rate of other types of dosage forms. It is therefore recommended that the sampling probes used with automated sampling systems be made as small as possible, and that the horizontal sampling position be carefully maintained halfway between the paddle shaft and the kettle wall.

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Sequential Organ First-Pass Effects: Simple Methods for Constructing Compartmental Pharmacokinetic Models from Physiological Models of Drug Disposition by Several Organs

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Abstract □ The relationships between organ clearances derived from physiological pharmacokinetic models and the first-order rate constants in compartmental pharmacokinetic models are frequently difficult to visualize when drugs are eliminated simultaneously by several organs. Two simple methods for showing these relationships are illustrated in this paper.

Keyphrases □ Pharmacokinetics—construction of compartmental models from physiological models of drug disposition, first-pass effects □ First-pass effects—construction of compartmental pharmacokinetic models from physiological models of drug disposition □ Compartmental models—construction of pharmacokinetic models from physiological models of drug disposition, first-pass effects

Changes in the blood concentrations of drugs after their oral administration are frequently fitted to a pharmacokinetic equation representing a three-compartment model in which it is assumed that all eliminating organs are within the central compartment. In such a model, a first-order rate constant (k_{31}) is frequently used to represent the absorption of a drug from the GI tract into a central compartment and first-order microconstants (k_{12}, k_{21}) are frequently used to represent the passage of the drug between the central and peripheral compartments. The elimination of the drug from the body is represented by a first-order microconstant (k_{10}) emanating solely from the central compartment. This model would be identical to that pictured in Fig. 1 except that k_{13}, k_{20}, and k_{30} would be zero.

Despite the simplicity of this model, it adequately describes the major events in the absorption and disposition of most drugs and, thus, has gained wide acceptance. But it is invalid in many situations, particularly those in which drugs are very rapidly cleared by enzymes in the GI mucosa, liver, and lung (the first-pass organs) and those situations in which the drug passes into the GI tract by reversible diffusion from mucosal blood into the lumen of the GI tract or by biliary excretion. Moreover, the model also fails to describe adequately the pharmacokinetics of metabolites that are rapidly cleared by various organs. In these situations it is necessary to consider physiological models.

Several years ago, Bischoff and Dedrick (1) developed a physiological approach in which Fick's Principle is applied to individual organs. In this approach, each organ comprises three homogeneous compartments: the blood, the interstitial fluid, and an intracellular compartment. Since a differential equation is required to express the rate of change in the amount of drug in these subcompartments of each organ, the number of equations required to describe changes in the disposition of the drug in the body at any given time can be quite large; frequently as many as 15–20 equations are used. It is possible to integrate a set of such equations by means of LaPlace transforms. Unfortunately, the pharmacokinetic constants obtained by integration of the simultaneous equations or from measurements of drug concentrations in blood are virtually impossible to interpret in physiological terms.

The present paper describes a general approach for developing pharmacokinetic models that combine some of the complexities that can occur during rapid simultaneous elimination of drugs by several organs with the simplicity of the linear three-compartment model. The approach is essentially intuitive and, thus, requires very little mathematical ability. It is illustrated by a model in which a drug is rapidly cleared by the GI mucosa, the liver, the lungs, and the kidneys.

THEORY

As in the three-compartment model, it is assumed that after rapid injection into the aorta, a drug is almost instantaneously distributed into a central compartment that includes most of the organs of elimination such as the kidneys, the GI mucosa, the liver, and the lungs. Thus, by the time the arterial concentration of the drug is estimated, the ratios of the intracellular concentrations of the drug in the organs included within the central compartment to the drug concentration in arterial blood have reached constant values. (This is usually estimated indirectly by measuring the drug concentration in systemic venous blood: draining a nonelimination organ such as an arm.) Under these quasi steady-state

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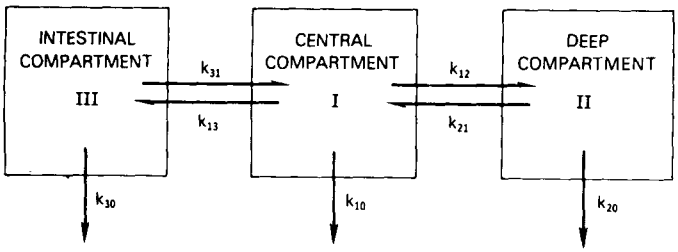

