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Contribution of Lungs to Total Body Clearance: Linear and Nonlinear Effects

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Abstract □ The contribution of the lungs to the total body clearance of drugs is examined in a framework that emphasizes their anatomical position. For intravenous administration, the lung is the only organ other than blood that can account for a total body clearance in excess of the cardiac output. Systemic arterial drug concentration and tissue drug exposure are inversely proportional to total body clearance. Although the role of the lung has been overshadowed by that of the liver, several examples are presented to demonstrate that a relatively small amount of pulmonary activity can produce a large reduction in systemic arterial drug concentration. For oral administration, first-pass elimination by the liver and lungs in series results in a synergistic increase in total body clearance. Nonlinear effects caused by saturation of elimination pathways are also examined. Increased emphasis on experimental investigation of the pulmonary contribution is warranted, especially for drugs with high apparent clearance.

Keyphrases □ Lungs—role in total body clearance, linear and nonlinear effects □ Pharmacokinetics—role of lungs in total body clearance, linear and nonlinear effects □ Pulmonary metabolism—role in total body clearance, linear and nonlinear effects

Application of the techniques used to study hepatic drug metabolism to the lung has led to a growing literature on pulmonary metabolism. Although smaller in weight than the liver (600 *versus* 1500 g for humans), the processing of the entire cardiac output (*versus* 25% for the liver) places the lungs in a unique position for drug metabolism.

This report describes the contribution of the lungs to drug metabolism, including interaction with other drug-eliminating organs. Both saturating and nonsaturating conditions were examined.

BACKGROUND

Of the three types of clearance mechanisms (metabolism, excretion, and irreversible binding), this report concentrates on metabolic clearance. Transport, including excretion, of volatile substances is a primary function of the lungs; however, this topic was previously detailed (1). Uptake and/or binding of substances by the lung was documented by Junod (2). He suggested that the lungs can function as a capacitor that dampens out large variations in plasma concentration by rapid uptake and slow release processes. While such a role could have major importance for the pharmacodynamics of drug effect, reversible uptake or binding makes no net contribution to apparent clearance. Only irreversible binding decreases the total amount of drug delivered to the systemic circulation.

The demonstration of drug metabolism at the cellular (3) and subcellular level (4, 5) was a first step in the stimulation of more interest in pulmonary metabolism. Although some metabolic activity was shown in subcellular preparations from the lungs, recent work (6) raised the possibility that pulmonary activity has been substantially underestimated due to undetermined methodological factors. The isolated perfused lung preparation was shown to possess 10 times more drug clearance capability than was projected on the basis of experiments using subcellular preparations.

The isolated perfused lung has had a major role in demonstrating the importance of pulmonary metabolism. An earlier report (7) detailed the capability of this preparation to extract certain endogenous substances, especially the prostaglandins (8), serotonin (9), and other hormones. Metabolic clearance by the isolated perfused lung has now been demonstrated for many exogenous substances including drugs such as mescaline (10), isoproterenol hydrochloride (11), and the tetrahydrocannabinols (12) and chemicals such as *N*-methylaniline (13), aldrin (14), and trichloroethylene (15).

Direct comparisons of lung and liver elimination capacity were made by Roth and coworkers for three substances. In all cases, the effect of blood flow limitation increased the relative role of the lungs *versus* the liver when organ clearance was compared with organ enzyme capacity. Using literature values (16, 17) for benzpyrene in rats with induced enzymes, Roth and Wiersma (18) calculated nearly equal organ clearances for the liver and lungs, despite the fact that the liver contained 64 times more total enzyme capacity than the lungs. Similar calculations were reported (10) for data on mescaline metabolism in homogenates of rabbit lungs and liver. Approximately equal organ clearances were predicted, despite five times more enzyme capacity in the liver. For serotonin, Wiersma and Roth (6) found 17 times as much activity in the liver as in the lungs and predicted five times more clearance in the liver than the lungs. Their predictions for the perfused liver agreed well with their experimental results, but they underpredicted perfused lung clearance by a factor of 10. This discrepancy may be attributed to either suboptimal lung homogenate experiments or strong binding of serotonin by lung tissue.

