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Generalized Consideration of Administration Route Dependence of Drug Disposition and Use of Urinary Data for Prediction of the Dependence

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Route dependence of area under blood (or plasma) concentration curve (AUC) of drug, or first-pass effect was considered based on a generalized perfusion model where drug is supposed to be disposed in liver and kidney. The results verified the Gibaldi's equation based on a three compartment model to describe the route dependence with hepatic blood flow and hepatic clearance. From this consideration, the equation to described and to predict the dose dependence of AUC with urinary excretion and only one blood concentration at a steady state during a constant infusion was proposed and verified experimentally.

And further the correspondence of the generalized perfusion model to a multi-compartment mammillary model for AUC was discussed and the equation for the route dependence was proposed in the case in which drug circulates through enterohepatic system and is disposed in small intestine as well as in liver and kidney.

Keywords——pharmacokinetics; route dependence; first-pass effect; bioavailability; perfusion model; hepatic blood flow; hepatic clearance; phenolsulfonphthalein

Administration route dependence of bioavailability or area under plasma concentration curve (AUC) of drug, *i.e.* first-pass effect, has been studied by many workers.[2] Gibaldi, *et al.*[3] pointed out pharmacokinetically that even if the absorption of drug from the digestive tract is complete, the ratio of AUC after oral administration, $(AUC)_{po}$, to AUC after intravenous administration, $(AUC)_{iv}$, *i.e.* $(AUC)_{po}/(AUC)_{iv}$ $(=f)$ is essentially less than one, and gave the equation to describe f with the ratio of hepatic clearance of drug to hepatic blood flow. It can be seen from the equation that f reaches one assymptotically as the ratio of hepatic clearance to hepatic blood flow becomes smaller and that the difference between $(AUC)_{po}$ and $(AUC)_{iv}$ is hardly observed experimentally when the clearance of drug is small. They[3] gave further the equations to predict f only from $(AUC)_{po}$ or $(AUC)_{iv}$. These equations are very useful to evaluate the absorption of drug from an oral dosage form, since when f is observed significantly less than one, it is a practically important problem to determine whether the low ratio should be ascribed to the large hepatic clearance of drug or to the uncomplete absorption. And these equations have been successfully used for various drugs such as propranolol,[3] nortriptyline,[4a] propoxyphene[4b] and chlormethiazole[4c] in human study.

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3) M. Gibaldi, R.N. Boyes, and S. Feldman, *J. Pharm. Sci.*, **60**, 1338 (1971).

4) *a*) M. Gibaldi, *J. Pharm. Sci.*, **64**, 1036 (1975); *b*) D. Perrer, M. Gibaldi, and R.N. Boyes, *J. Pharm. Pharmacol.*, **25**, 256 (1973); *c*) R.G. Morre, E.J. Trigs, C.A. Shanks, and J. Thomas, *Europ. J. Clin. Pharmacol.*, **8**, 353 (1975).

Gibaldi's theoretical consideration is very excellent, however his kinetic model is limited and based on only a three compartment model which is composed of central, tissue and hepato-portal compartment. In his original model[2b,3] drug was supposed to be disposed exclusively from hepato-portal compartment. And afterwards Gibaldi and Feldman[5] gave the similar equation to describe the route dependence of the total excreted amount of drug in urine from the three compartment model where drug is disposed from central compartment into urine as well as from hepato-portal compartment. Although they did not give the equation for the route dependence of AUC in this case, it is very easy to understand that the same equation with blood flow and hepatic clearance as in the former case can be given even when drug is disposed both from hepato-portal and central compartment. But the method to obtain hepatic clearance was not given.

Then, in spite of usefulness, it is a problem in the Gibaldi's theoretical consideration that a three compartment model is assumed a priori, in other words, why a multi-compartment model is unnecessary to describe the route dependence since a body is composed of various organs and tissues. And other problems are why liver is treated as hepato-portal compartment while kidney is included in central compartment, and how to obtain hepatic clearance of drug when it is disposed in kidney as well as in liver.

In contrast, Rowland[2b] pointed out the importance of clearance concept which is model independent and derived the same equation for the route dependence but he did not consider the case where drug is disposed in kidney as well as in liver. And recently, Chiou[2f] derived the equation which describes the route dependence with hepatic blood flow, AUC and a fraction of drug metabolised in liver when drug is administered orally and it is disposed in kidney, pulumonary as well as in liver. Since in this case Chiou used a three compartment model, a similar question arises whether a three compartment model is enough or why all disposing organs belong to the same compartment *i.e.* central compartment.

To solve these problems, in the present paper the route dependence is examined from the generalized perfusion model of drug disposition and the Gibaldi's equation is confirmed as well as in his three compartment model. The other purpose of the present paper is to report the equation to predict the route dependence from the urinary excretion rate and plasma concentration at steady state which is obtained by constant rate infusion. The merit of this equation is that urinary concentration which is determined often more easily than plasma concentration is used and plasma concentration only at steady state which is usually high is needed. In contrast, the wide range plasma concentration which includes low as well as high is necessary to obtained AUC which has been usually used to predict the route dependence as stated above. And this equation is examined experimentally with phenolsulfonphthalein (PSP) data in rat.