Figure 1—*Three-compartment pharmacokinetic model.*

conditions, virtually all of the drug entering a given organ in the central compartment leaves the organ by the venous blood and by excretion and metabolism; the rate of change in the amount of drug retained by the organ is negligible. When the drug is eliminated from the central compartment by a single organ, the rate of elimination under steady-state conditions may be described by the equivalent terms shown in Table I. In these terms Q_{organ} is the blood flow rate through the organ of elimination, C_{art} is the drug concentration in the arterial blood, and C_{out} is the drug concentration in the systemic blood leaving the organ. The organ availability of the drug (F_{organ}) equals C_{out}/C_{art} for that organ. As will be shown, it is also important to realize that Q_{organ}/C_{art} is the rate, expressed in amount per time, at which the drug enters the organ under steady-state conditions; *i.e.*, rate into organ. Moreover, F_{organ} may also be expressed as the rate out of organ/rate into organ. Thus, the clearance (Cl_{organ}) may be expressed by the equivalent terms shown in Table I.

When a drug is eliminated from the body by several organs, the total clearance from the central compartment is sometimes difficult to visualize. When all of the organs of elimination are perfused solely by arterial blood, the total clearances of elimination from the central compartment is the sum of the clearances of the individual organs. But some organs (notably the liver and the lungs) are perfused by venous blood as well as by arterial blood, and thus, the calculation of the total clearance of elimination from the central compartment depends on whether the drug is eliminated from the body by several organs in sequence. If the drug is eliminated by two or more organs in sequence, the total clearance of elimination from the central compartment contributed by organs is less than the sum of the individual organ clearances as calculated from the equation shown in Table I.

One approach that may be used to derive the equations for multiorgan clearances is to write the differential equations for the organs comprising the central compartment as in the Bischoff-Dedrick approach. The equations may then be set to zero, because the rate of change in the amount of drug present in the organs under the stated steady-state conditions is virtually negligible. The solution of the set of equations, however, is laborious and requires considerable mathematical skill. Moreover, the concept of organ clearances is lost, and the resulting equations are model dependent, in that each organ is assumed to be a well-stirred compartment (2).

For the present paper, two much simpler methods for the derivation of total clearance of elimination from the central compartment have been developed. In both methods a clearance term is defined as the rate of elimination of the drug divided by the concentration of the drug in a reference compartment, namely the systemic arterial blood.

In the first method, the partitioned blood flow method (Method A), the cardiac output is partitioned according to the arterial flow rates through the individual organs in the central compartment. One then visualizes the organs that a given blood supply must pass through before it reenters the systemic arterial circulation. For example, the blood serving the intestinal mucosa must also pass through the liver and the lung before it reenters the aorta (Fig. 2). Thus, in accordance with the rate equation in Table I, the rate of elimination of the drug from mucosal blood (G-1 flow) by the mucosa (G-1) may be written:

Table I—Equivalent Equations for the Rate and Clearance of Elimination of Drugs by Single Organs

(Rate of elimination) organ $= Q_{organ}(C_{art} - C_{out})$
$= Q_{organ}C_{art}[1 - (C_{out}/C_{in})] = Q_{organ}C_{art}(1 - F_{organ})$
= (Rate into organ)$(1 - F_{organ})$
$= Q_{organ}C_{art}E_{organ}$ = (Rate into organ) E_{organ}
$Cl_{organ} = Q_{organ}E_{organ}$
$= Q_{organ}(1 - F_{organ})$
= Rate of elimination by organ/C_{art}
= (Rate into organ) $(1 - F_{organ})/C_{art}$
= (Rate into organ) E_{organ}/C_{art}

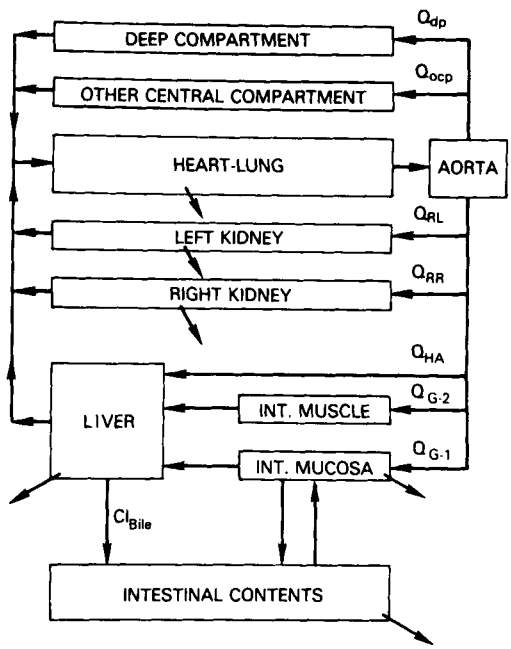

Figure 2—*A physiological pharmacokinetic model.*

rate of elimination from G-1 flow by G-1
$$= (\text{rate into } G\text{-}1 \textit{ via } G\text{-}1 \text{ flow})(1 - F_{G\text{-}1}) = C_{art}\,Q_{G\text{-}1}\,(1 - F_{G\text{-}1}) \quad \text{(Eq. 1)}$$

in which $F_{G\text{-}1}$ is the ratio of the rates at which the drug in amount per minute enters and leaves the capillary bed serving the intestinal mucosa.

