Theoretical Considerations on Two Equations for Estimating the Extent of Absorption After Oral Administration of Drugs

Younggil Kwon[1,2] and Philip B. Inskeep[1]

Received September 20, 1995; accepted December 28, 1995

Purpose. The amount of drug absorbed into portal blood after oral dosing ($D_{p.o,g}$) has been estimated using Fick's principle (Q-method), i.e., $D_{p.o,g} = Q_h \cdot (AUC_{p.o,g} - AUC_{p.o,c})$, where Q_h is the portal blood flow rate, and $AUC_{p.o,g}$ and $AUC_{p.o,c}$ are the areas under the concentration-time curves of portal vein and systemic blood after oral dosing, respectively. However, this method may underestimate $D_{p.o,g}$, when the drug is subject to systemic intestinal elimination. An alternate equation (CL-method; $D_{p.o,g} = CL_s \cdot AUC_{p.o,g}$) is described using a simple pharmacokinetic model, to estimate $D_{p.o,g}$ in the presence of systemic intestinal elimination, where CL_s is systemic clearance.

Methods. The model is composed of central, intestine and liver compartments, assuming that drug is eliminated by intestinal and/or hepatic pathways only. A comparison of both methods for estimating $D_{p.o,g}$ was made using computer-simulation or experimental data of phenacetin from the literature.

Results. The simulation study demonstrated that the Q-method underestimated $D_{p.o,g}$ in the presence of significant intrinsic intestinal clearance, compared to the CL-method,. The similar results were observed using the experimental data of phenacetin.

Conclusions. The CL-method can provide a better estimate of $D_{p.o,g}$, while the Q-method may underestimate $D_{p.o,g}$, when there is significant systemic intestinal elimination of drugs after oral administration. In addition, useful information for understanding the relationship between the extent of absorption and the first-pass effect by intestine and/or liver after oral dosing of drugs can be obtained from the present approach.

KEY WORDS: oral absorption; bioavailability; intestinal elimination; first pass effect.

INTRODUCTION

It has been suggested that the amount of drug absorbed into the portal vein after oral administration of drugs ($D_{p.o,g}$) can be estimated using Fick's principle, i.e., $D_{p.o,g} = Q_h \cdot (AUC_{p.o,g} - AUC_{p.o,c})$, where Q_h is the portal blood flow rate, and $AUC_{p.o,g}$ and $AUC_{p.o,c}$ are the areas under the concentration time curves (AUC) of portal vein and systemic blood, respectively, after oral dosing (1–3). This equation indicates that at any particular time period, the amount of newly absorbed drug into the portal vein is equal to the portal blood volume times the difference between portal vein and systemic blood concentrations. However, if the previously absorbed drug returning to the mesenteric artery from systemic circulation becomes subject to further intestinal metabolism prior to reaching the portal circulation, the difference between the portal vein and systemic blood concentrations underestimates the true concentration of newly absorbed drug into the portal vein, resulting in the underestimation of $D_{p.o,g}$, when using the Fick's principle. In addition, a substrate that is well absorbed, but undergoes extensive first-pass metabolism within enterocytes could have a concentration profile in the portal vein similar to an agent that is poorly absorbed. Thus, the use of Fick's principle can not distinguish between these two very different causes of incomplete oral bioavailability.

A pharmacokinetic model to address presystemic elimination of drugs by the intestine and liver after oral dosing was developed by Colburn and Gibaldi (4). In this model, disposition kinetics of drugs subjected to first-pass intestinal and hepatic metabolism can be determined by measuring systemic and portal blood levels after intravenous and oral dosing, and measuring or estimating gastrointestinal blood flow rates. We have adapted the model of Colburn and Gibaldi, and described a simple equation to estimate $D_{p.o,g}$, while eliminating the requirements to obtain portal blood concentrations of drug following intravenous dosing and to estimate the portal blood flow rate. With a few assumptions, the amount of drug actually absorbed into enterocytes from the intestinal lumen can be also assessed, in order to distinguish limited absorption from first-pass intestinal elimination.