The demonstration of *in vivo* pulmonary metabolism fully established the key role of the lungs in the overall process of drug elimination from the body. Two studies (19, 20) demonstrated a pulmonary extraction for phenol of ~60% in the rat by comparing the area under the plasma concentration–time curve following intravenous and intra-aortic administration.

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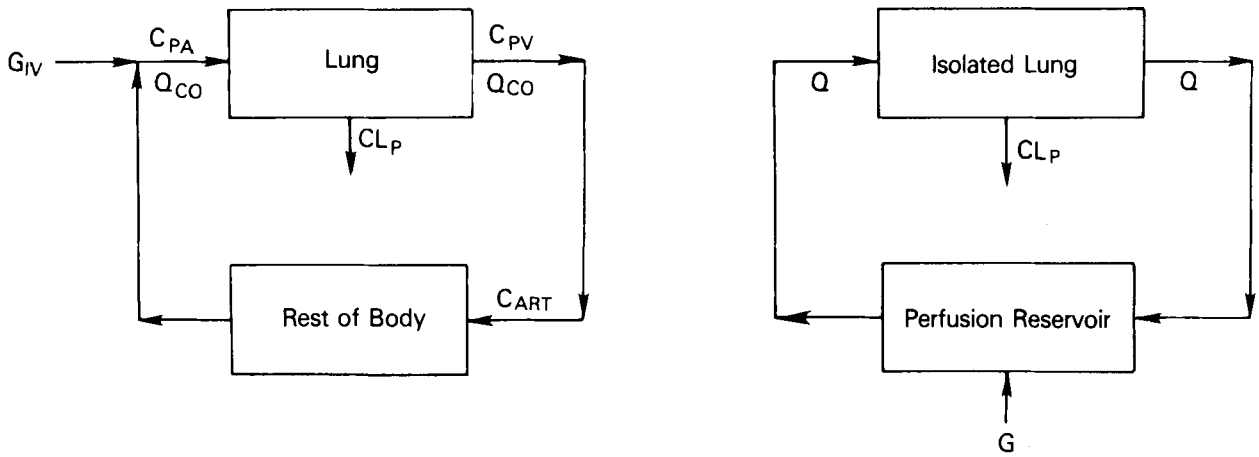


Scheme I—Pulmonary clearance in vivo *(left) and in isolated perfused lung (right).*

Pulmonary clearance should be examined for drugs that exhibit an apparent clearance in excess of liver blood flow. The lungs and blood are the only organs capable of generating an apparent clearance greater than the cardiac output. Elsewhere, a major role was suggested for pulmonary clearance of fluorouracil (21) and thymidine on the basis of high apparent clearance (5 and 25 liters/min, respectively) and the apparent lack of substantial clearance by the blood; however, direct confirmation of the lung's role has not been made. An apparent clearance of 14 liters/min for nitroglycerin was reported (20).

When indicated for patient care, placement of a pulmonary artery catheter in combination with any peripheral arterial drug measurement effectively isolates the lungs *in vivo* for determination of pulmonary extraction. The high apparent clearance of lorcainide, 1.7 liters/min, suggests a possible pulmonary role, but Jahnchen *et al.* (23) was unable to measure any concentration differences in samples obtained from catheters in the pulmonary artery and the aorta.

Kates and Leier (24) determined an apparent clearance of 4.4 liters/min for dobutamine based on mixed venous blood obtained *via* a pulmonary artery catheter as the reference concentration. Unfortunately, no peripheral measurements were reported. With more widespread appreciation of the potential role for pulmonary metabolism, especially in cases in which apparent clearance exceeds liver blood flow, it is anticipated that more investigators will directly determine pulmonary clearance. However, the clearance contribution of the lung *in vivo* will be difficult to determine for drugs with an apparent clearance of ≤500 ml/min. If the apparent clearance is 500 ml/min and only the lung eliminates the drug, pulmonary extraction is ~10%, which may be difficult to measure. On the other hand, if the liver were the exclusive organ of elimination, an easily measured difference of ~30–50% would be expected.