The rate of elimination of the drug from the mucosal blood by the liver (H) depends on the concentration of the drug in blood leaving the mucosa and only indirectly on the concentration of the drug in the arteries. Thus:

rate of elimination from G-1 flow by H
$$= (\text{rate into } H \textit{ via } G\text{-}1 \text{ flow})(1 - F_H) = C_{art}Q_{G\text{-}1}F_{G\text{-}1}(1 - F_H) \quad \text{(Eq. 2)}$$

In Eq. 2, F_H is the ratio of the rates at which the drug leaves the liver by the hepatic vein (HV) and enters the liver by both the portal vein and the hepatic artery:

$$F_H = \frac{(Q_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})C_{HV}}{(Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})C_{art}} \quad \text{(Eq. 3)}$$

In Eq. 3 $Q_{G\text{-}2}$ represents the portal venous flow of the blood that does not perfuse the mucosa. In rats this has been estimated to be ~75% of the total intestinal blood flow (3). In addition to intestinal blood, it also includes the gastric and splenic blood.

By the same reasoning, the rate of elimination of the drug in mucosal blood by the lung will depend on the hypothetical concentration that would have been present in the hepatic venous blood if the mucosal blood perfusing the mucosa were the only blood perfusing the liver. Thus:

rate of elimination from G-1 flow by L
$$= (\text{rate into } L \textit{ via } G\text{-}1 \text{ flow})\,(1 - F_L) = C_{art}Q_{G\text{-}1}F_{G\text{-}1}F_H\,(1 - F_L) \quad \text{(Eq. 4)}$$

In Eq. 4, F_L is the rate at which the drug leaves the lung by the pulmonary vein divided by the rate at which it enters the lung by the pulmonary artery. The total rate of elimination of the drug from the mucosal blood, $\text{rate}_{(G\text{-}1\text{ flow})}$ is the sum of the expressions given by Eqs. 1, 2, and 4:

$$\text{rate}_{(G\text{-}1\text{ flow})} = C_{art}Q_{G\text{-}1}(1 - F_{G\text{-}1}) + C_{art}Q_{G\text{-}1}F_{G\text{-}1}\,(1 - F_H) + C_{art}Q_{G\text{-}1}F_{G\text{-}1}F_H\,(1 - F_L) \quad \text{(Eq. 5)}$$

which on expansion and collection of terms becomes:

$$\text{rate}_{(G\text{-}1\text{ flow})} = C_{art}Q_{G\text{-}1}(1 - F_{G\text{-}1}F_HF_L) \quad \text{(Eq. 6)}$$

The mucosal blood clearance of the drug thus becomes:

$$Cl_{(G\text{-}1\text{ flow})} = \frac{\text{rate}_{(G\text{-}1\text{ flow})}}{C_{art}} = Q_{G\text{-}1}(1 - F_{G\text{-}1}F_HF_L) \quad \text{(Eq. 7)}$$

Table II—Poly Input Organ Clearances

Intestinal Mucosa
- metabolic: $Cl_{G\text{-}1(met)} = Q_{G\text{-}1}E_{G\text{-}1}f_{G\text{-}1(met)}$
- diffusion: $Cl_{G\text{-}1(dif)} = Q_{G\text{-}1}E_{G\text{-}1}f_{G\text{-}1(dif)}$
- since, $f_{G\text{-}1(met)} + f_{G\text{-}1(dif)} = 1$,
- total: $Cl_{G\text{-}1} = Q_{G\text{-}1}E_{G\text{-}1}$

Liver
- metabolic: $Cl_{pinH(met)} = (Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})E_Hf_{H(met)}$
- biliary: $Cl_{pinH(biliary)} = (Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})E_Hf_{H(biliary)}$
- since, $f_{H(met)} + f_{H(biliary)} = 1$,
- total: $Cl_{pinH} = (Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})E_H$

