Arch. Pharm. Res. Vol.20, No.1, pp. 24-28, 1997

Effects of Diffusional Barriers on the Extent of Presystemic and Systemic Intestinal Elimination of Drugs

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(Received September 6, 1996)

In the present study, a pharmacokinetic model to address the effects of the diffusional barrier between splanchnic bed and enterocytes on the extent of presystemic and systemic intestinal elimination of drugs was developed. The model is composed of five compartments, *i.e.*, gut lumen, enterocyte, splanchnic bed, liver and central compartments. The equations for various pharmacokinetic parameters important for estimating the quantitative differences between presystemic and systemic intestinal and hepatic elimination of drugs were derived. A simulation study demonstrated that the diffusional barrier present between splanchnic blood and enterocytes can have significant effects on oral bioavailability and systemic clearance of drugs. In conclusion, the model can be useful for a better understanding of the effects of diffusional barrier on the extent of administration-route dependent intestinal and hepatic elimination of drugs, especially those with high hydrophilicity and/or charge(s) under physiological conditions.

Key words: Presystemic, Systemic, Intestine, Liver, Diffusional barrier, Pharmacokinetics

INTRODUCTION

It has been well recognized that presystemic intestinal elimination can have significant effects on bioavailability of drugs after oral administration (Greenblatt, 1993). For some compounds, the intestinal metabolism of drugs has been also considered as an important clearance pathway after intravenous administration (Routledge and Shand, 1979; Koster *et al.*, 1985; deVries *et al.*, 1992). There is, however, lack of understanding on the extent of contribution of intestinal metabolism to overall presystemic and systemic elimination of drugs, and pharmacokinetic relationship between presystemic and systemic intestinal elimination of drugs.

Studies on the extent of presystemic and systemic intestinal elimination of isoprenaline in dogs demonstrated that extraction ratio of the drug after oral administration was significantly higher than that after infusion into the mesenteric artery (Ilett *et al.*, 1980), whereas the presystemic intestinal extraction of chlorpromazine in rats appeared to be similar to that after intravenous administration (Routledge and Shand, 1979). This can be due to differences in administration route-dependent accessibility of drugs to the intestinal metabolism. After oral administration, the drug molecules absorbed from the gut lumen become directly subject to metabolic enzymes within the enterocytes before reaching the portal circulation. However, the intestinal elimination of drugs after intravenous administration depends not only on metabolic activities within enterocytes, but also the rate of transport of drug molecules across the basal membranes between blood and enterocytes. The rate of transport of drugs across the basal membrane could be affected by several factors including physicochemical properties of drug molecules, such as ionizability, tissue-partition coefficient, lipophilicity, etc., and physiological factors including different pH or protein-binding affinity between enterocytes and blood, blood flow rate in the splanchnic bed, etc. (Ilett and Davies, 1982). Due to the differences in diffusibility of molecules via the basal membrane, the extent of intestinal elimination of drugs after intravenous administration can be different from that after oral administration.

A physiological pharmacokinetic model to address presystemic elimination of drugs by the intestine and liver after oral administration was developed by Colburn (Colburn, 1979; Cotler *et al.*, 1983). In his model, the gut was considered as a homogenous well-stirred compartment, so that the extent of intestinal elimination of drugs was assumed to be administration route-independent. This may not be true for many

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drugs, especially those with high hydrophilicity and/or charge(s) under physiological conditions, due to the diffusional barrier discussed above. In the present study, the gut compartment of the model of Colburn was further divided into splanchnic bed and enterocyte compartments, and transport of drug molecules between these two compartments was assumed to be via passive diffusion. The new model provided explicit equations for presystemic and systemic extraction ratios by the intestine and liver after oral and intravenous administrations of drugs, and the pharmacokinetic relationship between these processes. Applicability of the model was further investigated by computer simulations.

