Interplay of Drug Metabolism and Transport: A Real Phenomenon or an Artifact of the Site of Measurement?

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Running Title: “Apparent” Interplay of Hepatic Drug Metabolism and Transport

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Supporting Information

A. Rate Equations and Derivation of Concentration-Time Profile and AUC

Derivation

The rate equations for the reservoir,

\[ \frac{dC_R}{dt} = -\left(\frac{Q_L + CL_{other}}{V_R}\right) \cdot C_R + \frac{Q_L}{V_R} \cdot C_{PL} \]  
Eq. A-1

hepatic plasma,

\[ \frac{dC_{PL}}{dt} = -\left(\frac{Q_L + f_p CL_{in}^s}{V_{PL}}\right) \cdot C_{PL} + \frac{Q_L}{V_{PL}} \cdot C_R + \frac{f_L CL_{ef}^s}{V_{PL}} \cdot C_L \]  
Eq. A-2

liver,

\[ \frac{dC_L}{dt} = \frac{f_p CL_{in}^s}{V_L} \cdot C_{PL} - \frac{f_L}{V_L} \left( CL_{ef}^s + CL_{int} + CL_{ef}^s \right) \cdot C_L \]  
Eq. A-3

metabolite (in the liver),

\[ \frac{dC_M}{dt} = \frac{f_L CL_{int}}{V_M} \cdot C_L - \frac{CL_M}{V_M} \cdot C_M \]  
Eq. A-4

and bile

\[ \frac{dC_{Bile}}{dt} = \frac{f_L CL_{ef}^s}{V_{Bile}} \cdot C_L - \frac{Q_{Bile}}{V_{Bile}} \cdot C_{Bile} \]  
Eq. A-5

were represented in the matrix form

\[ \frac{dC}{dt} = XC \]  
Eq. A-6

where
The solution of Eq. A-6 gives an expression of the concentration-time profile in matrix form,

\[
C(t) = e^{\mathbf{X}t} \mathbf{C}_0
\]

where \( \mathbf{C}_0 \) is the initial condition matrix. When the dose is administered as a bolus into the reservoir, the initial condition matrix is given by
The AUC matrix

\[
\mathbf{AUC} = \begin{bmatrix}
AUC_R \\
AUC_{PL} \\
AUC_L \\
AUC_M \\
AUC_{Bile}
\end{bmatrix}
\]

was solved using the inverse matrix technique, whereby the AUC matrix is equal to

\[
\mathbf{AUC} = \int_{0}^{\infty} e^{\mathbf{X} t} \mathbf{C}_0 dt = -\mathbf{X}^{-1} \mathbf{C}_0
\]

**B. Derivation of Apparent and True Metabolic and Biliary Clearance**

**B.1. Apparent Metabolic Clearance**

For the hepatic metabolic clearance, the total amount metabolized \((A_M^\infty)\) was determined by multiplying the AUC of the metabolite by the clearance of the metabolite

\[
A_M^\infty = AUC_M \cdot CL_M
\]

\[
A_M^\infty = D \cdot \frac{Q_L f_p CL_{in}^{L} CL_{int}}{f_p CL_{in}^{L} CL_{other} (CL_{cf}^{L} + CL_{int}) + Q_L (CL_{other} (CL_{cf}^{L} + CL_{int} + CL_{cf}^{L}) + f_p CL_{in}^{L} (CL_{cf}^{L} + CL_{int}))}
\]

and is equal to the dose multiplied by the fraction metabolized \((F_{Met})\).
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\[ F_{\text{Met}} = \frac{Q_L f_p CL_{\text{int}}^s \cdot CL_{\text{int}}}{f_p CL_{\text{int}}^s \cdot CL_{\text{other}} (CL_{\text{eff}} + CL_{\text{int}}) + Q_L (CL_{\text{other}} (CL_{\text{eff}} + CL_{\text{int}} + CL_{\text{eff}}^s) + f_p CL_{\text{int}}^s (CL_{\text{eff}} + CL_{\text{int}}))} \]

Eq. B-3

Intuitively, the fraction metabolized depends on both the hepatic elimination pathways and the non-hepatic elimination pathways.

The apparent metabolic clearance (\( CL_{\text{metabolic}}^{\text{app}} \)) was determined by dividing the total amount metabolized by the reservoir AUC

\[ CL_{\text{metabolic}}^{\text{app}} = \frac{A_M^\infty}{AUC_R} = \frac{Q_L f_p CL_{\text{int}}^s \cdot CL_{\text{int}}}{f_p CL_{\text{int}}^s \cdot CL_{\text{other}} (CL_{\text{eff}} + CL_{\text{int}}) + Q_L (CL_{\text{other}} (CL_{\text{eff}} + CL_{\text{int}} + CL_{\text{eff}}^s) + f_p CL_{\text{int}}^s (CL_{\text{eff}} + CL_{\text{int}}))} \]

Eq. B-4

which is equivalent to the relationship

\[ CL_{\text{metabolic}}^{\text{app}} = CL_H - CL_{\text{biliary}} \]

Eq. B-5

previously derived using this alternate technique.\(^8\)