THEORY

The model is composed of three compartments, i.e., central, intestine and liver compartments (Fig. 1). Assumptions for this model include; 1) linear, route-independent pharmacokinetic behavior, 2) only intestinal and/or hepatic elimination, 3)

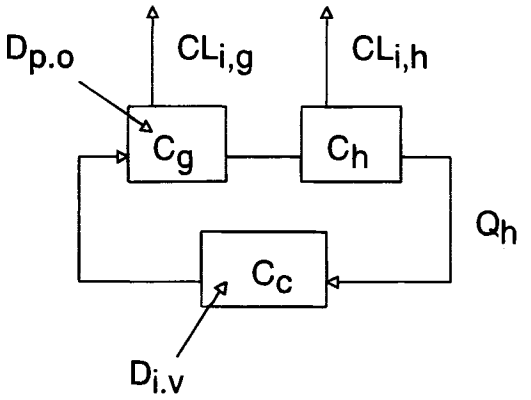

Fig. 1. The model consists of three compartments, i.e., central, intestine and liver compartments.

[1] Drug Metabolism Department, Central Research Division, Pfizer Inc., Groton, Connecticut 06340.

[2] To whom correspondence should be addressed.

ABBREVIATIONS: AUC: area under the concentration time curve; $AUC_{i.v,c}$: AUC in the central compartment (vena cava) after intravenous dosing; $AUC_{p.o,c}$: AUC in the central compartment (vena cava) after oral dosing; $AUC_{p.o,g}$: AUC in the intestine compartment (portal vein) after oral dosing; $C_{c,g,h}$: concentration of drug in the central, intestine and liver compartments, respectively; $CL_{i,g}$: intrinsic intestinal clearance; $CL_{i,h}$: intrinsic hepatic clearance; CL_s: systemic clearance; $D_{i.v}$: intravenous dose; $D_{p.o}$: amount of drug (absorbed into enterocytes from the lumen after oral dosing) dosed into the intestine compartment; $D_{p.o,g}$: amount of drug available prior to reaching the liver compartment (absorbed into the portal vein) after oral dosing; $E_{g,h}$: Intestinal and hepatic extraction ratios, respectively; F: bioavailability; f_u: fraction of drug unbound to blood components; Q_h: portal blood flow rate; $X_{c,g,h}$: amount of drug in the central, intestine and liver compartments, respectively.

0724-8741/96/0400-0566$09.50/0

only unbound drug is available for clearance, 4) instant complete mixing of drug within compartments, 5) blood flow of the hepatic artery is ignored, and 6) no lymphatic absorption. Equations were derived based on administration of dose into the central or intestine compartments to simulate intravenous or oral administration, respectively. The rates of change of drug amounts in central (X_c), intestine (X_g), and liver (X_h) can be expressed by the following equations. Please refer to abbreviations for symbols.

$$dX_c/dt = Q_h \cdot C_h - Q_h \cdot C_c \quad (1)$$

$$dX_g/dt = Q_h \cdot C_c - CL_{i,g} \cdot f_u \cdot C_g - Q_h \cdot C_g \quad (2)$$

$$dX_h/dt = Q_h \cdot C_g - CL_{i,h} \cdot f_u \cdot C_h - Q_h \cdot C_h \quad (3)$$

where C_c, C_g, and C_h are drug concentrations in central, intestine and liver compartments, respectively, and Q_h and f_u are blood flow rate and the fraction of drug unbound to blood components, respectively. After integrating equations 1, 2, and 3 from 0 to ∞ for intravenous dosing, systemic clearance (CL_s) can be expressed as a function of Q_h, f_u, $CL_{i,g}$, and $CL_{i,h}$ (intrinsic intestinal and hepatic clearances, respectively).

$$CL_s = D_{i.v}/AUC_{i.v,c} = Q_h \cdot E_g + (1 - E_g) \cdot Q_h \cdot E_h \quad (4)$$

$$E_g = f_u \cdot CL_{i,g}/(Q_h + f_u \cdot CL_{i,g}) \quad (5)$$

$$E_h = f_u \cdot CL_{i,h}/(Q_h + f_u \cdot CL_{i,h}) \quad (6)$$

where $D_{i.v}$ is an intravenous dose, and E_g and E_h are intestinal and hepatic extraction ratios, respectively. $AUC_{i.v,c}$ is AUC in the central compartment after intravenous dosing and can be expressed as in equation 7.

$$AUC_{i.v,c} = D_{i.v} \cdot (Q_h + f_u \cdot CL_{i,g}) \cdot (Q_h + f_u \cdot CL_{i,h})/ (Q_h \cdot (Q_h \cdot f_u \cdot CL_{i,h} + f_u \cdot CL_{i,g} \cdot (Q_h + f_u \cdot CL_{i,h}))) \quad (7)$$

