metabolism on absorption, even if the metabolic activity in the intestine is lower than that in the liver. This is true of drugs with poor transport activity, such as large molecular drugs. Further study of the TMF model with more sets of data should identify the best model for the estimation of the intestinal extraction ratio/availability.

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