B.2. Apparent Biliary Clearance

For the hepatic biliary clearance, the total amount excreted in the bile (\( A_{\text{Bile}}^\infty \)) was determined by multiplying the AUC of the bile (AUC\(_{\text{Bile}}\)) by the bile flow (Q\(_{\text{Bile}}\))

\[ A_{\text{Bile}}^\infty = AUC_{\text{Bile}} \cdot Q_{\text{Bile}} \]

Eq. B-6

\[ A_{\text{Bile}}^\infty = D \cdot \frac{Q_L f_p CL_{\text{int}}^s \cdot C_{\text{eff}}^c}{f_p CL_{\text{int}}^s \cdot CL_{\text{other}} (CL_{\text{eff}}^c + CL_{\text{int}}) + Q_L (CL_{\text{other}} (CL_{\text{eff}}^c + CL_{\text{int}} + CL_{\text{eff}}^s) + f_p CL_{\text{int}}^s (CL_{\text{eff}}^c + CL_{\text{int}}))} \]

Eq. C-7

which is equal to the dose multiplied by the fraction eliminated in the bile (F\(_{\text{Bile}}\)).
As was observed for the fraction metabolized, the fraction eliminated in the bile is also dependent on both the hepatic and non-hepatic elimination pathways.

The apparent biliary clearance ($\text{CL}_{\text{app}}^\text{biliary}$) was determined by dividing the total amount excreted in the bile by the reservoir AUC

$$\text{CL}_{\text{app}}^\text{biliary} = \frac{A_{\text{Bile}}^\infty}{AUC_R} = \frac{Q_L f_p \text{CL}_{\text{in}}' \text{CL}_{\text{ef}}'}{f_p \text{CL}_{\text{in}}' (\text{CL}_{\text{ef}}' + \text{CL}_{\text{int}}') + Q_L (\text{CL}_{\text{ef}}' + \text{CL}_{\text{int}}' + \text{CL}_{\text{in}}')}$$

Eq. B-9

which is also equivalent to the relationship previously derived by Sirianni and Pang.

B.3. True Metabolic and Biliary Clearance

More appropriately, when the hepatic AUC ($\text{AUC}_L$) is used as the reference in calculating metabolic and biliary clearance, the intuitive expressions for the true metabolic

$$\text{CL}_{\text{metabolic}} = \frac{A_M^\infty}{\text{AUC}_L} = f_L \cdot \text{CL}_{\text{int}}$$

Eq. B-10

and true biliary clearance

$$\text{CL}_{\text{biliary}} = \frac{A_{\text{Bile}}^\infty}{\text{AUC}_L} = f_L \cdot \text{CL}_{\text{ef}}$$

Eq. B-11

become apparent.

C. Derivation of $F_H$
C.1. Fraction Bypassing First-Pass Hepatic Elimination

The fraction of the dose available to the systemic circulation after oral dosing ($F_H$) is classically calculated using the definition

$$F_H = 1 - ER = 1 - \left( \frac{CL_H}{Q_L} \right)$$

Eq. C-1

where ER is the extraction ratio. When calculated using the expression for hepatic clearance in Eq. 11 is equal to

$$F_H = 1 - ER = 1 - \frac{f_p CL_{in} \left( CL_{sf} + CL_{int} \right)}{f_p CL_{in} \left( CL_{sf} + CL_{int} \right) + Q_L \left( CL_{sf} + CL_{int} + CL_{ef} \right)}$$

Eq. C-2

By definition, it is possible that in this relationship, $F_H$ represents the fraction of drug bypassing the liver on the “first-pass” which could be due either to distribution into the liver (a reversible process) or irreversible hepatic clearance by metabolic or biliary elimination. In order to test whether the reversible distribution contributes to $F_H$ when it is calculated this way, an alternative technique to calculate $F_H$ was developed. A model was developed where a bolus dose was administered into the portal blood flow (for simplicity, assumed to be $Q_L$; Figure 2). In this model the entire dose in the portal-vein compartment (PV) must undergo an obligatory first-pass through the hepatic plasma compartment prior to distribution into the reservoir. In this model where the dose is administered into the portal vein compartment, the AUC of the reservoir was determined by the inverse matrix technique described in Supporting Information A, and the ratio of the reservoir AUC after administration in the portal vein compartment ($AUC_{PV}^R$) to that after administration into the reservoir ($AUC_{R}^B$) was used to determine $F_H$.
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\[ F_H = \frac{AUC_{PV}^{R}}{AUC_{R}^{*}} \]  

Eq. C-3

\[ F_H = \frac{Q_{L} \left( CL_{ef}^c + CL_{ef}^s + CL_{int} \right)}{f_{p} \left( CL_{ef}^c + CL_{int} \right) + Q_{L} \left( CL_{ef}^c + CL_{ef}^s + CL_{int} \right)} \]  

Eq. C-4

Upon rearrangement, this expression is equivalent to the expression of \( F_H \) calculated using the classical 1-ER method. Additionally, it is noteworthy that in using Eq. B-3 to calculate \( F_H \) in the classical well-stirred model, the correct relationship for \( F_H \) in the well-stirred model

\[ F_H = 1 - \frac{f_{p}CL_{int}}{Q_{L} + f_{p}CL_{int}} \]  

Eq. C-5

is obtained.