It can be assumed that $AUC_{i.v,c}$ physiologically corresponds to AUC measured in the vena cava after intravenous dosing of drugs. After integrating equations 1, 2, and 3 from 0 to ∞ for oral dosing, $CL_{i,h}$ can be derived as in equation 8.

$$CL_{i,h} = Qh \cdot (AUC_{p.o,g} - AUC_{p.o,c})/(f_u \cdot AUC_{p.o,c}) \quad (8)$$

From equations 4 and 8, $CL_{i,g}$ can be further defined as in equation 9.

$$CL_{i,g} = Q_h \cdot (CL_s \cdot AUC_{p.o,g} - Q_h \cdot (AUC_{p.o,g} - AUC_{p.o,c}))/(f_u \cdot (Q_h - CL_s) \cdot AUC_{p.o,g}) \quad (9)$$

where $AUC_{p.o,c}$ and $AUC_{p.o,g}$ are AUC in the central and intestine compartments after oral dosing, respectively. It can be assumed that $AUC_{p.o,c}$ and $AUC_{p.o,g}$ physiologically correspond to AUC measured in the vena cava and the portal vein after oral dosing of drugs, respectively. $AUC_{p.o,g}$ can be expressed as in equation 10.

$$AUC_{p.o,g} = D_{p.o} \cdot (Q_h + f_u \cdot CL_{i,h})/(Q_h \cdot f_u \cdot CL_{i,h} + f_u \cdot CL_{i,g} \cdot (Q_h + f_u \cdot CL_{i,h})) \quad (10)$$

where $D_{p.o}$ is the amount of the drug dosed into the intestinal compartment and can be viewed as the amount of the drug absorbed into enterocytes from the lumen after oral administration. From equations 4, 7, and 10, the amount of the drug available prior to reaching the liver compartment after oral dosing of the drug ($D_{p.o,g}$) can be derived as a function of CL_s and $AUC_{p.o,g}$, which is equal to the amount of drug available after first-pass intestinal elimination, as shown in equation 11.

$$D_{p.o,g} = CL_s \cdot AUC_{p.o,g} = (1 - E_g) \cdot D_{p.o} \quad (11)$$

It can be assumed that $D_{p.o,g}$ physiologically corresponds to the amount of the drug absorbed into the portal vein after oral dosing. According to equation 11, $D_{p.o,g}$ can be estimated experimentally by measuring systemic drug concentrations after intravenous dosing and portal vein drug concentrations after oral dosing. From equations 5, 9, and 11, $D_{p.o}$ can be further estimated as in equation 12.

$$D_{p.o} = CL_s \cdot AUC_{p.o,g}/(1 - E_g) \quad (12)$$

SIMULATIONS AND DATA ANALYSIS

The simulations for estimating $D_{p.o,g}$ using Fick's principle (Q-method) or the equation derived above (CL-method: CL_s ·

Table 1. Simulation for Estimating % of the Orally Dosed Drug Which Is Available Prior to the Liver Compartment (% $D_{p.o,g}$) Using the Q-Method or the CL-Method

No	Dose	Q_h	$CL_{i,g}$	$CL_{i,h}$	$AUC_{i.v,c}$	CL_s	$AUC_{p.o,g}$	$AUC_{p.o,c}$	F	% $D_{p.o,g}$	
										Q-method	CL-method
1	100	10	0	0.1	1010	0.099	1010	1000	99.0	100	100
2	100	10	0	1	110	0.909	110	100	90.9	100	100
3	100	10	0	10	20	5.000	20	10	50.0	100	100
4	100	10	1	0.1	100	0.999	90.99	90.09	90.1	9.0	90.9
5	100	10	1	1	58	1.736	52.38	47.62	82.1	47.6	90.9
6	100	10	1	10	18	5.455	16.67	8.33	46.3	83.4	90.9
7	100	10	100	0.1	11	9.100	1.00	0.99	9.0	0.1	9.1
8	100	10	100	1	11	9.174	0.99	0.90	8.2	0.9	9.1
9	100	10	100	10	10	9.545	0.95	0.48	4.8	4.7	9.1

Note: Q-method: $\%D_{p.o,g} = 100 \cdot Q_h \cdot (AUC_{p.o,g} - AUC_{p.o,c})/Dose$; CL-method: $\%D_{p.o,g} = 100 \cdot CL_s \cdot AUC_{p.o,g}/Dose$;
F: bioavailability (%, $100 \cdot AUC_{p.o,c}/AUC_{i.v,c}$).

