Pharmaceutical Research, Vol. 8, No. 3, 1991

Research Article

Relationship of Apparent Systemic Clearance to Individual Organ Clearances: Effect of Pulmonary Clearance and Site of Drug Administration and Measurement

Reza Mehvar[1]

Received May 14, 1990; accepted September 25, 1990

The relationships between apparent total-body clearance (CL) and individual organ clearances were mathematically defined with respect to the site of drug administration and measurement. The derived equations can be applied to drugs undergoing different pathways of elimination, including pulmonary clearance. A physiological pharmacokinetic model was used to test the validity of the equations. The apparent systemic clearance values obtained through the equations, using the individual organ clearance values, were identical to those calculated utilizing the model-generated data, indicating the validity of the equations. Furthermore, it was shown that the conventional estimation of CL of drugs subject to pulmonary clearance is highly dependent upon the site of drug administration and measurement. The relationships were further utilized to explain the reported CL values which are higher than the cardiac output. The equations developed here may be used to predict the contribution of different organs, such as the lungs, to the apparent systemic clearance of drugs.

KEY WORDS: apparent systemic clearance; organ clearance; pulmonary clearance; hepatic clearance; arteriovenous concentration gradient; first-pass metabolism.

INTRODUCTION

Although the liver is the major site of drug metabolism, the contribution of other organs, especially the lung, to the overall elimination of xenobiotics must not be neglected. The importance of the lung as an eliminating organ stems from the fact that, because of its unique anatomical position, it receives total cardiac output in each circulation (1). Hence, even a relatively low pulmonary extraction ratio may result in a significant pulmonary clearance (CL_p). Consequently, it is necessary to evaluate the contribution of CL_p to the overall apparent systemic clearance (CL) of drugs.

The CL of a drug after its intravascular administration is conventionally calculated from the following equation (2):

$$CL = \text{dose/AUC} \quad (1)$$

Based on the concept of additivity of clearance terms (3), CL can also be defined in terms of organ clearances involved in the elimination of the drug:

$$CL = \Sigma CL_i \quad (2)$$

where CL_i is the individual organ clearance value. Equation (2), however, is valid only in the absence of pulmonary elimination (3). This is due to the fact that the lungs receive their blood supply in series relative to other eliminating organs. On the other hand, the blood supplies to other eliminating organs, such as liver and kidneys, are in parallel. Therefore, in the presence of pulmonary elimination, simple additivity of the clearance terms, as expressed by Eq. (2), does not hold (3).

Few reports (4–6) have attempted to describe mathematically the contribution of CL_p to CL of drugs. The derived equations, however, are valid only for a specific case with regard to sampling and administration sites. It is the intention of this communication to define and test the relationship between pulmonary and apparent systemic clearances for different sites of drug administration and measurement.

THEORETICAL

A complete list of symbols and abbreviations along with their definitions are presented under Nomenclature.

Kinetic Model

The kinetic model used for this study is depicted in Fig. 1. For the sake of simplicity, it is assumed that, besides elimination by the lungs, the liver is the only site of drug elimination. Based on this model, the total elimination rate of a drug from the body at any time after its administration (dX_T/dt) equals the sum of the individual elimination rates by the lungs (dX_p/dt) and the liver (dX_h/dt) at that time:

$$dX_T/dt = dX_p/dt + dX_h/dt \quad (3)$$

Under linear conditions, the organ clearance (CL_i) is a proportionality constant relating the elimination rate by that or-

[1] College of Pharmacy and Health Sciences, Drake University, Des Moines, Iowa 50311.

0724-8741/91/0300-0306$06.50/0

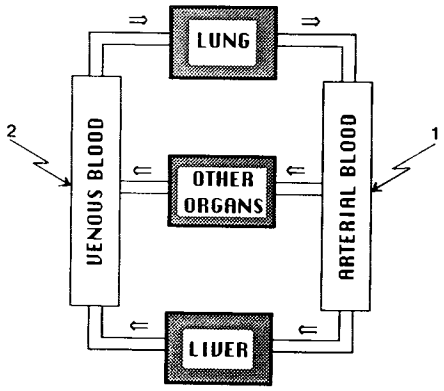

Fig. 1. Physiological pharmacokinetic model incorporating lung and liver as two eliminating organs. The arrows indicate direction of blood flow. 1 and 2 refer to the sites of arterial and venous administration or sampling, respectively.

gan (dX_i/dt) to the concentration of the drug in blood entering the organ (C_{in}) (3):

$$dX_i/dt = CL_i \cdot C_{in} \quad (4)$$

Substitution of Eq. (4) into Eq. (3) results in the following relationship:

$$dX_T/dt = (CL_p \cdot C_{pa}) + (CL_h \cdot C_{ia}) \quad (5)$$

where C_{pa} and C_{ia} are concentrations of the drug in blood entering the lung (pulmonary artery) and liver (systemic artery), respectively. Furthermore, it must be realized that C_{pa} is the same as the concentration of the drug in systemic venous blood (C_{iv}). Substitution of C_{iv} for C_{pa} and integration of Eq. (5) from time zero to infinity results in Eq. (6):

$$X_T^{0-\infty} = (CL_p \cdot AUC_{iv}^x) + (CL_h \cdot AUC_{ia}^x) \quad (6)$$

where AUC_{iv}^x and AUC_{ia}^x are ia and iv AUCs, respectively, obtained after administration of the drug through route x.