Theoretical

An animal body may be depicted schematically as in Fig. 1. According to Rowland, *et al.*,[6] in this model it is assumed that drug is delivered by blood flow to various organs and tissues and that the concentrations of drug in emergent blood are in equilibrium with the organs or tissues (perfusion rate or flow rate limiting model). And further the disposition process is assumed the first order. Mathematical description of drug in this model is given as the following equations:

$$V_b \frac{dC_b}{dt} = -FC_b + F_h C_h^\circ + F_r C_r^\circ + \sum_{j=1}^{j=n} F_j C_j^\circ \qquad \text{Eq. (1)}$$

$$V_h K_h \frac{dC_h^\circ}{dt} = F_h C_b - F_h C_h^\circ - k_h V_h K_h C_h^\circ \qquad \text{Eq. (2)}$$

5) M. Gibaldi and S. Feldman, *Europ. J. Pharmacol.*, **19**, 323 (1973).
6) M. Rowland, L.Z. Benet, and G.G. Graham, *J. Pharmacok. Biopharmc.*, **1**, 123 (1973).

$$V_r K_r \frac{dC_r^\circ}{dt} = F_r C_b - F_r C_r^\circ - k_r V_r K_r C_r^\circ \qquad \text{Eq. (3)}$$

$$V_j K_j \frac{dC_j^\circ}{dt} = F_j C_b - F_j C_j^\circ \quad (j=1,\ n) \qquad \text{Eq. (4)}$$

$$\frac{dH}{dt} = k_h V_h K_h C_h^\circ \qquad \text{Eq. (5)}$$

$$\frac{dU}{dt} = k_r V_r K_r C_r^\circ \qquad \text{Eq. (6)}$$

$$F = F_h + F_r + \sum_{j=1}^{j=n} F_j \qquad \text{Eq. (7)}$$

The terms in Eqs. (1) to (7) are defined below. C is concentration of drug, V is volume of organ, tissue or blood pool, F is blood flow rate, K is partition coefficient of drug (given as K=concentration in organ or tissue/C_j°), k is first order rate constant of disposition, H is amount of drug disposed in liver, U is amount of drug excreted in urine and t is time, and the subscripts b, h, r, j, and o refer to blood, hepatic, renal, j-th organ or tissue other than liver and kidney, and emergent, respectively. Needless to say, these equations can be used for plasma concentration, replacing the subscript of b by p, and defining F as plasma flow rate. Drug is assumed to be administered by the rate of I which is an arbitrary function of t. And the term of I is added to the right side of Eq. (1) or (2) corresponding to intravenous or oral administration.

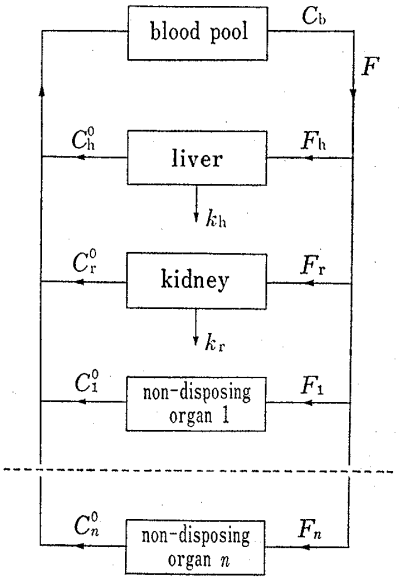

Fig. 1. Generalized Perfusion Model (for details, see text)

According to Rowland, *et al.*[6] to obtain AUC, the total disposed amount of drug in liver (H_∞) and the total excreted amount of drug in urine (U_∞), Eqs. (1) to (6) are integrated between $t=0$ and $t=\infty$, and the following equations are obtained, putting all C's are zero at $t=0$ and $t=\infty$. For non-disposing organ or tissue,

$$F_j \int_0^\infty C_b dt = F_j \int_0^\infty C_j^\circ dt \qquad \text{Eq. (8)}$$

Then,

$$AUC = \int_0^\infty C_b dt = \int_0^\infty C_j^\circ dt \qquad \text{Eq. (9)}$$

Putting Eq. (8) to the equation after the integration of Eq. (1), and integrating Eqs. (2), (3), and I $\left(\int_0^\infty I dt = \text{dose}\right)$, the following simultaneous equations are given for $\int_0^\infty C_b dt$, $\int_0^\infty C_h^\circ dt$ and $\int_0^\infty C_r^\circ dt$, corresponding to administration route.