Kidney
- left kidney: $Cl_{RL} = Q_{R1}E_{RR}$
- right kidney: $Cl_{RR} = Q_{RR}E_{RR}$
- total: $Cl_R = Q_{RL}E_{RL} + Q_{RR}E_{RR}$

Deep Compartment
- total: $Cl_{dp} = Q_{dp}E_{dp}$

Lung
- metabolism: $Cl_{pinL(met)} = [Q_{G\text{-}1}F_{G\text{-}1}F_H + (Q_{G\text{-}2} + Q_{HA})F_H + Q_{RL}F_{RL} + Q_{RR}F_{RR} + Q_{ocp} + Q_{dp}F_{dp}]E_Lf_{L(met)}$
- diffusion: $Cl_{pinL(dif)} = [Q_{G\text{-}1}F_{G\text{-}1}F_H + (Q_{G\text{-}2} + Q_{HA})F_H + Q_{RL}F_{RL} + Q_{RR}F_{RR} + Q_{ocp} + Q_{dp}F_{dp}]E_Lf_{L(dif)}$
- total: $Cl_{pinL} = [Q_{G\text{-}1}F_{G\text{-}1}F_H + (Q_{G\text{-}2} + Q_{HA})F_H + Q_{RL}F_{RL} + Q_{RR}F_{RR} + Q_{ocp} + Q_{dp}F_{dp}]E_L$

The partitioned blood flow clearance of drug from blood passing through several organs, thus, may be expressed as the partitioned blood flow rate times one minus the mathematical product of the drug availabilities of the organs through which the blood passes.

By similar reasoning, the clearance of the drug from the partitioned blood flow perfusing other organs may be written:

hepatic arterial blood clearance and G-2 arterial blood clearance

$$Cl_{(H\ flow)} + Cl_{(G\text{-}2\ flow)} = (Q_H + Q_{G\text{-}2})(1 - F_HF_L) \quad \text{(Eq. 8)}$$

left (RL) and right (RR) renal arterial blood clearances

$$Cl_{(RL\ flow)} = Q_{RL}(1 - F_{RL}F_L) \quad \text{(Eq. 9)}$$

$$Cl_{(RR\ flow)} = Q_{RR}(1 - F_{RR}F_L) \quad \text{(Eq. 10)}$$

Clearance from blood perfusing the nonelimination organs in the central compartment ($Cl_{ocp\ flow}$) and the deep compartment ($Cl_{dp\ flow}$) is:

$$Cl_{(ocp\ flow)} + Cl_{(dp\ flow)}F_{dp} = (Q_{ocp} + Q_{dp}F_{dp})(1 - F_L) \quad \text{(Eq. 11)}$$

In which F_{dp} is the fraction of the drug in blood perfusing the deep compartment tissues that does not enter the deep compartment, *i.e.*, $(1 - F_{dp})$ equals the rate of diffusion of the drug into the deep compartment divided by $Q_{dp}C_{art}$.

The total clearance of elimination of the drug from the central compartment (Cl_{10}) is, thus, the sum of the individual partitioned blood flow clearances:

$$Cl_{10} = Q_{G\text{-}1}(1 - F_{G\text{-}1}F_HF_L) + (Q_H + Q_{G\text{-}2})(1 - F_HF_L) + Q_{RL}(1 - F_{RL}F_L) + Q_{RR}(1 - F_{RR}F_L) + Q_{ocp}(1 - F_L) + Q_{dp}F_{dp}(1 - F_L) \quad \text{(Eq. 12)}$$

The rate constant of elimination from the central compartment is obtained from the relationship, $k_{10} = Cl_{10}/V_c$ in which V_c is the apparent volume of the central compartment.

Although the partitioned blood flow method (Method A) provides a simple, concise way of expressing Cl_{10}, it will fail when significant amounts of the drug are reabsorbed after the drug enters the lumen of the intestine either by biliary excretion or by passive diffusion from the blood across GI membranes. Method A also provides equations that are difficult to interpret when the various F_{organ} values approach 1.0 or when the investigator wishes to visualize the relative importance of the individual organs in clearing the drug from the body.