Equation (6) was used to describe the relationship among CL_p, CL_h, and CL for four different cases with regard to the site of drug administration and measurement as discussed below.

Intravenous Drug Administration and Measurement. After iv administration, only a fraction of the dose which escapes first-pass elimination by the lungs (F_p) reaches the arterial blood (Fig. 1). Therefore, the relationship between AUC_{ia} (AUC_{ia}^{iv}) and AUC_{iv} (AUC_{iv}^{iv}) after iv administration can be defined by Eq. (7):

$$F_p = AUC_{ia}^{iv}/AUC_{iv}^{iv} \quad (7)$$

Equation (7) can be used to replace the AUC_{ia}^x in Eq. (6) by ($F_p \cdot AUC_{iv}^x$):

$$X_T^{0-\infty} = (CL_p \cdot AUC_{iv}^{iv}) + (CL_h \cdot F_p \cdot AUC_{iv}^{iv}) \quad (8)$$

Equation (8) can be rearranged:

$$X_T^{0-\infty}/AUC_{iv}^{iv} = CL_p + (F_p \cdot CL_h) \quad (9)$$

Substitution of the administered dose (D^{iv}) for $X_T^{0-\infty}$ results in the following equation:

$$CL_{iv}^{iv} = CL_p + (F_p \cdot CL_h) \quad (10)$$

where CL_{iv}^{iv} is defined as D^{iv}/AUC_{iv}^{iv}.

Intravenous Drug Administration and Arterial Blood Measurement. Based on Eq. (7), AUC_{iv}^x in Eq. (6) can be replaced by (AUC_{ia}^x/F_p):

$$X_T^{0-\infty} = (CL_p \cdot AUC_{ia}^{iv}/F_p) + (CL_h \cdot AUC_{ia}^{iv}) \quad (11)$$

The same argument used for the above case can be used to derive Eq. (12):

$$CL_{ia}^{iv} = (CL_p/F_p) + CL_h \quad (12)$$

where CL_{ia}^{iv} is defined as D^{iv}/AUC_{ia}^{iv}.

Intraarterial Drug Administration and Measurement. After ia administration, the iv blood may not receive the complete dose. This is because a portion of the administered dose may be eliminated by the liver before reaching the venous blood (Fig. 1). Therefore, the relationship between AUC_{ia}^{ia} and AUC_{iv}^{ia} can be defined by

$$AUC_{iv}^{ia} = f_h \cdot (AUC_{ia}^{ia} \cdot F_h) + (f_o \cdot AUC_{ia}^{ia}) \quad (13)$$

where f_h and f_o are fractions of cardiac output which pass through the liver and all the other organs, respectively ($f_h + f_o = 1$), and F_h is the fraction of the drug which is available after one-passage through the liver. Substitution of Eq. (13) in Eq. (6) results in the following relationship:

$$X_T^{0-\infty} = CL_p \cdot [f_h \cdot (AUC_{ia}^{ia} \cdot F_h) + (f_o \cdot AUC_{ia}^{ia})] + (CL_h \cdot AUC_{ia}^{ia}) \quad (14)$$

Equation (14) can be rearranged:

$$X_T^{0-\infty} = AUC_{ia}^{ia}[CL_p \cdot (f_h \cdot F_h + f_o) + CL_h] \quad (15)$$

$$CL_{ia}^{ia} = [CL_p \cdot (f_h \cdot F_h + f_o)] + CL_h \quad (16)$$

where CL_{ia}^{ia} is defined as D^{ia}/AUC_{ia}^{ia}.

Intraarterial Drug Administration and Venous Blood Measurement. Based on Eq. (13), AUC_{ia}^x in Eq. (6) can be replaced by $[AUC_{iv}^x/(f_h \cdot F_h + f_o)]$:

$$X_T^{0-\infty} = (CL_p \cdot AUC_{iv}^{ia}) + [CL_h \cdot AUC_{iv}^{ia}/(f_h \cdot F_h + f_o)] \quad (17)$$

$$CL_{iv}^{ia} = CL_p + [CL_h/(f_h \cdot F_h + f_o)] \quad (18)$$

where CL_{iv}^{ia} is defined as D^{ia}/AUC_{iv}^{ia}.