THEORY

The model is composed of five compartments, *i.e.*, gut lumen, enterocyte, splanchnic bed, liver and central compartments (Fig. 1). Assumptions for the model include; 1) linear pharmacokinetic behavior, 2) only intestinal and/or hepatic elimination, 3) only unbound drug is available for clearance and 4) instant complete mixing of drug within compartments. Equations were derived based on administration of the drug into the central or gut-lumen compartment to simulate intravenous (*iv*) or oral (*po*) administration, respectively. The differential equations for describing the rate of change in amount of drug in the gut lumen (X_L), enterocyte (X_E), splanchnic bed (X_S), liver (X_H) and central (X_C) compartments were derived as follows. All the symbols were summarized in appendix.

$$dX_L/dt=-(k_a+k_l)\cdot X_L \quad \text{eq. 1}$$

$$dX_E/dt=k_a\cdot X_L+CL_d\cdot f_b\cdot C_S-CL_d\cdot f_t\cdot C_E-CL_{i,e}\cdot f_t\cdot C_E \quad \text{eq. 2}$$

$$dX_S/dt=Q_p\cdot C_C+CL_d\cdot f_t\cdot C_E-CL_d\cdot f_b\cdot C_S-Q_p\cdot C_S \quad \text{eq. 3}$$

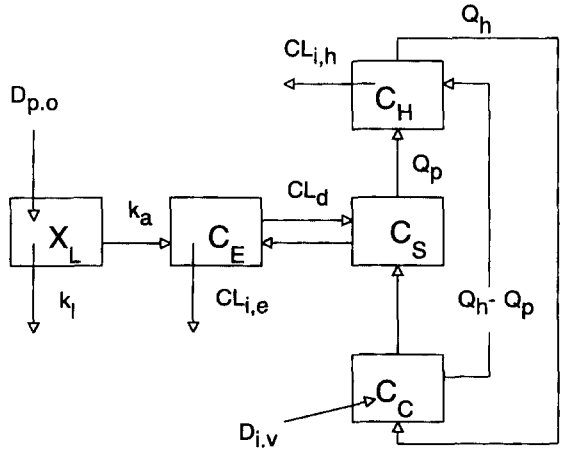

Fig. 1. The model consists of five compartments *i.e.*, gut lumen, enterocyte, splanchnic bed, liver and central compartments.

$$dX_H/dt=Q_p\cdot C_S+(Q_h-Q_p)\cdot C_C-CL_{i,h}\cdot f_b\cdot C_H-Q_h\cdot C_H \quad \text{eq. 4}$$

$$dX_C/dt=Q_h\cdot C_H-Q_h\cdot C_C \quad \text{eq. 5}$$

C terms are concentrations of drug in each compartment. Q_h and Q_p are hepatic and portal blood flow rates, respectively. CL_d, $CL_{i,e}$ and $CL_{i,h}$ are diffusional, intrinsic intestinal and intrinsic hepatic clearances, respectively. k_a is an absorption rate constant. k_l can be considered as a gut microflora metabolic rate constant (Colburn, 1979) and/or a fractional factor describing incomplete absorption of the drug from the lumen, *i.e.*, a fraction of drug unabsorbed is k_l/k_a+k_l (Rescigno, 1994). f_b and f_t are fractions of drug unbound to blood and tissue (enterocytes) components, respectively.

Integrating equations from time 0 to ∞ yields equations describing the areas under the drug concentration-time curves (AUC) for drug in the central (AUC_C) and splanchnic bed (AUC_S) compartments after *iv* or *po* dosing.

$$AUC_{iv,C}=D_{iv}\cdot(Q_h+f_b\cdot CL_{i,h})\cdot(Q_p+f_b\cdot CL_{i,app})/(f_b\cdot Q_h\cdot(Q_p\cdot CL_{i,h}+CL_{i,app}\cdot(Q_p+f_b\cdot CL_{i,h}))) \quad \text{eq. 6}$$

$$AUC_{iv,S}=(Q_h\cdot AUC_{iv,C}\cdot(Q_p+f_b\cdot CL_{i,h})-D_{iv}\cdot(Q_h+f_b\cdot CL_{i,h}))/Q_h\cdot Q_p \quad \text{eq. 7}$$

$$AUC_{po,C}=D_{po,abs}\cdot Q_p\cdot CL_{i,app}/(f_b\cdot CL_{i,e}\cdot(Q_p\cdot CL_{i,h}+CL_{i,app}\cdot(Q_p+f_b\cdot CL_{i,h}))) \quad \text{eq. 8}$$