For intravenous administration:

$$\boldsymbol{A} \begin{pmatrix} \int_0^\infty C_b dt \\ \int_0^\infty C_h^\circ dt \\ \int_0^\infty C_r^\circ dt \end{pmatrix} = \begin{pmatrix} D \\ 0 \\ 0 \end{pmatrix} \qquad \text{Eq. (10)}$$

where D is dose, and

$$A=\begin{pmatrix} F_h+F_r & -F_h & -F_r \\ -F_h & F_h+k_hV_hK_h & 0 \\ -F_r & 0 & F_r+k_rV_rK_r \end{pmatrix}$$

For oral administration:

$$A\begin{pmatrix} \int_0^\infty C_b dt \\ \int_0^\infty C_h^\circ dt \\ \int_0^\infty C_r^\circ dt \end{pmatrix}=\begin{pmatrix} 0 \\ D \\ 0 \end{pmatrix} \qquad \text{Eq. (11)}$$

The solutions of these equations for $\int_0^\infty C dt$ are given in Table I. From the results of Table I the route dependences are given:

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}}=\frac{(U_\infty)_{po}}{(U_\infty)_{iv}}=\frac{F_h}{F_h+k_hV_hK_h} \qquad \text{Eq. (12)}$$

$$\frac{(H_\infty)_{po}}{(H_\infty)_{iv}}=1+\frac{k_rV_rK_r}{F_r+k_rV_rK_r}\left(\frac{F_r}{F_h}\right) \qquad \text{Eq. (13)}$$

Table I. Solutions of Eqs. (10) and (11)

	Intravenous administration	Oral administration
$\int_0^\infty C_b dt$ (AUC)	$\dfrac{D}{\dfrac{F_hk_hV_hK_h}{F_h+k_hV_hK_h}+\dfrac{F_rk_rV_rK_r}{F_r+k_rV_rK_r}}$	$\dfrac{\dfrac{F_h}{F_h+k_hV_hK_h}D}{\dfrac{F_hk_hV_hK_h}{F_h+k_hV_hK_h}+\dfrac{F_rk_rV_rK_r}{F_r+k_rV_rK_r}}$
$\int_0^\infty C_h^\circ dt$	$\dfrac{F_h(\mathrm{AUC})_{iv}}{F_h+k_hV_hK_h}$	$\dfrac{D+F_h(\mathrm{AUC})_{po}}{F_h+k_hV_hK_h}$ or[a] $\left\{\left(\dfrac{F_hk_hV_hK_h}{F_h+k_hV_hK_h}+\dfrac{F_rk_rV_rK_r}{F_r+k_rV_rK_r}\right)\left(\dfrac{F_h+k_hV_hK_h}{F_h}\right)+F_h\right\}\times(\mathrm{AUC})_{po}/(F_h+k_hV_hK_h)$
$\int_0^\infty C_r^\circ dt$	$\dfrac{F_r(\mathrm{AUC})_{iv}}{F_r+k_rV_rK_r}$	$\dfrac{F_r(\mathrm{AUC})_{po}}{F_r+k_rV_rK_r}$
H_∞[b]	$k_hV_hK_h\int_0^\infty C_h^\circ dt$	$k_hV_hK_h\int_0^\infty C_h^\circ dt$
U_∞[c]	$k_rV_rK_r\int_0^\infty C_r^\circ dt$	$k_rV_rK_r\int_0^\infty C_r^\circ dt$

a) D was substituted by $(\mathrm{AUC})_{po}$.
b) obtained by the integration of Eq. (5) between $t=0$ and $t=\infty$
c) obtained by the integration of Eq. (6) between $t=0$ and $t=\infty$

The term of $k_hk_hv_h$ (hepatic clearance) is obtained from the results of Table I. From intravenous administration data:

$$k_hV_hK_h=\left\{\frac{D-(U_\infty)_{iv}}{(\mathrm{AUC})_{iv}}\right\}F_h\Big/\left[F_h-\frac{\{D-(U_\infty)_{iv}\}}{(\mathrm{AUC})_{iv}}\right] \qquad \text{Eq. (14)}$$

From oral administration data:

$$k_hV_hK_h=\frac{F_h\{D-(U_\infty)_{po}\}}{F_h(\mathrm{AUC})_{po}+(U_\infty)_{po}} \qquad \text{Eq. (15)}$$

Putting Eqs. (14) and (15) to Eq. (12), respectively:

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}}=f=\frac{F_h(\mathrm{AUC})_{iv}-\{D-(U_\infty)_{iv}\}}{F_h(\mathrm{AUC})_{iv}}=1-\frac{D-(U_\infty)_{iv}}{F_h(\mathrm{AUC})_{iv}} \qquad \text{Eq. (16)}$$

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}}=f=\frac{F_h+(U_\infty)_{po}/(\mathrm{AUC})_{po}}{F_h+D/(\mathrm{AUC})_{po}} \qquad \text{Eq. (17)}$$