KINETIC ANALYSIS

The basic equations needed for kinetic analysis of pulmonary clearance are presented. Most examples in this section can be conceptualized in terms of a steady-state analysis, in which the rate of drug elimination equals a constant rate of drug input to the body. Variables are defined in the *Appendix*.

Exclusive Pulmonary Clearance–Scheme I (left) illustrates the role of the lung *in vivo* for the case in which the lungs eliminate a drug administered by intravenous infusion. Apparent clearance is G_{iv}/C_{art} or G_{iv}/C_{pv} (21):

$$Cl_{app} = Q_{co}E_p/(1 - E_p) \quad \text{(Eq. 1)}$$

Equation 1 illustrates a key principle of pulmonary elimination, namely that the apparent clearance will exceed organ blood flow and cardiac output whenever E_p is greater than 50%. This result is a direct consequence of first-pass elimination since only $(1 - E_p)$ of the delivered dose is actually available to systemic tissues (*i.e.*, tissues that obtain their drug supply *via* the arterial system).

Clearance by the perfused lung (Scheme I, right) is usually calculated from the decline in concentration observed in samples taken from the reservoir. When appropriately calculated, this method yields identical results to those obtained when steady state is achieved during single-pass operation and clearance is calculated from pulmonary extraction:

$$Cl_{organ} = Q_{co}E_p \quad \text{(Eq. 2)}$$

This quantity is always less than the clearance suggested by Eq. 1 for *in vivo* elimination. The key difference is that organ clearance is referred to reservoir concentration, which is equivalent to C_{PA}, while *in vivo* clearance is referred to C_{PV} (or C_{art}). To compare perfused lung experiments with the *in vivo* situation, E_p should be measured (or calculated as $E_p = Cl_{organ}/Q_{co}$) and used to evaluate Eq. 1. Perfused lung experiments are often operated at flow rates below cardiac output, which requires correction of the observed pulmonary extraction before substitution into Eq. 1.

Pulmonary extraction may be expressed in terms of intrinsic pulmonary clearance, Cl_p, and blood flow:

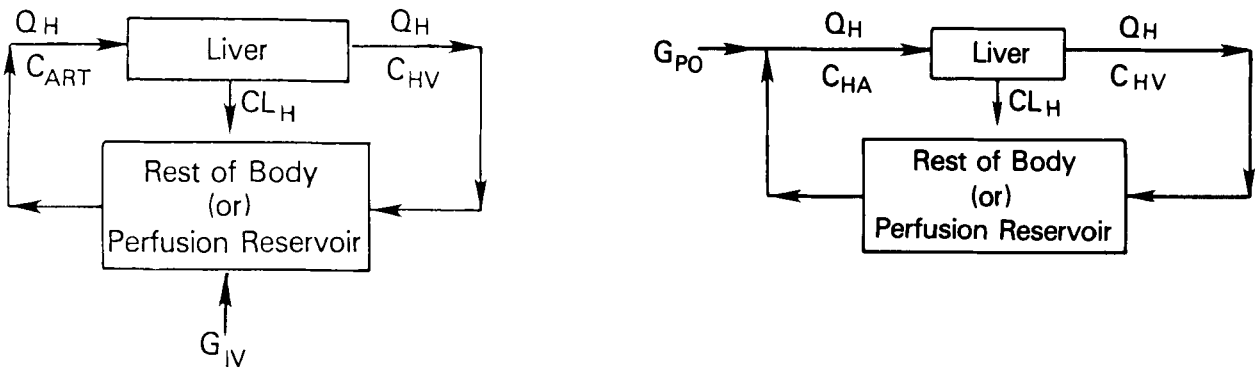
$$E_p = Cl_p/(Cl_p + Q_{co}) \quad \text{(Eq. 3)}$$

It will be assumed that the clearance process follows Michaelis–Menten kinetics:

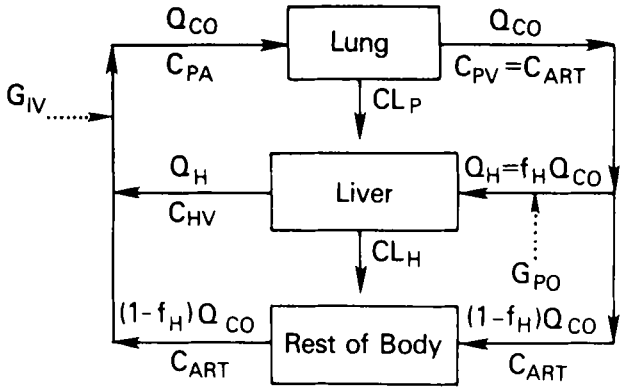
$$Cl_p = V_{max,p}/(K_M + C_{PV}) \quad \text{(Eq. 4)}$$

Substitution of Cl_p from Eq. 4 into Eq. 3 yields:

$$E_p = V_{max,p}/(Q_{co}K_M + Q_{co}C_{PV} + V_{max,p}) \quad \text{(Eq. 5)}$$



Scheme II—Hepatic clearance for in vivo *intravenous infusion or in an isolated perfusion circuit (left) and for oral (or portal vein or hepatic artery) infusion (right). For simplicity, the hepatic artery and portal vein are combined into a single input.*



Scheme III—Simultaneous pulmonary and hepatic clearance. For simplicity, the hepatic artery and portal vein are combined into a single input.

If Eqs. 1 and 5 are combined and simplified:

$$Cl_{app} = V_{max,p}/(K_M + C_{PV}) = Cl_p \qquad \text{(Eq. 6)}$$

Equation 6 shows that the apparent clearance of the lungs (calculated on the basis of peripheral arterial blood concentration) during intravenous infusion is equal to intrinsic clearance.

Exclusive Hepatic Clearance—Scheme II (left) depicts clearance by the liver during *in vivo* intravenous infusion or in an isolated perfusion circuit. Apparent clearance for the liver is based on a reference concentration in arterial blood (or reservoir blood), while the elimination mechanisms operate at the liver concentration, which may be approximated by C_{HV}. Therefore, flow limitation is expressed as:

$$Cl_{app} = Q_H E_H = Q_H Cl_H/(Q_H + Cl_H)$$
$$= Q_H V_{max,H}/(Q_H K_M + Q_H C_{HV} + V_{max,H}) \qquad \text{(Eq. 7)}$$

The role of the liver following oral administration or hepatic artery or portal vein infusion is analogous to the role of the lungs during intravenous or other systemic administration. As shown in Scheme II (right), the liver receives the full drug input before it reaches the measurement location. Since the liver is the sole organ of elimination in this example, $C_{art} = C_{HV}$:

$$Cl_{app} = Cl_H = V_{max,H}/(K_M + C_{art}) \qquad \text{(Eq. 8)}$$

Thus, there is no flow limitation, and the intrinsic clearance of the liver is fully expressed.

Simultaneous Pulmonary and Hepatic Clearance—When the lungs and liver both eliminate a drug, the relative contribution of each organ to apparent clearance should be determined. Scheme III illustrates both the lungs and liver as eliminating organs *in vivo*. For intravenous administration, apparent clearance (G_{iv}/C_{art}) is the sum of the individual clearances:

$$Cl_{app} = Cl_P + Q_H Cl_H/(Q_H + Cl_H) = Cl_P + Q_H E_H \qquad \text{(Eq. 9)}$$

From this formula, the relative clearance contributions of the lungs and liver are:

$$\left(\frac{\text{lung}}{\text{liver}}\right) = \left(\frac{Cl_P}{Q_H E_H}\right) \qquad \text{(Eq. 10)}$$