Methods

In order to test the validity of the above equations, a physiological pharmacokinetic model (Fig. 1) was used to stimulate concentrations of a drug in arterial and venous blood after iv and ia administrations. The following equations were used to describe the rate of concentration changes for venous blood (dC_{iv}/dt), lung (dC_p/dt), arterial blood (dC_{ia}/dt), liver (dC_h/dt), and noneliminating organs (dC_o/dt):

$$dC_{iv}/dt = [(Q_o \cdot C_o/K_o) + (Q_h \cdot C_h/K_h) - (Q_T \cdot C_{iv})]/V_v \quad (19)$$

$$dC_p/dt = [(Q_T \cdot C_{iv}) - (Q_T + CL_p^{int}) \cdot C_p/K_p)]/V_p \quad (20)$$

$$dC_{ia}/dt = [(Q_T \cdot C_p/K_p) - (Q_o + Q_h) \cdot C_{ia}]/V_a \quad (21)$$

$$dC_h/dt = [(Q_h \cdot C_{ia}) - (CL_h^{int} + Q_h) \cdot C_h/K_h)]/V_h \quad (22)$$

$$dC_o/dt = [(Q_o \cdot C_{ia}) - (Q_o \cdot C_o/K_o)]/V_o \quad (23)$$

Fourth-order numerical integration method of Runge Kutta was used to simulate the respective concentrations at various times after the drug administration. This was accomplished by a simple program which was run on a Macintosh Plus computer with a Fortran Compiler. Results of these simulations were identical to those obtained using a commercial computer program (STELLA, High Performance Systems, Lyme, NH), which became available to the author after completion of this work.

Parameters used for simulations are listed in Tables I and II. The values of the physiological parameters (Table I) are approximations of those reported in the literature (7,8) for a 400-g rat. Rats were selected because the physiological values of this species are widely reported in the literature. However, simulations could be performed for any other species. Dose (1 mg) and partition coefficient values (1.0 for all the organs) were selected arbitrarily. Simulations were carried out for four drugs with different pulmonary and hepatic intrinsic clearance values (Table II). In addition to two extreme cases where pulmonary (drug 1) or hepatic elimination (drug 4) is absent, simulations were also carried out for two drugs with different values of CL_p^{int}, resulting in relatively low (drug 2) and high (drug 3) pulmonary extraction ratios (Table II). Except for the dosing site (ia or iv blood), the initial (time-zero) concentrations in all the other compartments and organs were zero. The initial concentration in the dosing site was calculated by dividing the dose by the volume of the compartment.

The AUC values were calculated by the linear trapezoidal rule using the generated concentration–time data. The CL values were subsequently calculated as dose divided by the AUC for iv or ia administration with venous or arterial measurements. These apparent CL values were then compared with those obtained through Eqs. (10), (12), (16), and (18) based on the organ clearance (CL_i) values. The CL_i was calculated using the following equations, according to the "well-stirred" model of drug elimination (2):

$$E_i = CL_i^{int}/(CL_i^{int} + Q_i) \quad (24)$$

$$CL_i = Q_i \cdot E_i \quad (25)$$

RESULTS AND DISCUSSION

The arithmetic and venous AUC values obtained based on the physiological model after ia and iv administration of drugs 1–4 are listed in Table III. Apparent systemic clearance values calculated using these AUCs and Eq. (1) (D/AUC) for iv and ia administration and measurement are presented in Table IV. Also reported in Table IV are the CL values obtained using individual hepatic and pulmonary clearance values (Table II) and Eqs. (10), (12), (16), and (18). Both methods of calculation of CL resulted in the same value (Table IV), indicating that the equations appropriately define the relationship between individual organ clearance values and the apparent systemic clearance of a drug undergoing pulmonary and/or hepatic elimination. Furthermore, examination of the results presented in Table IV reveals that almost identical values are obtained for CL_{iv}^{iv} and CL_{ia}^{ia} for all four drugs studied. This suggests that Eqs. (10) and (16), although apparently different, are identical. A mathematical manipulation of these equations proves this conclusion (see Appendix). Accordingly, one may conclude that if sites of drug administration and measurement are the same, the AUC is independent of the site of administration (Table III).