At steady state of drug disposition and distribution during the constant rate infusion, one can obtain the equations similar to Eqs. (1) to (4), putting zero to the left sides of Eqs. (1) to (4) and replacing C by C^s (steady state concentration) in the right sides. Accordingly the simultaneous equations for C^s similar to Eqs. (10) and (11) are given, replacing $\int_0^\infty C dt$ and D by C^s and I_c (constant infusion rate), respectively. And steady state rate of drug disposition in liver ($\dot{H}_s$) and steady state rate of drug excret on in urine ($\dot{U}_s$) are:

$$\dot{H}_s = k_h V_h K_h C_h^{os} \qquad \text{Eq. (18)}$$

$$\dot{U}_s = k_r V_r K_r C_r^{os} \qquad \text{Eq. (19)}$$

The solutions of C^s are obtained from Table I, replacing $\int_0^\infty C_b dt$. *i.e.* AUC, $\int_0^\infty C_h^o dt$, $\int_0^\infty C_r^o dt$ and D by C_b^s, C_h^{os}, C_r^{so}, and I_c, respectively. Then, the similar equations to Eqs. (14) to (17) are given for steady state data:

$$k_h V_h K_h = \left\{\frac{I_c-(\dot{U}_s)_{iv}}{(C_b^s)_{iv}}\right\} F_h \Big/ \left[F_h - \frac{I_c-(\dot{U}_s)_{iv}}{(C_b^s)_{iv}}\right] \qquad \text{Eq. (20)}$$

$$k_h V_h K_h = \frac{F_h\{I_c-(\dot{U}_s)_{po}\}}{F_h(C_b^s)_{po}+(\dot{U}_s)_{po}} \qquad \text{Eq. (21)}$$

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}} = \frac{(C_b^s)_{po}}{(C_b^s)_{iv}} = f = 1 - \frac{I_c-(\dot{U}_s)_{iv}}{F_h(C_b^s)_{iv}} \qquad \text{Eq. (22)}$$

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}} = \frac{F_h+(\dot{U}_s)_{po}/(C_b^s)_{po}}{F_h+I_c/(C_b^s)_{po}} \qquad \text{Eq. (23)}$$

Experimental

Male albino rats (Donryu) weighing 250—280 g were used. Bladder cannulation and urethral ligation were operated for the excretion of drugs in urine. For the biliary excretion bile fistula was operated. Femoral artery cannulation was operated for blood sampling. These operations were given under ether anesthesia. After the rat was transferred into a Bollman cage and awaken, bile, urine and blood samples were taken at appropriate time intervals (see Fig. 2) through the respective cannulae while PSP in saline was infused at a constant rate (Natsume model 12H automatic micro-infusion pump) through a cannula inserted in femoral or portal vein. During the experiment, no food was given but water was taken *ad libitum*.

One tenth ml of bile sample was diluted with 5 ml of de-ionized water and centrifuged at 0—5° for 10 min at 12000 rpm (Kubota KRP-6 centrifuge). This supernatant and urine sample were adequately diluted 1/40 N NaOH. One tenth ml of plasma was diluted with 3 ml of 1/40 N NaOH. Then, PSP was determined at 558 nm (Hitachi 124 spectrometer). The working curves for PSP determination were made by dissolving a definite amount of PSP in bile, urine and blood, respectively.

Results

As shown in Fig. 2 and 3, the steady state urinary excretion rate and blood concentration of PSP during the constant rate infusion (10 mg/hr=167 μg/min) through femoral vein in the rat were 83.3 μg/min and 42 μg/ml, respectively. Putting these values and hepatic blood flow rate (16.0 ml/min: obtained from the authors' observed value in Donryu rat, 6.05 ml/min/100 g body weight,[7] using the mediam body weight of the rats used here) into Eq. (22), f was calculated as 0.875. And the observed value of f was calculated from the ratio, $(\dot{U}_s)_{po}/(\dot{U}_s)_{iv}$ and was 0.900 (see Fig. 2). The values are fairly consistent with each other. This consistence supports the generalized consideration in the present report and gives the use of urine data to predict the route dependence or the first-pass effect.

7) M. Yokota, T. Iga, S. Awazu, and M. Hanano, *J. Appl. Physiol.*, **41**, 439 (1976).

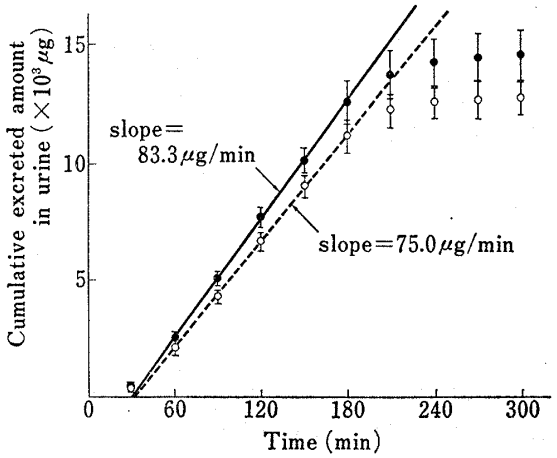

Fig. 2. Cumulative Urinary Excretion Curves of Phenolsulfonphthalein after Portal and Femoral Vein Infusion in Rat

○ : portal vein infusion ($n=4$)
● : femoral vein infusion ($n=5$)
⊥ : standard error
---, —: Lines were drawn by visual approximation.
infusion speed: 10 mg/hr

Although phenolsulfonphthalein is known to be excreted almost exclusively in urine in man and dog, in rat it was excreted in bile as well as in urine. The excretion ratios to dose in urine and in bile were about 47.7% and 34.0%, respectively.