$$AUC_{po,s}=AUC_{po,c}\cdot(Q_p+f_b\cdot CL_{i,h})/Q_p \quad \text{eq. 9}$$

$$CL_{i,app}=CL_d\cdot CL_{i,e}/(CL_d+CL_{i,e}) \quad \text{eq. 10}$$

$CL_{i,app}$ is apparent intrinsic intestinal clearance. D_{iv} is an *iv* dose and $D_{po,abs}$ is amount of drug absorbed from the lumen into enterocytes after *po* dosing. It can be assumed that $AUC_{iv,C}$ and $AUC_{po,C}$ physiologically correspond to AUC in the vena cava after *iv* and *po* dosing, and $AUC_{iv,S}$ and $AUC_{po,S}$ physiologically correspond to AUC in the portal vein after *iv* and *po* dosing, respectively. From equations 6 and 7, and 8 and 9, $CL_{i,app}$ and $CL_{i,h}$ can be derived as in equations 11 and 12, respectively.

$$CL_{i,app}=Q_p\cdot(AUC_{iv,C}-AUC_{iv,S})/(f_b\cdot AUC_{iv,S}) \quad \text{eq. 11}$$

$$CL_{i,h}=Q_p\cdot(AUC_{po,S}-AUC_{po,C})/(f_b\cdot AUC_{po,C}) \quad \text{eq. 12}$$

Systemic clearance (CL_s) can be described as follows.

$$CL_s=D_{iv}/AUC_{iv,C}=CL_g+CL_h=Q_h\cdot E_{iv,sys} \quad \text{eq. 13}$$

$$CL_g=Q_p\cdot E_{iv,g} \quad \text{eq. 14}$$

$$CL_h=Q_h\cdot E_{iv,h} \quad \text{eq. 15}$$

CL_g and CL_h are intestinal and hepatic clearances, respectively, and $E_{iv,sys}$, $E_{iv,g}$ and $E_{iv,h}$ are systemic, intestinal and hepatic extraction ratios estimated after *iv* administration of drugs, respectively.

$$E_{iv,sys}=CL_s/Q_h=E_{iv,g}\cdot(Q_p/Q_h)+E_{iv,h} \quad \text{eq. 16}$$

$$E_{iv,g}=f_b\cdot CL_{i,app}/(Q_p+f_b\cdot CL_{i,app}) \quad \text{eq. 17}$$

$$E_{iv,h}=(f_b\cdot CL_{i,h}/(Q_h+f_b\cdot CL_{i,h}))\cdot(1-E_{iv,g}\cdot(Q_p/Q_h)) \quad \text{eq. 18}$$

Oral bioavailability (F) can be expressed as follows.

$$F=AUC_{po,C}\cdot D_{iv}/(AUC_{iv,C}\cdot D_{po})$$
$$=(D_{po,abs}/D_{po})\cdot(Q_p\cdot CL_{i,app}/(CL_{i,e}\cdot(Q_p+f_b\cdot CL_{i,app})))\cdot$$
$$(Q_h/(Q_h+f_b\cdot CL_{i,h}))=F_{abs}\cdot F_{po,g}\cdot F_{po,h} \quad \text{eq. 19}$$

where F_{abs}, $F_{po,g}$ and $F_{po,h}$ are availability of the drug after absorption from the lumen into enterocytes, presystemic intestinal and hepatic elimination after *po* dosing, respectively. Presystemic extraction ratios by the intestion ($E_{po,g}$) and the liver ($E_{po,h}$) after *po* administration of drugs can be derived from equation 19.

$$E_{po,g}=1-F_{po,g}=((Q_p+f_b\cdot CL_d)/(f_b\cdot CL_d))\cdot E_{iv,g} \quad \text{eq. 20}$$

$$E_{po,h}=1-F_{po,h}=(Q_h/(Q_h-CL_g))\cdot E_{iv,h} \quad \text{eq. 21}$$

From equations 16, 20 and 21, $E_{iv,sys}$ can be expressed as a function of $E_{po,g}$ and $E_{po,h}$.

$$E_{iv,sys}=E_{po,g}\cdot(1-E_{po,h})\cdot Q_p\cdot f_b\cdot CL_d/(Q_h\cdot(Q_p+f_b\cdot CL_d))+E_{po,h} \quad \text{eq. 22}$$