Arterial and venous blood concentration–time courses of drugs 1–4 after iv and ia administrations are presented in Fig. 2. Except for drug 1 ($CL_p = 0$), concentrations of the drugs in arterial blood are less than the corresponding venous concentrations at any time after achieving pseudoequilibrium; the arteriovenous concentration difference widens as CL_p increases (Fig. 2). For drug 1, which does not undergo pulmonary elimination, the arterial and venous concentrations are superimposable at the postpseudoequilibrium period. It is interesting to note that for all drugs tested, the route of drug administration (iv or ia) does not affect the pattern of arteriovenous concentration differences at the postpseudoequilibrium period. However, as expected, arte-

Table I. Physiologic Parameters Used in Simulation[a]

Organ/compartment	Volume (ml)	Blood flow (ml/min)
Total blood	21	74
Venous blood	14	74
Arterial blood	7.0	74
Lung	2.0	74
Liver	15	25
Other organs	200[b]	49[c]

[a] Based on literature values (7,8) for a 400-g rat.
[b] Arbitrarily selected.
[c] Blood flow to other organs = total blood flow − hepatic blood flow.

Table II. Pharmacokinetic Parameters of Four Hypothetical Drugs Used in Simulation

	Drug			
	1	2	3	4
CL_p^{int} (ml/min)	0.0	20	200	20
E_p[a]	0.0	0.213	0.730	0.213
CL_p (ml/min)[b]	0.0	15.8	54.0	15.8
CL_h^{int} (ml/min)	20	20	20	0.0
E_h[a]	0.444	0.444	0.444	0.0
CL_h (ml/min)[b]	11.1	11.1	11.1	0.0

[a] Calculated using Eq. (24).
[b] Calculated using Eq. (25).

Table III. Arterial and Venous AUCs (ng · hr/ml) After iv and ia Administration of a Single 1-mg Dose[a]

Drug	AUC_{iv}^{iv}	AUC_{ia}^{iv}	AUC_{iv}^{ia}	AUC_{ia}^{ia}
1	1500[a]	1505[a]	1265	1497[a]
2	682[b]	543	586	679[b]
3	294[c]	80.3	245	290[c]
4	1060[d]	841	1067[d]	1057[d]

[a] Identical values are expected for the AUC values bearing the same superscript letter.

Table IV. Comparison of the Apparent Systemic Clearance Values (ml/min) Obtained Using the Simulation Experiment [Eq. (1)] and Those Obtained Using the Individual Organ Clearance Values [Eqs. (10), (12), (16), and (18)]

	Drug			
	1	2	3	4
CL_{iv}^{iv}				
D_{iv}/AUC_{iv}^{iv}	11.1	24.4	56.6	15.7
Eq. (10)	11.1	24.5	57.0	15.7
CL_{ia}^{iv}				
D_{iv}/AUC_{ia}^{iv}	11.1	30.7	208	19.8
Eq. (12)	11.1	31.1	211	20.0
CL_{ia}^{ia}				
D_{ia}/AUC_{ia}^{ia}	11.1	24.5	57.5	15.7
Eq. (16)	11.1	24.5	57.0	15.7
CL_{iv}^{ia}				
D_{ia}/AUC_{iv}^{ia}	13.2	28.4	68.1	15.6
Eq. (18)	13.1	28.8	67.1	15.7

riovenous concentration–time profiles are route dependent before pseudoequilibrium is achieved (Fig. 2). Arteriovenous concentration differences have been recognized for some drugs such as propranolol (9) and nitroglycerin (10) and have been the subject of an elaborate two-part review (11,12). Results of our simulations indicate that these differences may be due, at least in part, to presence of pulmonary elimination.

Drugs 1 and 4 represent two extreme cases of the model presented in Fig. 1, where pulmonary or hepatic elimination is absent. In the absence of pulmonary elimination ($CL_p = 0$, $F_p = 1$; drug 1), Eqs. (10), (12), (16), and (18) would simplify to the following equations:

$$CL_{iv}^{iv} = CL_h \tag{26}$$

$$CL_{ia}^{iv} = CL_h \tag{27}$$

$$CL_{ia}^{ia} = CL_h \tag{28}$$

$$CL_{iv}^{ia} = CL_h/(f_h \cdot F_h + f_o) \tag{29}$$

Furthermore, based on a lung bioavailability of 1 and Eq. (7), the AUC_{iv}^{iv} and AUC_{ia}^{iv} are equal; the same conclusion can be made based on Eqs. (26) and (27). This is because in the absence of pulmonary extraction, arterial blood, like venous blood, receives 100% of the iv dose. However, after ia administration, the venous blood does not receive the total dose, and therefore, AUC_{iv}^{ia} is less than AUC_{ia}^{ia}. This is due to hepatic elimination of a portion of the ia dose before reaching venous blood (Fig. 1). It is obvious that the AUC_{iv}^{ia} is less than AUC_{ia}^{ia} for all the drugs with nonzero hepatic clearance (drugs 1–3, Table III).