Method B was developed to overcome these difficulties. For this method, a general concept of clearance was envisioned, the poly input organ clearance or $Cl_{pin\ organ}$. In this concept, the rate of elimination of the drug by an organ is the difference in the rates at which the drug enters and leaves the organ *via* the blood under steady-state conditions. Thus, $Cl_{pin\ organ}$ may be expressed as:

$$Cl_{pin\ organ} = (\text{total rate in} - \text{total rate out})/C_{art}$$
$$= \text{total rate in}\ (1 - \text{total rate out/total rate in})/C_{art} \quad \text{(Eq. 13)}$$

The term (total rate out/total rate in), however, is the organ availability, F_{organ}. Thus:

$$Cl_{pin\ organ} = \frac{(\Sigma\ Q_iC_i)(1 - F_{organ})}{C_{art}} \quad \text{(Eq. 14)}$$

In turn, $1 - F_{organ}$ may be expressed as the extraction ratio of the drug by the organ, E_{organ}. Thus:

$$Cl_{pin\ organ} = \frac{(\Sigma\ Q_iC_i)E_{organ}}{C_{art}} \quad \text{(Eq. 15)}$$

However the C_i values may be expressed in terms of steady-state arterial concentration of the drug and the mathematical product (Π) of the individual availabilities of the organs through which the blood passes before it reaches the organ under consideration, *i.e.*, $\Pi\ F_{preorgan}$, where $F_{preorgan}$ is the F_{organ} of a given preorgan. Thus:

$$Cl_{pin\ organ} = \frac{C_{art}(\Sigma Q_i \Pi F_{preorgan})E_{organ}}{C_{art}} = (\Sigma Q_i \Pi F_{preorgan})E_{organ} \quad \text{(Eq. 16)}$$

From this general equation, equations may be written (Table II) for the poly input organ clearances in a system in which a drug is eliminated by the intestinal mucosa (both metabolically and by passive diffusion into the intestinal lumen), the liver (both metabolically and by biliary excretion), the lungs (both metabolically and by exhalation), and the kidneys (both metabolically and by excretion) (Fig. 2).

The model also includes an effective shunt in which it is recognized that only ~25% of the intestinal blood perfuses the intestinal mucosa (3); thus, $Q_{G\text{-}1}$ represents the intestinal blood that perfuses the mucosa and $Q_{G\text{-}2}$ represents the portion of the portal blood that has bypassed the mucosa. The equations in Table II also indicate how the poly input organ clearance by any given organ may be distributed between elimination by excretion or metabolism. The metabolic clearance by an organ may be expressed as a fraction, $f_{organ\ (met)}$, of the poly input organ total clearance. For example, the metabolic clearance by the mucosa is $Cl_{G\text{-}1\ (met)} = Cl_{G\text{-}1}f_{G\text{-}1\ (met)}$, in which $f_{G\text{-}1\ (met)}$ is the fraction of the total organ clearance due to metabolism. Similarly, the diffusional clearance may be written as $Cl_{G\text{-}1\ (dif)} = Cl_{G\text{-}1}f_{G\text{-}1\ (dif)}$, in which $f_{G\text{-}1\ (dif)}$ is the fraction of the total mucosal clearance due to diffusion. Thus, $f_{G\text{-}1\ (met)} + f_{G\text{-}1\ (dif)} = 1.0$. The equations may then be expanded to those shown in Table II.

The next step in the development of the compartmental model is to distribute the sequential organ clearances among the rate constants that emanate from the central pool. By *definition, any clearance by which* the drug irreversibly leaves the central compartment is a part of Cl_{10}. Thus, the investigator must decide whether a drug that leaves the central compartment by biliary excretion or passive diffusion across the intestinal mucosa into the intestinal lumen will be reabsorbed from the intestines. If the compound is not reabsorbed the clearances of these processes should be included in Cl_{10}. But if the drug is reabsorbed, the sum of the clearances of these processes equals Cl_{13}, the clearance for the passage of the drug into the GI tract. The investigator also must decide whether the drug that leaves the body by exhalation is reabsorbed. If the animal is in the open air, which contains negligible amounts of the drug, then the effective lung clearance by exhalation of the drug is part of Cl_{10}. But if the animal is placed into a closed chamber in which the drug vapor is at a significant concentration, the chamber becomes a pharmacokinetic compartment, which may be either closed or open. In this situation, the effective lung clearance by exhalation of the drug is not included in Cl_{10}, but is represented by a separate clearance. For the purpose of the present discussion, however, we will assume that the drug is reabsorbed from the GI tract and the animal is in the open air. With these assumptions, the components of Cl_{10}, Cl_{12}, and Cl_{13} are those shown in Table III.