SIMULATIONS

The simulations for estimating $E_{iv,g}$, $E_{iv,h}$, $E_{iv,sys}$, $E_{po,g}$, $E_{po,h}$, CL_s and F were performed by varying CL_d and $CL_{i,e}$ (the same to, or lower or higher than Q_h by ten fold) with constant blood flow rates (1 and 0.8 mL/min/kg for Q_h and Q_p, respectively) at the same intravenous and oral doses under linear conditions. It was assumed that the drug was completely absorbed after oral administration and there was no protein binding. The results are shown in Table I.

RESULTS AND DISCUSSION

The numerical approximation studies done by Gwilt *et al.* (Gwilt *et al.*, 1988) suggested that in the presence of a significant diffusional barrier at the blood-mucosal interface, the intestinal extraction ratio of the drug after oral administration might be greater than that after intravenous administration. By incorporating the diffusional clearance for transport of drug molecules across membranes between splanchnic blood and enterocytes, the present model was able to describe the quantitative differences between presystemic and systemic intestinal elimination of drugs, with explicit equations. In their simulation studies, Minchin and Ilet (Minchin and Ilett, 1982) introduced a proportionality factor, α ($0\leq\alpha\leq1$), to address the quantitative differences between systemic and presystemic intestinal extraction ratios of drugs. According to the present model, α can be readily described as a function of portal blood flow rate, fraction unbound in blood and diffusional clearance (equation 20). When $f_b\cdot CL_d$ is much larger than Q_p, the intestinal extraction ratio of the drug is administration route-independent; however, if $f_b\cdot CL_d$ is smaller than Q_p, presystemic intestinal extraction ratio becomes greater than systemic intestinal extraction ratio.

Due to the sequential anatomical arrangement of the intestine and liver, the rate of elimination of the drug by the liver and, hence, hepatic clearance are less than those when the intestinal elimination of the drug is negligible (Pang, 1983). Similar findings were observed in a once-through in situ rat intestine-liver perfusion study with salicylamide (Xu *et al.*, 1989). The study demonstrated that hepatic extraction ratio (0.99) estimated from differences in substrate concentrations between the portal and hepatic vein was higher than that (0.74) estimated based on relative contribution of the liver to total metabolite-formation rates. Equation 21 indicated that $E_{po,h}$ which is the absolute extraction ratio by the liver is always greater than $E_{iv,h}$ which reflects the extent of relative contribution of the liver to total systemic clearance, unless the systemic intestinal elimination is negligible. In the studies on presystemic elimination of cyclosporin in humans, We *et al.* (We *et al.*, 1995) assumed that hepatic extraction ratio (nonrenal clearance divided by hepatic blood flow rate) of cy-

Table I. Simulations for estimating $E_{iv,g}$, $E_{iv,h}$, $E_{iv,sys}$, $E_{po,g}$, $E_{po,h}$, CL_s and F were performed by varying CL_d and $CL_{i,e}$ at the same intravenous and oral doses with constant blood flow rates under linear conditions

No	Q_n	Q_p	CL_d	$CL_{i,e}$	$CL_{i,h}$	$CL_{i,app}$	$E_{iv,g}$	$E_{iv,h}$	$E_{iv,sys}$	$E_{po,g}$	$E_{po,h}$	CL_s	F(%)
1	1	0.8	0.1	0.1	1	0.05	0.06	0.48	0.52	0.53	0.50	0.52	23.53
2	1	0.8	0.1	1	1	0.09	0.10	0.46	0.54	0.92	0.50	0.54	4.08
3	1	0.8	0.1	10	1	0.10	0.11	0.46	0.54	0.99	0.50	0.54	0.44
4	1	0.8	1	0.1	1	0.09	0.10	0.46	0.54	0.18	0.50	0.54	40.82
5	1	0.8	1	1	1	0.50	0.38	0.35	0.65	0.69	0.50	0.65	15.38
6	1	0.8	1	10	1	0.91	0.53	0.29	0.71	0.96	0.50	0.71	2.13
7	1	0.8	10	0.1	1	0.10	0.11	0.46	0.54	0.12	0.50	0.54	44.05
8	1	0.8	10	1	1	0.91	0.53	0.29	0.71	0.57	0.50	0.71	21.28
9	1	0.8	10	10	1	5.00	0.86	0.16	0.84	0.93	0.50	0.84	3.45

All blood flow rates and clearance values are expressed in mL/min/kg.

closporin estimated from intravenous administration is the same to that during first pass after oral administration. However, as they pointed out, this is true, only if there is no systemic intestinal elimination of the drug, as described in equation 21.