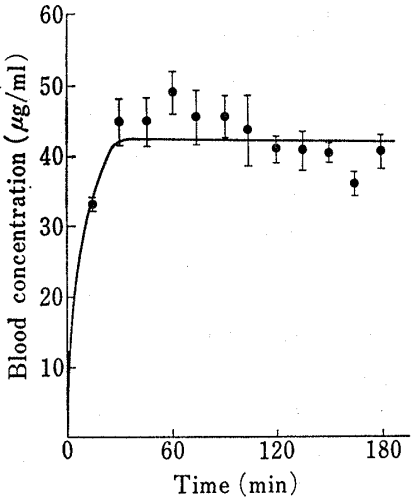

Fig. 3. Blood Concentration Time Course of Phenolsulfonphthalein after Femoral Vein Infusion in Rat

$n=3$
● : average observed value
⊥ : standard error
——: Line was drawn by visual approximation.
infusion speed: 10 mg/hr

Discussion

As can be seen from Eq. (8) or (9), the term of non drug-disposing organ or tissue is eliminated by the term of blood pool. Therefore, however many organs and tissues in an animal body there may be, only blood pool and disposing organs are enough to describe AUC and total excreted amount of drug in urine (see Eqs. (10) and (11)). This is the similar conclusion to that which Rowland[2d] derived from the simpler case where drug is disposed exclusively from liver. And Eq. (12) shows that Gibaldi's equation for the route dependence derived from three compartment model[5] is correct even when drug is disposed in kidney as well as in liver. But in this case to predict the route dependence only from $(AUC)_{iv}$ or $(AUC)_{po}$, some correction as Eq. (16) or (17) is necessary since an intrinsic hepatic clearance which is model independent is given with Eq. (14) or (15).

Correspondence to Compartment Model

Although a perfusion model is instructive from a physiological standpoint, it is essentially equivalent to a conventional compartment model. The model in Fig. 1 can be rewritten to a mammillary model,[8] and similarly to Vaughan and Trainor,[9] amount of drug (X) in any compartment is given in Laplace transform:
for *i.v.* administration,

$$\boldsymbol{B}\begin{pmatrix} x_1 \\ x_2 \\ x_n \end{pmatrix} = \begin{pmatrix} i \\ 0 \\ 0 \end{pmatrix} \qquad \text{Eq. (24)}$$

for *p.o.* administration,

8) A. Rescigno and G. Segre, "Drug and Tracer Kinetics," Blaisdel Publishing Co., London, 1966, p. 91.
9) D.P. Vaughan and A. Trainor, *J. Pharmacok. Biopharmc.*, 3, 203 (1975).

$$\boldsymbol{B}\begin{pmatrix}x_1\\x_2\\x_n\end{pmatrix}=\begin{pmatrix}0\\i\\0\end{pmatrix} \qquad \text{Eq. (25)}$$

where the determinant of the square matrix of B, Δ is given:

$$\Delta=\begin{vmatrix} s+K_1 & -k_{21} & -k_{31} & -k_{41} & \cdots\cdots & -k_{n1} \\ -k_{12} & s+K_2 & 0 & 0 & \cdots\cdots & 0 \\ -k_{13} & 0 & s+K_3 & 0 & \cdots\cdots & 0 \\ -k_{14} & 0 & 0 & s+K_4 & \cdots\cdots & 0 \\ \cdots\cdots & & & & & \\ -k_{1n} & 0 & 0 & 0 & \cdots\cdots & s+K_n \end{vmatrix} \qquad \text{Eq. (26)}$$

And x and i are Laplace transforms of X and I (input rate of drug, arbitrary function of t), respectively: k_{ij} is the first order rate constant from compartment i to compartment j, and $K_i=\sum_{j=1}^{j=n}k_{ij}+k_{io}$. Subscripts 1, 2, 3, and i denote blood pool, hepatic, renal and other compartment, respectively, and subscript, o denotes an out compartment of the mammillary model. Then,

$$(x_1)_{iv}=(-1)^{1+1}i\Delta_{1:1}/\Delta \qquad \text{Eq. (27)}$$

$$(x_1)_{po}=(-1)^{2+1}i\Delta_{2:1}/\Delta \qquad \text{Eq. (28)}$$

where $\Delta_{i:j}$ corresponding to the determinant obtained by suppressing the i-th row and the j-th column from Δ. According to Theorem,[10]

$$f(s)\Big|_{s=0}=\int_0^\infty F(t)dt,\ (\mathrm{AUC})_{iv}=\frac{\int_0^\infty (X_1)_{iv}dt}{V_1}=\frac{1}{V_1}\times i(0)\times\frac{\Delta_{1:1}}{\Delta}\Big|_{s=0} \qquad \text{Eq. (29)}$$