The other microclearances for the three-compartment model may also be written, although some of them may not be immediately obvious. For example, the microclearance representing the passage of the drug from the deep compartment to the central compartment, Cl_{21}, may be visualized as a diffusional clearance, $Cl_{dp(dif)}$, but after leaving the deep compartment the drug must first pass through the lungs before it reenters the arterial circulation and, thus, Cl_{21} equals $Cl_{dp(dif)}F_L$. The drug that is removed by the lungs as it passes from the deep compartment into the arterial blood must also be accounted for. Thus, the microclearance, Cl_{20}, that represents an irreversible removal of the drug from the deep com-

Table III—Relationship between Various Microconstants of the Three-Compartment Model and the Poly Input Organ Clearance

Micro Clearance	Volume Times Microconstants	Components of Micro Clearances	Expanded Version of Micro Clearances
	Central Compartment to Gastrointestinal Tract		
Cl_{13}	V_1k_{13}	$Cl_{G\text{-}1(\text{dif})} + Cl_{\text{pin}H(\text{biliary})}$	$Q_{G\text{-}1}E_{G\text{-}1}f_{G\text{-}1(\text{dif})} + (Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})E_Hf_{H(\text{biliary})}$
	Central Compartment to Deep Compartment		
Cl_{12}	V_1k_{12}	Cl_{dp}	$Q_{\text{dp}}E_{\text{dp}}$
	Central Compartment Irreversible Elimination		
Cl_{10}	V_1k_{10}	$Cl_{G\text{-}1(\text{met})} + Cl_{\text{pin}H(\text{met})} + Cl_{RL} + Cl_{RR} + Cl_{\text{pin}L}$	$Q_{G\text{-}1}E_{G\text{-}1}f_{G\text{-}1(\text{met})}$ $(Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})E_Hf_{H(\text{met})}$ $Q_{RL}E_{RL} + Q_{RR}E_{RR}$ $[(Q_{G\text{-}1}F_{G\text{-}1} + Q_{G\text{-}2} + Q_{HA})F_H + Q_{RL}F_{RL}$ $+ Q_{RR}F_{RR} + Q_{\text{ocp}} + Q_{\text{dp}}F_{\text{dp}}]E_L$
	Deep Compartment to Central Compartment		
Cl_{21}	V_2k_{21}	$Cl_{\text{dp}(\text{dif})}F_L$	$Q_{\text{dp}}E_{\text{dp}}F_L$
	Deep Compartment Irreversible Elimination		
Cl_{20}	V_2k_{20}	$Cl_{\text{dp}(\text{met})} + Cl_{\text{dp}(\text{dif})}E_L$	$Cl_{\text{dp}(\text{met})} + Q_{\text{dp}}F_{\text{dp}}E_L$
	Gastrointestinal Tract to Central Compartment		
Cl_{31}	V_3k_{31}	—	$Cl_{g(\text{dif})}F_{G\text{-}1}F_HF_L$
	Gastrointestinal Tract Irreversible Elimination		
Cl_{30}	V_3k_{30}	—	$Cl_{g(\text{met})} + Cl_{g(\text{dif})}[E_{G\text{-}1}f_{G\text{-}1(\text{met})} + F_{G\text{-}1}E_Hf_{H(\text{met})} + F_{G\text{-}1}F_HE_L]$

partment will include not only the metabolism of the drug that takes place in the deep compartment, $Cl_{\text{dp}(\text{met})}$, but also the drug that is eliminated by the lungs as the drug passes from the deep compartment to the arterial circulation, $Cl_{\text{dp}(\text{dif})}E_L$. For this reason, a three-compartment model in which a drug is rapidly eliminated by the lungs theoretically should always include both Cl_{10} and Cl_{20}.

By a similar line of reasoning, a drug absorbed from the intestinal tract passes through the intestinal mucosa, the liver, and the lungs before it enters the arterial circulation; therefore, Cl_{31} must include not only the clearance of diffusion across the intestinal wall, $Cl_{g(\text{dif})}$, but also the availability of the drug as it passes through the various organs before it reaches the arterial circulation. Thus, Cl_{31} equals $Cl_{g(\text{dif})}F_{G\text{-}1}F_HF_L$. Moreover, Cl_{30} must include not only the drug that is eliminated in the feces or metabolized by intestinal flora, but also the metabolic clearance of the drug as it passes through the intestinal mucosa, the liver, and the lungs. Therefore, as shown in Table III:

$$Cl_{30} = Cl_{g(\text{met})} + Cl_{g(\text{dif})}[E_{G\text{-}1}f_{G\text{-}1(\text{met})} + F_{G\text{-}1}E_Hf_{H(\text{met})} + F_{G\text{-}1}F_HE_Lf_{L(\text{met})}] \quad \text{(Eq. 17)}$$

Thus, any compartmental model in which a drug is rapidly eliminated by the intestinal mucosa, the liver, or the lungs should theoretically always include Cl_{30} as well as Cl_{10}.