Table 2. Comparison of the Q-Method and the CL-Method for Estimating $\%D_{p.o,g}$ of Phenacetin After Oral Dosing in Rats (Data from Literature (5))

Dose (mg/kg)	AUC(μg·min/mL)[a]			CL_s[b] (mL/min·kg)	F (%)	$\%D_{p.o,g}$	
	$AUC_{i.v,c}$	$AUC_{p.o,g}$	$AUC_{p.o,c}$			Q-method[c]	CL-method
20	1741	843	729	11.5	41.9	22.3	48.5

[a] $AUC_{i.v,c}$, $AUC_{p.o,g}$, and $AUC_{p.o,c}$ are AUC of plasma in inferior vena cava after intravenous dosing (20 mg/kg), in portal vein and inferior vena cava after oral dosing (20 mg/kg), respectively.
[b] systemic plasma clearance.
[c] Portal blood flow rate in rats (Q_h) is assumed 39.2 mL/min·kg (6) and a blood/plasma partition ratio of phenacetin is assumed one (7).

$AUC_{p.o,g}$ (eq. 11)) were performed by varying $CL_{i,g}$ and $CL_{i,h}$ at the same intravenous and oral doses and a constant Q_h (Table 1). It was assumed that drug was completely absorbed after oral dosing and there was no protein binding. The comparison of both methods for estimating $D_{p.o,g}$ with kinetic data of phenacetin from the literature (5) was shown in Table 2.

RESULTS AND DISCUSSION

Both methods provided correct assessments of % $D_{p.o,g}$, when $CL_{i,g}$ was negligible, as shown in the simulation (rows 1 to 3 of Table 1). However, when a significant $CL_{i,g}$ term was introduced in the model (rows 4 to 9), the Q-method consistently underestimated % $D_{p.o,g}$, compared to the CL-method. In addition, when $CL_{i,g}$ was similar to or greater than $CL_{i,h}$, only the CL-method provided realistic estimates of % $D_{p.o,g}$. The Q-method provided estimates of % $D_{p.o,g}$ that were less than the oral bioavailability (F), (rows 4, 5, 7, 8, and 9), a clearly impossible outcome. A similar situation appears to be applicable to the kinetics of phenacetin after oral dosing in rats, which is known to be metabolized in both intestine and liver (5). Comparison of both methods for the analysis of phenacetin data demonstrated that % $D_{p.o,g}$ estimated using the Q-method (22.3%) was lower than F (41.9%), assuming a blood/plasma ratio of unity (similar to the ratio of 1.2 observed for paracetamol (7)), while the CL-method produced % $D_{p.o,g}$ (48.5%) greater than F (Table 2).

These discrepancies when using the Q-method can be due to the fact that previously absorbed drug molecules coming from the systemic circulation are also subject to further systemic intestinal elimination before appearing in the portal vein (8). Therefore, $AUC_{p.o,c}$ overestimates the true AUC of the previously absorbed drug returning to the portal vein from the systemic circulation in the presence of intestinal metabolism, resulting in the underestimated $D_{p.o,g}$ using the Q-method. A notable discrepancy in % $D_{p.o,g}$ between the Q-method and the CL-method may indicate that intestinal metabolism is an important systemic elimination pathway of the drug.

The CL-method does not require measuring the partition ratio of the drug between blood and plasma for estimation of $D_{p.o,g}$, because CL_s and $AUC_{p.o,g}$ measured from plasma data can be used. For drugs which may have effects on the portal vein blood flow rate (9), the CL-method should offer a more reliable estimate of $D_{p.o,g}$ than the Q-method which needs an accurate estimate of the blood flow rate. The present model can also allow for the estimation of other important pharmacokinetic parameters such as $CL_{i,h}$ (eq. 8), $CL_{i,g}$ (eq. 9), and amount of the dose actually absorbed into intestinal enterocytes from the lumen after oral dosing ($D_{p.o}$, eq. 12), with further measurement of the portal blood flow rate and blood/plasma ratio. Thus, this model can help to distinguish the extent of absorption *per se* from first-pass intestinal elimination by comparing $D_{p.o}$ and $D_{p.o,g}$.