In the other extreme, in the absence of hepatic clearance (drug 4, Tables II and III), Eqs. (10), (12), (16), and (18) would simplify to the following equations:

$$CL_{iv}^{iv} = CL_p \tag{30}$$

$$CL_{ia}^{iv} = CL_p/F_p \tag{31}$$

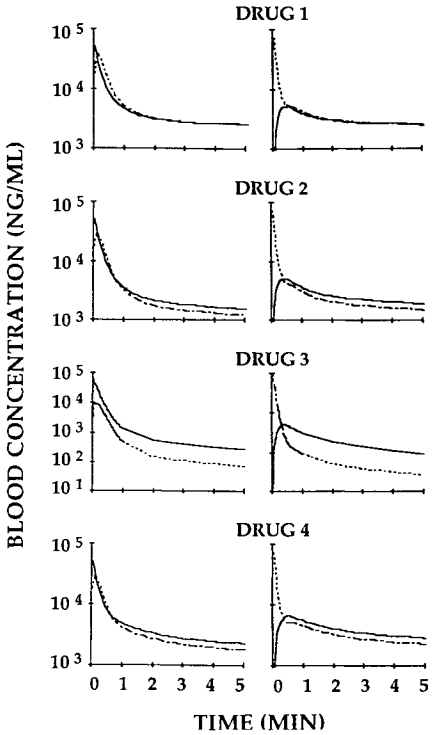

Fig. 2. Arterial (dotted line) and venous (solid line) blood concentrations of drugs 1–4 after iv (left) and ia (right) administrations.

$$CL_{ia}^{ia} = CL_p \tag{32}$$

$$CL_{iv}^{ia} = CL_p \tag{33}$$

In contrast to drug 1 ($CL_h^{int} \neq 0$), the iv and ia AUCs are expected to be equal for drug 4 ($CL_h^{int} = 0$) after ia drug administration [Eqs. (32) and (33)]. However, after iv administration, the arterial blood receives a fraction of the drug which escapes the first-pass elimination by lungs (F_p). Hence, after iv administration, AUC_{ia} is less than AUC_{iv} by a factor of F_p [Eqs. (7), (30), and (31)].

Based on the same argument presented above, in the presence of both hepatic and pulmonary clearances (drugs 2 and 3, Table II), the AUC_{ia} is less than the AUC_{iv} after iv administration, whereas the reverse is true after ia administration (Table III).

The AUC values presented in Table III are in complete agreement with the above equations and conclusions. The slight differences in the AUC values where similar values are expected are due to the inexactness of the computation method used for calculation of the AUCs.

Using a different approach, Collins and Dedrick (5) have previously defined the relationship between CL_p and CL by an equation similar to our Eq. (12) (Eq. 9, Ref. 5) for iv drug administration and ia drug measurement. However, the other situations which may arise from different site of administration or measurement (iv or ia) were not discussed. Equation (12) was also derived by Chiou (6), assuming iv drug administration and ia drug measurement. However, it was stated that the AUC is independent of the type of blood used for the drug measurement. Hence, it was concluded that the derived equation is applicable for iv drug adminis-

tration, irrespective of the site of drug measurement (6). Our simulations, on the other hand, clearly indicate that in the presence of pulmonary clearance, AUC_{ia}^{iv} is always smaller than AUC_{iv}^{iv} (drugs 2–4, Table III); only in the absence of CL_p are AUC_{iv}^{iv} and AUC_{ia}^{iv} equal (drug 1, Table III). Hence, the relationships reported by Collins and Dedrick (5) and Chiou (6), like our Eq. (12), are valid only for the specific case of iv administration and ia measurement of a drug.

Using a linear stochastic recirculating model, Vaughan and Hope (4) described the relationship between systemic clearance and individual organ clearance values after iv drug administration and measurement. The derived equation, however, is similar to our Eq. (12), which is applicable for iv drug input and ia, rather than iv, drug measurement. This discrepancy may be due to the fact that Vaughan and Hope (4) defined iv administration as introduction of the drug into the heart–lung system rather than into a systemic vein. Nevertheless, the three reports in the literature dealing with the relationship of apparent systemic clearance and CL_p (4–6) have all resulted in derivation of one equation similar to our Eq. (12). However, the same equation has been stated to be valid when AUC is based on measurement of the drug in venous (4), arterial (5), or either (6) blood. Our definition of Eq. (12), however, is in agreement with that of Collins and Dedrick (5).

Based on the model presented in Fig. 1, pulmonary bioavailability of a drug (F_p) may be obtained through two different approaches. One approach is based on the iv drug administration and simultaneous iv and ia drug measurements; F_p can then be calculated as the AUC_{ia}:AUC_{iv} ratio [Eq. (7)]. A second approach utilizes the same sampling site (arterial blood) with different sites of drug administration (ia and iv routes). In the latter case, F_p can be estimated as the ratio of the arterial AUC after iv administration to that obtained after ia dosing ($F_p = AUC_{ia}^{iv}/AUC_{ia}^{ia}$). Cassidy and Houston (13) used the second approach to estimate F_p for phenol in rats. Phenol was administered through different routes, and its concentrations were measured in arterial blood obtained through a carotid artery cannula. In agreement with our model, after iv administration (jugular vein) the AUC_{ia} was substantially less than that after ia administration (carotid artery). This was attributed to a significant first-pass metabolism of intravenously administered phenol in the lung.