Once the microconstants have been written they may be incorporated into the equations derived for the appropriate compartmental models. The equations for the blood concentrations of a drug in the three-compartment model shown in Fig. 1 are given in the *Appendix*.

DISCUSSION

It is interesting that the intestinal mucosa and the liver are simultaneously a part of the intestinal compartment and the central compartment; and that the lung is simultaneously a part of the intestinal compartment, the central compartment, and the deep compartment. What the equations illustrate, however, is the artificiality of compartmental models when applied to complex physiological systems. Therefore, it is evident that the visualization of the body as a set of compartments is fraught with difficulties, not only because the volume of the various compartments is difficult to determine, but also because the clearances by which the drug is transferred from one compartment to another and eliminated from the body are difficult to visualize.

Both methods illustrated in this paper are based solely on the conservation of mass and the anatomy and function of the cardiovascular system. The investigator is at liberty to choose any model he or she wishes, to illustrate the effects of altering blood flow rates or reversible binding of drugs to blood components on the availabilities (F values) and extraction ratios (E values). Indeed, he or she may wish to choose different models for different organs. For example, the investigator may wish to use the well-stirred model (4) [in which $F = Q/(Q + f_B\,Cl^u_{\text{int}})$] and $E = f_B\,Cl^u_{\text{int}}/(Q + f_B\,Cl^u_{\text{int}})$ for the liver and the parallel tube model [in which $F = (\exp - f_B\,Cl^u_{\text{int}}/Q)$] and $E = 1 - [\exp - (f_B\,Cl^u_{\text{int}}/Q)]$ for the kidney (5), where Cl^u_{int} represents the free intrinsic clearance of the organ and f_B is the unbound fraction of drug in the blood.

With the principles for the partitioned blood clearances and the poly input organ clearances in mind, the investigator may construct other models. For example, a separate compartment to represent the gall bladder or blood shunts such as the portal vena cava may be introduced. Alternatively, the investigator may wish to simplify the model by setting the F values equal to one and the E values equal to zero when such simplifications seem warranted. Thus, the methods are not only simple, but also versatile.

With measurements of drug concentrations in blood alone, it is not possible to differentiate between the model described in Fig. 1 from the three-compartment model described by Gibaldi and Perrier (6) in which the drug is eliminated solely from a central compartment. The main purpose of the model described here is to provide the investigator with insights by which he or she may infer possible meanings of the individual microconstants of compartmental models and how changes in them might affect the pharmacokinetics of drugs. The use of these simplified physiological approaches should help investigators to understand the relationship between poly input first-pass effects in physiological systems and the pharmacokinetics as predicted by compartmental models. They also should clarify some of the problems that can arise in the interpretation of such models.

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APPENDIX

The solution of the three-compartment model shown in Fig. 1 by La-Place transforms gives the following equations for the drug concentration in blood:

Oral Administration:

$$C = \frac{\text{dose}}{V_1}\left[\frac{k_{31}(k_{20}+k_{21}-\gamma)}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma t} + \frac{k_{31}(k_{20}+k_{21}-\alpha)}{(\gamma-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{k_{31}(k_{20}+k_{21}-\gamma)}{(\gamma-\beta)(\alpha-\beta)}e^{-\beta t}\right]$$

Intravenous administration:

$$C = \frac{\text{dose } F_L}{V_1}\left[\frac{(k_{30}+k_{31}-\gamma)(k_{20}+k_{21}-\gamma)}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma t} + \frac{(k_{30}+k_{31}-\alpha)(k_{20}+k_{21}-\alpha)}{(\gamma-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{(k_{30}+k_{31}-\beta)(k_{20}+k_{21}-\beta)}{(\gamma-\beta)(\alpha-\beta)}e^{-\beta t}\right]$$

In these equations, γ, α, and β are the roots[1] of the transformed equation

$$0 = (s+\gamma)(s+\alpha)(s+\beta)$$
$$= (s+k_{30}+k_{31})(s+k_{10}+k_{12}+k_{13})(s+k_{20}+k_{21}) - k_{12}k_{21}(s+k_{30}+k_{31}) - k_{13}k_{31}(s+k_{20}+k_{21})$$

[1] When hypothetical values of the microconstants based on their physiological components are substituted into the transformed equation, the roots may be determined by iteration of synthetic division. Decreasing values of s (0 to $-\infty$) are iterated with a programmable calculator until all three values of s that satisfy the equation, $F(s) = 0$, are found. Unfortunately, the presence of k_{20} and k_{30} in the model precludes the calculation of the microconstants from actual data. In the three-compartment model of Gibaldi and Perrier (6), the elimination of a drug is represented solely by k_{10}. Thus, their method would overestimate the values of k_{31}, k_{21}, and k_{10} and would provide no adequate way of estimating k_{20} or k_{30}. However, simulations are still possible by substituting reasonable numerical values of the various microconstants into the equation.