Equation 10 is applicable to both linear and nonlinear kinetic regions. For nonlinear kinetics, Cl_P and E_H are not constants but are functions of C_{art} and C_{HV}. For linear kinetics ($C \ll K_M$), the expression for the Cl_P (Eq. 4) reduces to:

$$Cl_P = V_{max,P}/K_M \qquad \text{(Eq. 11)}$$

The expression for $Q_H E_H$ (Eq. 7), reduces to:

$$Q_H E_H = \frac{Q_H V_{max,H}}{Q_H V_{max,H}/(Q_H K_M + V_{max,H})} \qquad \text{(Eq. 12)}$$

Thus, the relative clearance contributions of the lungs and liver are:

$$\left(\frac{\text{lung}}{\text{liver}}\right) = \left(\frac{V_{max,P}/K_M}{Q_H V_{max,H}/(Q_H K_M + V_{max,H})}\right) \qquad \text{(Eq. 13)}$$

For oral administration, the apparent clearance (G_{po}/C_{art}) can be viewed as a modification of the expression for intravenous administration (Eq. 9). Due to the elimination by the liver of a certain fraction, E_H, of the administered dose, only the remainder is available for elimination by the lungs. Once this remainder, $1 - E_H$, leaves the liver, it is immaterial to the lungs whether the drug was given intravenously or orally. Hence, the right side of Eq. 9 can be divided by the available dose, $1 - E_H$, to yield an expression for apparent clearance for oral administration:

$$Cl_{app} = Cl_P/(1 - E_H) + Q_H E_H/(1 - E_H) = Cl_P/(1 - E_H) + Cl_H \qquad \text{(Eq. 14)}$$

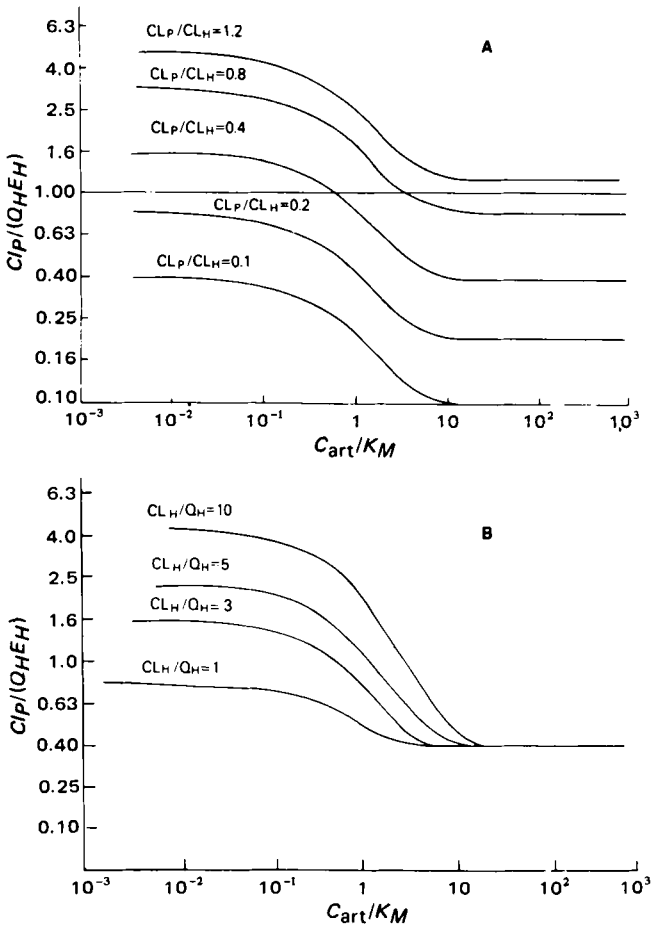


Figure 1—*Ratio of pulmonary clearance to hepatic clearance for intravenous infusion (Eq. 10) A:* Cl_H *fixed at three times* Q_H, *with* Cl_p/Cl_H *variable. B:* Cl_p/Cl_H *fixed at 0.4, with* Cl_H/Q_H *variable.*

It can be seen from Eq. 14 that the contributions of the lungs and liver to apparent clearance are interconnected. The contribution of pulmonary clearance is magnified by hepatic first-pass elimination, $1 - E_H$. Thus, there is no simple relationship similar to Eq. 10 that can be used to evaluate the relative clearance of the two organs.