The present model assumes that the intestinal extraction of drug after oral dosing is the same as after intravenous administration, by considering the intestine as a well-stirred compartment with no diffusional barrier. However, the extent of the intestinal extraction can be different, depending on the routes of administration of drugs (8, 10). This can be due to physicochemical properties of drugs such as lipophilicity, tissue partition coefficients, etc., and/or physiological differences between serosal and mucosal membranes (11, 12). This route-dependent extent of the extraction by the intestine may have effects on $CL_{i,g}$ and $CL_{i,h}$ estimation, using the present model; however, $D_{p.o,g}$ calculated by the CL-method should not be affected.

The role of hepatic artery blood flow, used in the model of Colburn and Gibaldi (4), was not incorporated into the present model. Due to this simplification, the CL-method could overestimate the extent of the true $D_{p.o,g}$ by up to 20–30% in various laboratory animals, depending on the ratio of blood flow rates between hepatic artery and portal vein (6). In fact, the estimates of $D_{p.o,g}$ by the CL-method were only 1–17% higher than those calculated with equation 11, i.e., $(1\text{-}E_g) \cdot D_{p.o}$, using the simulation data by Colburn and Gibaldi (4). Thus, the exclusion of the blood flow rate of hepatic artery from our model should not be a major limitation in assessing the extent of oral absorption of drugs.

In conclusion, the CL-method can provide a better estimate of $D_{p.o,g}$ than the Q-method, when the drug is subject to significant systemic intestinal elimination after oral administration. In addition, useful information for understanding the relationship between the extent of absorption and the first-pass effect by the intestine and/or liver after oral dosing of drugs can be obtained.

REFERENCES

1. G. Schmalzing. Metabolism and disposition of trifluoperazine in the rat. II. kinetics after oral and intravenous administration in acutely and chronically treated animals. *Drug Metab. Dispos.* **5**:104–115 (1977).
2. K. Takeda, K. Shibakawa, M. Sudo, S. Sasatani, and H. Terashima. Comparison of the two methods for calculating hepatic first-pass effect of ONO-4057 by a dog model with multiple cannulas and effect of food on the portal blood flow. *Pharm. Res.* **11**:S417 (1994).
3. D. J. Hoffman, T. Seifert, A. Borre, and H. N. Nellans. Method to estimate the rate and extent of intestinal absorption in conscious rats using an absorption probe and portal blood sampling. *Pharm. Res.* **12**:889–894 (1995).

4. W. A. Colburn, and M. Gibaldi. Pharmacokinetic model of presystemic metabolism. *Drug Metab. Dispos.* **6**:193–196 (1978).
5. R. M. Welch, C. Hughes, and R. L. Deangelis. Effect of 3-methylcholanthrene pretreatment on the bioavailability of phenacetin in the rat. *Drug Metab. Dispos.* **4**:402–406 (1976).
6. B. Davies, and T. Morris. Physiological parameters in laboratory animals and humans. *Pharm. Res.* **10**;1093–1095 (1993).
7. L. F. Prescott. Kinetics and metabolism of paracetamol and phenacetin. *Br. J. Clin. Pharmac.* **10**:291S–298S (1980).
8. P. A. Routledge, and D. G. Shand. Presystemic drug elimination. *Ann. Rev. Pharmacol. Toxicol.* **19**:447–468 (1979).
9. D. W. Schneck, and J. E. Vary. Mechanism by which hydralazine increases propranolol bioavailability. *Clin. Pharmacol. Ther.* **35**:447–453 (1984).
10. K. F. Ilett, C. T. Dollery, and D. S. Davies. Isoprenaline conjugation-a true first-pass effect in the dog intestine. *J. Pharm. Pharmacol.* **32**:362 (1980).
11. R. F. Minchin, and K. F. Ilett. Presystemic elimination of drugs: theoretical considerations for quantifying the relative contribution of gut and liver. *J. Pharm. Sci.* **71**:458–460 (1982).
12. P. R. Gwilt, S. Comer, P. R. Chaturvedi, and D. H. Waters. The influence of diffusional barriers on presystemic gut elimination. *Drug Metab. Dispos.* **16**:521–526 (1988).