Biological Effects of Nonalkaloid-Containing Fractions of *Erythroxylon coca*

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Abstract □ Water soluble nonalkaloid fractions of *Erythroxylon coca* were screened in mice for their effects on oxygen utilization and central nervous system (CNS) activity. The fractions were screened in dogs for cardiovascular, blood glucose, and respiratory changes. No CNS effects were demonstrated in mice; however, there was a reduction in the oxygen utilization rate. Intravenous administration of the extract to dogs produced hyperglycemia, a reduction in heart rate, and a decrease in blood pressure. No substantial change in the respiratory rate and tidal or minute volumes were observed.

Keyphrases □ *Erythroxylon coca*—biological effects of nonalkaloid-containing fractions □ Nonalkaloids—fractions in *Erythroxylon coca*, effects □ Oxygen utilization rate—effects of *Erythroxylon coca* on oxygen utilization rate, mice, dogs □ CNS activity—effect of nonalkaloid-containing fractions of *Erythroxylon coca*

The plant *Erythroxylon coca* has been used in the cultures of many Latin American societies for medicinal, nutritional, and religious purposes for centuries (1). The pharmacological and possible psychological effects of coca have made its use by natives commonplace. It is reported to aid them in performing strenuous work and in coping with the harsh mountain environment. While cocaine is not the only biologically active compound in the coca plant, it is the principal alkaloid and the most studied of the active compounds. Alkaloid free fractions of the coca leaf extracts recently have been shown to reduce food consumption but do not show alterations in locomotor activity (2). Cocaine, at doses ranging from 3.45 to 27.6 mg/kg, produced dose-related increases in locomotor activity and decreases in food consumption (3).

It has been reported that chewing coca leaves causes the Latin American native to be more resistant to cold and fatigue and decreases the need for food and sleep (4, 5). Most of these effects have been considered to be related to cocaine, since cocaine has been shown to increase the heart rate and blood pressure and to elevate blood glucose levels (6).

The present study was undertaken to determine whether cocaine-free extracts would produce changes in oxygen utilization, blood glucose levels, respiration, and/or cardiovascular effects that could be related to the alleged enhancement of physical stamina in humans.

EXPERIMENTAL

Test Compounds—Coca leaves (*Erythroxylon coca*)[1] were obtained from Tingo Maria, Peru, and extracted as described previously (2). Briefly, the crude ethanol extract of coca leaves was partitioned between water (fraction A) and chloroform (fraction B). Fraction A was made cocaine free by dissolving in ammonium hydroxide solution and extracting 10 times with chloroform. Each chloroform fraction was subjected to GLC analysis. These fractions each showed the absence of cocaine peaks. Fraction A was further partitioned between butanol and water yielding two fractions: fraction C, the butanol phase; fraction D, the water phase. The fractions were dried on a rotary evaporator at 40°.

All test solutions were prepared in distilled water from dried fractions immediately prior to testing.

Test Animals—The mice were male ICR Swiss, weighing 26–30 g[2]. They were housed in shoe box caging on pelleted corncobs[3] with food[4] and water freely available. Food was withheld overnight prior to testing. The mice were maintained in an environment of 21 ± 1° and a 12 hr light–dark cycle.

[1] The plant material was obtained through Mr. Ing Alberto Trelles Barnett, Impresa Nacionale de la Coca, Lima, Peru, and through the United States Department of Justice and the United States State Department. It was identified as *Erythroxylon coca* by Dr. M. W. Quimby, Department of Pharmacognosy. Voucher specimens are stored in the drug plant herbarium at the School of Pharmacy, University of Mississippi, University, MS 38677.

[2] Harlan Industries, Cumberland, Ind.

[3] San-i-cel, Paxton Processing, Paxton, Ill.

[4] Purina Laboratory Chow 5001, Purina Mills, St. Louis, Mo.

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