RESULTS

The importance of pulmonary clearance for the determination of drug concentration is clearcut whenever the elimination capacity of the lungs is greater than that of any other organ (such as the liver). Even when the pulmonary elimination capacity is less than that of the liver, pulmonary clearance can dominate nonpulmonary clearance, or at least have a substantial impact on apparent clearance. For intravenous administration, hepatic clearance may not be fully expressed due to flow limitation so the relative impact of the lungs is enhanced. For oral administration, the coupling of pulmonary and hepatic clearances can accentuate the pulmonary impact.

Figures 1A and 1B demonstrate the relative contribution of the lungs and liver to overall drug elimination during intravenous infusion (Eq. 10). It is assumed that K_M is identical for liver and lung tissue. When $C_{art} \ll K_M$, elimination processes in both the lungs and liver are linear. At these low concentrations, the lung–liver elimination ratio is maximal since hepatic elimination is flow limited but pulmonary elimination is not. As the arterial concentration increases, the lung–liver elimination ratio

decreases since elimination processes are beginning to saturate, organ extraction is decreasing, and flow limitation is less pronounced. Finally, at $C_{art} \gg K_M$, the elimination ratio is simply the ratio of enzyme capacity, $V_{max,P}/V_{max,H}$.

As shown in Figs. 1A and 1B, for some parameter combinations the dominant role for elimination can be held by either organ or can shift from the lungs to the liver as C_{art} increases. For the lungs to dominate in the linear region, the following relationship must be satisfied, based on Eq. 13:

$$\left(\frac{V_{max,P}}{K_M}\right) > \left(\frac{Q_H V_{max,H}}{Q_H K_M + V_{max,H}}\right) \quad (15)$$

The liver always dominates in the zero-order region as long as $V_{max,H} > V_{max,P}$. As a reference point, the weight ratio of the lungs to the liver in humans is ~0.6 kg/1.5 kg or 0.4 (25). Since the clearances of both the lungs and liver are referred to the same arterial concentration, the mass elimination ratio (organ extraction times mass input to organ) is identical to the clearance ratio.

As already discussed, the contribution of the lungs to apparent clearance for oral administration is difficult to separate from the contribution of the liver. Figure 2 presents one possible interpretation of the lung's importance. Only the linear kinetic region is considered; Cl_{app} was calculated from Eq. (14) for various combinations of pulmonary and hepatic intrinsic clearance. The ability of the lungs to increase apparent clearance is rather substantial. As one example, a pulmonary elimination capacity that is 40% of hepatic capacity (*i.e.*, equivalent capacity per unit of weight multiplied by the organ weight ratio) produces a 133% increase in apparent clearance when the hepatic intrinsic clearance is three times the hepatic blood flow (75% extraction).

As a second example, a pulmonary elimination capacity of only 5% of hepatic capacity (*i.e.*, one-eighth the capacity per unit of weight multiplied by the organ weight ratio) increases Cl_{app} by 55% when hepatic clearance is 10 times the hepatic blood flow (91% extraction).

Since arterial concentration and systemic tissue exposure are inversely related to Cl_{app}, a relatively small amount of pulmonary activity can have a large impact. The mass elimination ratio does not provide the same perspective. The lungs account for 18% of mass elimination in the first example and only 3% in the second. These lower rates of mass elimination (as well as lower total elimination capacities) may lead one to ignore their role, while consideration of changes in Cl_{app} or systemic arterial concentration underscores the potential importance of pulmonary elimination.

DISCUSSION

Except for regionalized delivery such as topical, intraarterial, or intrathecal, the anatomical position of the lung presents it with the opportunity to modify the amount of drug available to the target tissues. Previous pharmacokinetic analyses focused primarily on the role of hepatic metabolism while essentially ignoring the lungs. In an earlier study that focused on the role of drug binding and GI or hepatic metabolism, Gillette and Pang (26) commented on the lack of flow limitation for the lung and the interactions of the liver with other organs for oral administration.