Since $i\ (0)=\int_0^\infty I(t)dt=D$, then (see Appendix)

$$(\mathrm{AUC})_{iv}=\frac{D}{V_1}\times\frac{\Delta_{1:1}}{\Delta}\Big|_{s=0}=\frac{D}{V_1}\times\frac{1}{\dfrac{k_{20}k_{12}}{k_{21}+k_{20}}+\dfrac{k_{30}k_{13}}{k_{31}+k_{30}}} \qquad \text{Eq. (30)}$$

$$=\frac{D}{\dfrac{k_{20}V_2k_{12}V_1}{k_{21}V_2+k_{20}V_2}+\dfrac{k_{30}V_3k_{13}V_1}{k_{31}V_3+k_{30}V_3}}$$

Since $k_{12}V_1=k_{21}V_2$, and $k_{13}V_1=k_{31}V_3$, and they correspond to hepatic and renal blood flow rate, respectively, and $k_{20}V_2$ and $k_{30}V_3$ correspond to hepatic and renal clearance, respectively, therefore, Eq. (30) is the same expression with the expression for $(\mathrm{AUC})_{iv}$ in Table I. And similarly, (see Appendix)

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}}=(-1)\frac{\Delta_{2:1}}{\Delta_{1:1}}\Big|_{s=0}=\frac{k_{21}}{k_{21}+k_{20}} \qquad \text{Eq. (31)}$$

This is the same expression with the Gibaldi's.

Further Consideration on Perfusion Model

The perfusion model in Fig. 1 might be criticized too simple, since hepatic arterial blood and venous blood from various organs, such as spleen, stomach, pancreas and duodenum get into portal vein in parallel. According to Jacquez, *et al.*,[11] these organs are divided into three groups. The first one includes spleen, stomach, pancreas and upper duodenum, and the second and third are small and large intestine, respectively. And further, drug might be metabolized during the passage through intestinal membrane, and be excreted in bile and absorbed again. How should route dependence be described in such a complicated case? When it is assumed that absorption occurs exclusively through small intestine and is complete even in enterohepatic circulation process and that biliary excretion obeys first order kinetics, Eq. (2) is rewritten as:

10) Ref. 8, p. 202.

11) J.A. Jacquez, R. Bellman, and R. Kalaba, *Bull. Math. Biophys.*, 22, 309 (1960).

$$V_h K_h \frac{dC_h^\circ}{dt} = F_{ha}C_b + F_{sp}C_{sp}^\circ + F_s C_s^\circ + F_l C_l^\circ - F_h C_h^\circ - k_h V_h K_h C_l^\circ \quad \text{Eq. (32)}$$

and

$$V_{sp}K_{sp}\frac{dC_{sp}^\circ}{dt} = F_{sp}C_b - F_{sp}C_{sp}^\circ \quad \text{Eq. (33)}$$

$$V_s K_s \frac{dC_s^\circ}{dt} = F_s C_b - F_s C_s^\circ - k_s V_s K_s C_s^\circ + k_{ab}X_l \quad \text{Eq. (34)}$$

$$V_l K_l \frac{dC_l^\circ}{dt} = F_l C_b - F_l C_l^\circ \quad \text{Eq. (35)}$$

$$\frac{dX_1}{dt} = k_b V_h K_h C_h^\circ - k_1 X_1 \quad \text{Eq. (36-a)}$$

$$\frac{dX_2}{dt} = k_1 X_1 - k_2 X_2 \quad \text{Eq. (36-b)}$$

.....

$$\frac{dX_i}{dt} = k_{i-1}X_{i-1} - k_{ab}X_i \quad \text{Eq. (36-c)}$$

$$F_h = F_{ha} + F_{sp} + F_s + F_l \quad \text{Eq. (37)}$$

$$k_h = k_m + k_b \quad \text{Eq. (38)}$$

where subscripts, ha, sp, s, and l denote hepatic artery, the first group, small intestine and large intestine, respectively, and subscripts b, ab, and m denote bile excretion, absorption and metabolism process, respectively. And X is amount of drug excreted in enterohepatic circulation system, and subscripts, 1,2, —, i denote consecutive process of bile excretion, as Dedrick, *et al.*[12] have reported that bile excretion process is composed of several consecutive processes. Other symbols have the same meaning as before.