It is necessary to mention that our model and the derived equations are based on the assumption of instantaneous mixing of the administered dose in the dosing compartment (systemic arterial or venous blood). Therefore, at time zero, immediately after the drug administration, the dosing compartment contains the maximum concentration of the drug, which can be measured by sampling that compartment. However, this assumption may be invalid when drug administration and sampling are carried out at different parts of the arterial or venous blood compartments (14). Such a situation, for instance, can occur when drug administration and sampling are performed using two peripheral veins from the opposite arms. In this case, concentration of the drug in the sampling vein immediately after the drug administration into the opposite arm's vein is zero, and the drug appears at the sampling site after one passage through the systemic circulation. In our model depicted in Fig. 1, this is analogous to administration of the drug into the lung, or administration of a fraction of the drug which escapes lung elimination (F_p) into the arterial blood, accompanied by iv measurements. Therefore, Eq. (18), developed for calculation of CL after ia administration and iv measurement (CL_{iv}^{ia}) may be modified for calculating CL after drug administration and sampling using two veins from the opposite arms [$CL_{iv(2)}^{iv(1)}$]:

$$CL_{iv(2)}^{iv(1)} = CL_{iv}^{ia}/F_p \tag{34}$$

Similarly, administration of the drug into a peripheral artery, rather than systemic artery, would resemble drug administration into the organ which that artery serves.

Although our model includes the liver as the only site of extrapulmonary drug elimination, the derived equations can be modified to include all other mechanisms which may be involved in the elimination of a drug. To do so, one can replace the terms CL_h, F_h, and f_h in Eqs. (10), (12), (16), and (18) with CL_s, F_s, and f_s, respectively:

$$CL_{iv}^{iv} = CL_p + (F_p \cdot CL_s) \tag{35}$$

$$CL_{ia}^{iv} = (CL_p/F_p) + CL_s \tag{36}$$

$$CL_{ia}^{ia} = [CL_p \cdot (f_s \cdot F_s + f_o)] + CL_s \tag{37}$$

$$CL_{iv}^{ia} = CL_p + [CL_s/(f_s \cdot F_s + f_o)] \tag{38}$$

where subscript s refers to all organs, other than the lungs, involved in the elimination of a drug from the body. The CL_s is a simple addition of the individual organ clearance values [Eq. (2)], whereas F_s is defined by the following equation:

$$F_s = \Sigma(Q_i \cdot F_i)/\Sigma Q_i \tag{39}$$

The same argument used for Eqs. (10) and (16) (see Appendix) can be utilized to prove that Eqs. (35) and (37) are identical.

There is a controversy in the literature as to whether pulmonary elimination can be responsible for unusually high CL values of some drugs (2,6,15). While some investigators (2,6) have suggested that in the presence of CL_p, apparent systemic CL values above the cardiac output are possible, the work of others (15) implies that even substantial CL_p cannot describe CL values higher than cardiac output. Equations (35) to (38) were used to examine this issue. For each equation, simulations were carried out for three different values of F_s (0.0, 0.5, and 1.0), and CL was calculated for varying values (0.0–1) of the pulmonary extraction ratio (E_p). The results of these simulations are presented in Fig. 3. As expected, Eqs. (35) and (37) resulted in identical relationships (Fig. 3A). Based on these results, the value of CL, calculated as D/AUC, cannot exceed cardiac output when administration and sampling sites are the same (Fig. 3A). However, when the drug is administered in one site and measurements are carried out in another site (iv administration and ia measurement, Fig. 3B; ia administration and iv measurement, Fig. 3C), apparent CL values higher than cardiac output are possible. Interestingly, Fig. 3C indicates that CL values significantly higher than cardiac output may be obtained also in the absence of CL_p; this is possible after ia administration and iv measurement of a drug with a systemic extraction ratio (E_s) >0.5 ($F_s < 0.5$). In all other cases, how-