The simulation study (Table I) demonstrated that the diffusional barrier between splanchnic bed and enterocytes can have significant effects on the extent of systemic clearance as well as bioavailability of drugs after oral administration. It was noticed that when CL_d increased, there were a significant increase in $E_{iv,g}$, and a slight decrease in $E_{iv,h}$ except at a high $CL_{i,e}$ and $E_{po,g}$ except at a low $CL_{i,e}$. There were no changes in $E_{po,h}$ under the present conditions. Due to the significant increase in $E_{iv,g}$, there was an increase in CL_s when CL_d increased, although the contribution on hepatic elimination to systemic clearance of the drug ($E_{iv,h}$) decreased. Interestingly, when CL_d increased, oral bioavailability also increased to a significant extent due to the decrease in $E_{po,g}$, despite the fact that CL_s increased. These findings implied that a compound with higher systemic clearance can show greater bioavailability after oral administration than a compound with lower systemic clearance, depending on diffusibility of the compounds via the basal membrances, when other pharmacokinetic parameters are similar.

The present approach can provide estimations for $CL_{i,app}$ and $CL_{i,h}$ of drugs by measuring systemic and portal blood exposure after intravenous and oral administration, with equations 11 and 12. In addition, the solutions for CL_d, $CL_{i,e}$ and $D_{po,abs}$ can be obtained from equations 10, 11, 12 and 19, if one of those parameters is experimentally measured. The estimations of CL_d and $CL_{i,e}$ can be important to understand the lack of *in vitro-in vivo* correlation of intestinal metabolism seen in many drugs (Thummel, 1995).

In summary, the present model provided the equations for estimating various pharmacokinetic parameters which can be useful for a better understanding of the effects of the diffusional barrier on the extent of presystemic and systemic intestinal elimination of drugs, especially those with high hydrophilicity and/or charge (s) under physiological conditions.

ABBREVIATIONS

AUC : area under the concentration time curve

$AUC_{iv,C}$, $AUC_{iv,S}$: AUC in the central (vena cava) and the splanchnic-bed (portal vein) compartments after intravenous dosing, respectively

$AUC_{po,C}$, $AUC_{po,S}$: AUC in the central (vena cava) and the splanchnic bed (portal vein) compartments after oral dosing, respectively

C_C, C_E, C_H, C_S : concentration of drug in the central, enterocyte, liver and splanchnic bed compartments, respectively

CL_d, $CL_{i,e}$, $CL_{i,h}$: diffusional, intrinsic intestinal and intrinsic hepatic clearances, respectively

CL_s, CL_g, CL_h : systemic, intestinal and hepatic clearances, respectively

D_{iv}, D_{po} : intravenous and oral doses, respectively

$D_{po,abs}$: amount of drug absorbed into enterocytes from the lumen after oral dosing

$E_{iv,sys}$, $E_{iv,g}$, $E_{iv,h}$: systemic, intestinal and hepatic extraction ratios of drugs after intravenous dosing, respectively

$E_{po,g}$, $E_{po,h}$: presystemic intestinal and hepatic extraction ratio of drugs after oral dosing, respectively

F:oral bioavailability

F_{abs}, $F_{po,g}$ $F_{po,h}$: availability of drugs after absorption from the lumen, presystemic intestinal and presystemic hepatic elimination, respectively

f_b, f_t : fraction of drug unbound to blood and tissue (enterocytes) components, respectively

k_a, k_l : absorption and luminal elimination rate constants, respectively

Q_h, Q_p : hepatic and portal blood flow rates, respectively

X_C, X_E, X_H, X_L, X_S : amount of drug in the central, enterocyte, liver, gut lumen and splanchnic bed compartments, respectively

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