When these equation are integrated between $t=0$ and $t=\infty$, similarly to Eqs. (8) and (9),

$$\text{AUC} = \int_0^\infty C_b dt = \int_0^\infty C_{sp}^\circ dt = \int_0^\infty C_l^\circ dt \quad \text{Eq. (39)}$$

And

$$k_b V_h K_h \int_0^\infty C_h^\circ dt = k_1 \int_0^\infty X_1 dt = k_2 \int_0^\infty X_2 dt = \cdots\cdots = k_{ab}\int_0^\infty X_i dt \quad \text{Eq. (40)}$$

Accordingly, as in Eqs. (10) and (11), the following simultaneous equations are given for $\int_0^\infty C_b dt$, $\int_0^\infty C_h^\circ dt$, $\int_0^\infty C_r^\circ dt$, and $\int_0^\infty C_s^\circ dt$, corresponding to administration route.

For *i.v.* administration:

$$\boldsymbol{A}' \begin{pmatrix} \int_0^\infty C_b^\circ dt \\ \int_0^\infty C_h^\circ dt \\ \int_0^\infty C_r^\circ dt \\ \int_0^\infty C_s^\circ dt \end{pmatrix} = \begin{pmatrix} D \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{Eq. (41)}$$

For *p.o.* administration:

$$\boldsymbol{A}' \begin{pmatrix} \int_0^\infty C_b^\circ dt \\ \int_0^8 C_h^\circ dt \\ \int_0^\infty C_r^\circ dt \\ \int_0^\infty C_s^\circ dt \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ D \end{pmatrix} \quad \text{Eq. (42)}$$

12) R.L. Dedrick, D.S. Zaharko, and R.J. Lutz. *J. Pharm. Sci.*, **62**, 882 (1973).

where

$$A' = \begin{pmatrix} F_h+F_r & -F_h & -F_r & 0 \\ -(F_h-F_s) & F_h+k_hV_hK_h & 0 & -F_s \\ -F_r & 0 & F_r+k_rV_rK_r & 0 \\ -F_s & -k_bV_hK_h & 0 & F_s+k_sV_sK_s \end{pmatrix}$$

Accordingly,

$$(\mathrm{AUC})_{iv} = (-1)^{1+1}\frac{\Delta_{1:1}}{\Delta}$$

$$= \left(\frac{1}{\Delta}\right) \times \{(F_h+k_hV_hK_h)(F_r+k_rV_rK_r)(F_s+k_sV_sK_s) - k_bV_hK_h(F_r+k_rV_rK_r)F_s\} \quad \text{Eq. (43-a)}$$

$$= \left(\frac{1}{\Delta}\right) \times [F_s\{F_h+(k_h-k_b)V_hK_h\}(F_r+k_rV_rK_r) + k_sV_s(F_h+k_hV_hK_h)(F_r+k_rV_rK_r)] \quad \text{Eq. (43-b)}$$

where $\Delta_{i:j}$ corresponds to the determinant obtained by suppressing the i-th row and the j-th column from Δ which is the determinant of matrix $\mathbf{A}'$. And.

$$\left(\int_0^\infty C_r{}^\circ dt\right)_{iv} = (-1)^{1+3}\frac{\Delta_{1:3}}{\Delta} D \quad \text{Eq. (46)}$$

Then

$$\left(\int_0^\infty C_r{}^\circ dt\right)_{iv} = \frac{F_r}{F_r+k_rV_rK_r}(\mathrm{AUC})_{iv} \quad \text{Eq. (47)}$$

And similarly,

$$\left(\int_0^\infty C_r{}^\circ dt\right)_{po} = \frac{F_r}{F_r+k_rV_rK_r}(\mathrm{AUC})_{po} \quad \text{Eq. (48)}$$

Therefore, the relations between (AUC) and $\int_0^\infty C_r{}^\circ dt$ in Table I apply even when both of k_b and k_s cannot be neglected.
And

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}} = \frac{(-1)^{4+1}\Delta_{4:1}}{(-1)^{1+1}\Delta_{1:1}}$$

$$= \frac{F_hF_s(F_r+k_rV_rK_r)}{F_s\{F_h+(k_h-k_b)V_hK_h\}(F_r+k_rV_rK_r)+k_sV_sK_s(F_h+k_hV_hK_h)(F_r+k_rV_rK_r)} \quad \text{Eq. (49)}$$

In order to find out any practical meaning from Eqs. (43) and (49), they look too complicated, but when $k_s=0$,

$$(\mathrm{AUC})_{iv} = \frac{D}{\frac{F_h(k_h-k_b)V_hK_h}{F_h+(k_h-k_b)V_hK_h}+\frac{F_rk_rV_rK_r}{F_r+k_rV_rK_r}} \quad \text{Eq. (50)}$$

$$\frac{(\mathrm{AUC})_{po}}{(\mathrm{AUC})_{iv}} = \frac{F_h}{F_h+(k_h-k_b)V_hK_h} \quad \text{Eq. (51)}$$

Eqs. (47) and (50) show that data treatment according to Eq. (14) gives $(k_h-k_b)V_hK_h$ which is intric hepatic clearance by metabolism. And it can be seen from Eq. (51) that route dependence depends only on metabolism. As the steady state data are essentially equivalent to AUC data as stated in THEORETICAL in this report, Eq. (20) gives also $(k_h-k_b)V_hK_h$. Accordingly, it is concluded that when $k_s=0$, enterohepatic circulation does not have any effect on route dependence and that AUC method and steady state method reported here can predict route dependence, whether enterohepatic circulation of drug occurs or not.