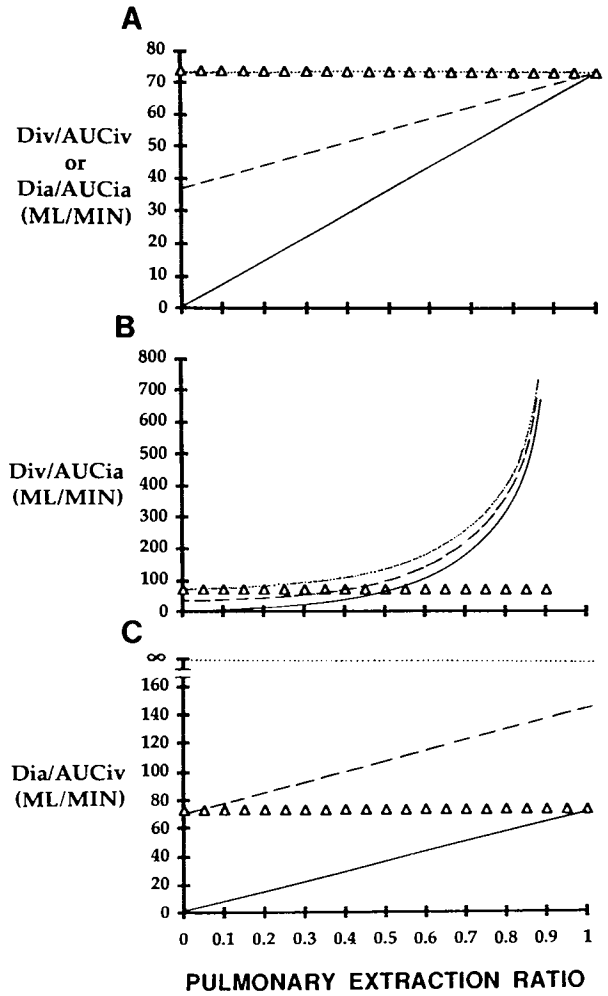

Fig. 3. The relationship between apparent systemic clearance and pulmonary extraction ratio for a drug with a systemic, nonpulmonary extraction ratio (E_s) of 0.0 (——), 0.5 (----), or 1.0 (·····). The total cardiac output is depicted by open triangles. The apparent clearance is calculated as D_{iv}/AUC_{iv} or D_{ia}/AUC_{ia} (A), D_{iv}/AUC_{ia} (B), or D_{ia}/AUC_{iv} (C).

ever, a CL higher than cardiac output is always associated with a $CL_p > 0$.

The equations presented here were developed for intravascular drug administration. However, simple modifications can be made to accommodate oral administration of drugs. The oral administration is similar to iv administration, with one difference: after oral administration, only a fraction of the drug (F_{po}) reaches venous blood. Hence, Eqs. (10) and (12) can be modified for application to oral data:

$$CL_{iv}^{po} = CL_{iv}^{iv}/F_{po} = (CL_p + F_p \cdot CL_h)/F_{po} \quad (40)$$

$$CL_{ia}^{po} = CL_{ia}^{iv}/F_{po} = (CL_p/F_p + CL_h)/F_{po} \quad (41)$$

where CL_{iv}^{po} and CL_{ia}^{po} are defined as D^{po}/AUC_{iv}^{po} and D^{po}/AUC_{ia}^{po}, respectively.

In conclusion, the relationships between organ clearance and total-body clearance values were defined with reference to the site of drug administration and measurement in the presence or absence of pulmonary elimination. Furthermore, results of simulations obtained through a physiological pharmacokinetic model attested to the validity of these equations. These relationships indicate that the apparent systemic clearance of a drug undergoing pulmonary elimination is highly dependent upon the site of drug administration and measurement.

APPENDIX

Replacement of the term F_p in Eq. (10) by $(1 - E_p)$ and further rearrangement would result in the following equations:

$$CL_{iv}^{iv} = CL_p + (1 - E_p) \cdot CL_h \quad (A1)$$

$$CL_{iv}^{iv} = CL_p + CL_h - (E_p \cdot CL_h) \quad (A2)$$

$$CL_{iv}^{iv} = CL_p + CL_h - (E_p \cdot f_h \cdot Q_p \cdot E_h) \quad (A3)$$

$$CL_{iv}^{iv} = CL_p + CL_h - (CL_p \cdot f_h \cdot E_h) \quad (A4)$$

$$CL_{iv}^{iv} = CL_p + CL_h - [CL_p \cdot f_h \cdot (1 - F_h)] \quad (A5)$$

$$CL_{iv}^{iv} = CL_p + CL_h - [(CL_p \cdot f_h) - (CL_p \cdot f_h \cdot F_h)] \quad (A6)$$

$$CL_{iv}^{iv} = CL_h + CL_p(1 - f_h + f_h \cdot F_h) \quad (A7)$$

The term $(f_o + f_h)$ can be used to replace 1 in Eq. (A7):

$$CL_{iv}^{iv} = CL_h + CL_p (f_o + f_h \cdot F_h) \quad (A8)$$

Equation (A8) is identical to Eq. (16) in the text, which proves that

$$CL_{iv}^{iv} = D_{iv}/AUC_{iv}^{iv} = CL_{ia}^{ia} = D_{ia}/AUC_{ia}^{ia} \quad (A9)$$

NOMENCLATURE

AUC	Area under the blood concentration–time curve
AUC_y^x	AUC of the drug measured in compartment y after route of administration of x
C_i	Concentration of drug in organ i
C_{ia}	Concentration of drug in systemic arterial blood
C_{in}	Concentration of drug in blood entering the organ
C_{iv}	Concentration of drug in systemic venous blood
C_{pa}	Concentration of drug in blood from pulmonary artery
CL	Apparent total-body clearance
CL_i	Clearance of organ i
CL_i^{int}	Intrinsic clearance of organ i
CL_y^x	Apparent clearance obtained by D^x/AUC_y^x
D^x	Dose as administered through route x
E_i	Extraction ratio of organ i
F_i	Availability of drug after one passage through organ i
F_{po}	Availability of drug in the venous blood after oral administration
F_s	Availability of drug in the venous blood after administration into the arterial blood
f_o	Fraction of cardiac output which passes through other organs
f_h	Fraction of cardiac output which passes through the liver

f_s	Fraction of cardiac output which passes through all the eliminating organs except lungs
K_i	Partition coefficient of the drug for organ i and blood
Q_i	Blood flow to organ i
V_v	Volume of venous blood
V_a	Volume of arterial blood
V_i	Volume of organ i
X_i	Amount of drug in organ i
$X_T^{0-\infty}$	Total amount of drug eliminated from the body
Superscript x	Route of drug administration: iv, ia, and po
Subscript y	Site of drug measurement: arterial (ia) or venous (iv) blood
Subscript i	Individual organs (lung, p; liver, h; other organs, o) or total body (T)

REFERENCES

1. R. A. Roth and D. A. Wiersma. Role of lung in total body clearance of circulating drugs. *Clin. Pharmacokin.* 4:355–367 (1979).
2. M. Gibaldi and D. Perrier. *Pharmacokinetics,* Marcel Dekker, New York, 1982.
3. M. Rowland and T. N. Tozer. *Clinical Pharmacokinetics, Concepts and Applications,* Lea and Febiger, Philadelphia, 1989.
4. D. P. Vaughan and I. Hope. Application of a recirculatory stochastic pharmacokinetic model: Limitation of compartmental models. *J. Pharmacokin. Biopharm.* 7:207–225 (1979).
5. J. M. Collins and R. L. Dedrick. Contribution of lungs to total body clearance: linear and nonlinear effects. *J. Pharm. Sci.* 71:66–70 (1982).
6. W. L. Chiou. The physiological significance of total body clearance in pharmacokinetic studies. *J. Clin. Hosp. Pharm.* 7:25–30 (1982).
7. J. L. Gabrielsson, P. Johanson, U. Bondesson, and L. K. Paalzow. Analysis of methadone disposition in the pregnant rat by means of a physiological flow model. *J. Pharmacokin. Biopharm.* 13:355–372 (1985).
8. Y. Igari, Y. Sugiyama, Y. Sawada, T. Iga, and M. Hanano. Prediction of diazepam disposition in the rat and man by a physiologically based pharmacokinetic model. *J. Pharmacokin. Biopharm.* 11:577–593 (1983).
9. W. L. Chiou, G. Lam, M. L. Chen, and M. G. Lee. Arterial-venous plasma concentration differences of six drugs in the dog and rabbit after intravenous administration. *Red. Commun. Chem. Pathol. Pharmacol.* 32:27–39 (1981).
10. P. W. Armstrong, J. A. Moffat, and G. S. Marks. Arterial-venous nitroglycerine gradient during intravenous infusion in man. *Circulation* 66:1273–1276 (1982).
11. W. L. Chiou. The phenomenon and rationale of marked dependence of drug concentration on blood sampling sites: Implication in pharmacokinetics, pharmacodynamics, toxicology and therapeutics (part I). *Clin. Pharmacokin.* 17:175–199 (1989).
12. W. L. Chiou. The phenomenon and rationale of marked dependence of drug concentration on blood sampling sites: Implication in pharmacokinetics, pharmacodynamics, toxicology and therapeutics (part II). *Clin. Pharmacokin.* 17:275–290 (1989).
13. M. K. Cassidy and J. B. Houston. In vivo assessment of extrahepatic conjugative metabolism in first pass effects using the model compound phenol. *J. Pharm. Pharmacol.* 32:57–59 (1980).
14. W. L. Chiou. Potential pitfalls in the conventional Pharmacokinetic studies: Effects of the initial mixing of drug in blood and the pulmonary first-pass elimination. *J. Pharmacokin. Biopharm.* 7:527–536 (1979).
15. M. Weiss and W. Forster. Pharmacokinetics of prostaglandins: Prediction of steady-state concentrations during intravenous infusion. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 18:344–347 (1980).