On the contrary, when $k_b=0$, but $k_s \neq 0$, from Eqs. (43-b) and (49),

$$\frac{(AUC)_{po}}{(AUC)_{iv}} = \frac{F_h F_s}{(F_h + k_h V_h K_h)(F_s + k_s V_s K_s)} \qquad \text{Eq. (52)}$$

This is the equation for route dependence or first-pass effect in the case where drug is disposed in small intestine as well as in liver and kidney. And when k_s and $k_b=0$, Eq. (49) reduces to Eq. (12).

From these discussions, it is clear as far as drug is not metabolized in intestinal membrane, that the Gibaldi's equation to describe route dependence with hepatic blood flow and hepatic clearance is a general rule, even when enterohepatic circulation occurs.

Appendix

Derivation of Eqs. (30) and (31)

Since in the model of Fig. 1, it is supposed that k_{20} and k_{30} are finite and other k_{jo}'s are zero,

$$\Delta|_{s=0} = \begin{vmatrix} \sum_{i=1}^{i=n} k_{1i} & -k_{21} & -k_{31} & -k_{41} & \cdots\cdots & -k_{n1} \\ -k_{12} & k_{21}+k_{20} & 0 & 0 & \cdots\cdots & 0 \\ -k_{13} & 0 & k_{31}+k_{30} & 0 & \cdots\cdots & 0 \\ -k_{14} & 0 & 0 & k_{41} & \cdots\cdots & 0 \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ -k_{1n} & 0 & 0 & 0 & \cdots\cdots & k_{n1} \end{vmatrix} \qquad \text{(a-1)}$$

Adding n-th, $(n-1)$-th, $(n-2)$-th,$\cdots\cdots$, and 2nd row to 1-st row in $\Delta|_{s=0}$,

$$\Delta|_{s=0} = \begin{vmatrix} 0 & k_{20} & k_{30} & 0 & \cdots\cdots & 0 \\ -k_{12} & k_{21}+k_{20} & 0 & 0 & \cdots\cdots & 0 \\ -k_{13} & 0 & k_{31}+k_{30} & 0 & \cdots\cdots & 0 \\ -k_{14} & 0 & 0 & k_{41} & \cdots\cdots & 0 \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ -k_{1n} & 0 & 0 & 0 & \cdots\cdots & k_{n1} \end{vmatrix}$$

$$= \begin{vmatrix} 0 & k_{20} & k_{30} \\ -k_{12} & k_{21}+k_{20} & 0 \\ -k_{13} & 0 & k_{31}+k_{30} \end{vmatrix} k_{41} \cdots\cdots k_{n1}$$

$$= \{k_{20}k_{12}(k_{31}+k_{30}) + k_{30}k_{13}(k_{21}+k_{20})\} k_{41} \cdots\cdots k_{n1} \qquad \text{(a-2)}$$

And eliminating the 1-st row and the 1-st column from the determinant of Eq. (a-1), a diagonal determinant is obtained and its value is shown simply as,

$$\Delta_{1:1}|_{s=0} = (k_{21}+k_{20})(k_{31}+k_{30})k_{41} \cdots\cdots k_{n1} \qquad \text{(a-3)}$$

And similarly,

$$\Delta_{2:1}|_{s=0} = -k_{21}(k_{31}+k_{30})k_{41} \cdots\cdots k_{n1} \qquad \text{(a-4)}$$

Putting Eqs. (a-2) and (a-3) into Eq. (29).

$$(AUC)_{iv} = \frac{D}{V_1} \times \frac{\Delta_{1:1}}{\Delta}\bigg|_{s=0} = \frac{D}{V_1} \times \frac{(k_{21}+k_{20})(k_{31}+k_{30})}{k_{20}k_{12}(k_{31}+k_{30}) + k_{30}k_{13}(k_{21}+k_{20})}$$

$$= \frac{D}{V_1} \times \frac{1}{\dfrac{k_{20}k_{12}}{k_{21}+k_{20}} + \dfrac{k_{30}k_{13}}{k_{31}+k_{30}}} \qquad \text{(a-5)}$$

And from Eqs. (a-3) and (a-4),

$$\frac{\Delta_{2:1}}{\Delta_{1:1}}\bigg|_{s=0} = \frac{-k_{21}}{k_{21}+k_{20}}$$

Then,

$$\frac{(AUC)_{po}}{(AUC)_{iv}} = (-1)\frac{\Delta_{2:1}}{\Delta_{1:1}}\bigg|_{s=0} = \frac{k_{21}}{k_{21}+k_{20}} \qquad \text{(a-6)}$$

Eqs. (a-5) and (a-6) are the same with Eqs. (30) and (31), respectively.