The role of the liver overshadowed that of the lungs in previous analyses for three major reasons:

1. The larger size of the liver may permit a greater total enzyme capacity. The actual magnitude of this difference is less for humans (1.5–2.5 times) than for other mammalian species: seven to 10 times for rats, eight times for rabbits, five times for monkeys, and three to four times for cats and dogs.

2. The well-known role of the liver in controlling the entry of exogenous substances into the body makes it a likely organ for drug elimination. Since the lungs play a major role in the regulation of endogenous substances, they might be expected to regulate exogenous substances also.

3. Lower specific enzyme activity (units per gram) has often been found in lung tissue compared with liver tissue. It was noted earlier that this apparently lower specific enzyme activity may be the result of suboptimal experimental conditions. In addition, interorgan differences in enzyme affinity for a drug (K_M) may offset a lower enzyme amount. Other studies (27) isolated an enzyme with a 10-fold lower K_M value in lung than liver tissue. Since intrinsic clearance under nonsaturating conditions is the ratio of enzyme capacity (V_{max}) to K_M, the lung can possess a larger intrinsic clearance than the liver, despite lower enzyme levels. On the other hand, studies by Gram (5) showed similar K_M values for other enzymes in the liver and lung. Finally, flow limitation can prevent expression of intrinsic clearance of the liver but not the lungs; thus, the lung can dominate even if it has lower intrinsic clearance.

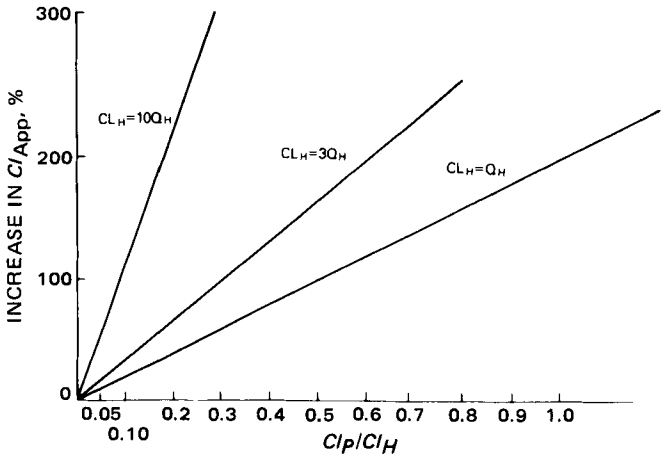


Figure 2—*Increase in apparent clearance for oral administration at various levels of pulmonary intrinsic clearance added to existing hepatic intrinsic clearance. Only the linear kinetic region is considered.*

Although it is suspected that the liver is a more important organ than the lungs for most drugs, the reasons for its dominance probably have been overstressed. Additional investigations are warranted to establish the actual pulmonary contribution, especially for drugs with high apparent clearance.

The concept of apparent clearance is especially relevant for a description of the lung's role in pharmacokinetics since it is simply a ratio of dose rate to arterial drug exposure. The related concept of organ clearance can be misleading when applied to the role of the lungs since it fails to account for first-pass effects. It is especially important that this difference is realized when the results from isolated perfused lung experiments are interpreted.

The synergism between the lung and liver for oral (or hepatic artery or portal vein) administration is especially noteworthy. The anatomical relationship of these organs results in a powerful filter, which can either protect systemic tissues from undesired exogenous chemicals or prevent achievement of therapeutic drug levels. For these two organs, neither the ratio of mass eliminated nor the ratio of elimination capacities is always a useful indicator of the control of tissue drug exposure. Although the liver may be responsible for the elimination of most of the drug mass eliminated from the body, the lung can still have a substantial impact on arterial drug concentration.

APPENDIX

Cl_p = intrinsic pulmonary clearance, $V_{max,P}/(K_M + C_{art})$
Cl_H = intrinsic hepatic clearance, $V_{max,H}/(K_M + C_{HV})$
Cl_{app} = apparent clearance, G/C_{art}
E_P = pulmonary extraction, (in–out)/in
E_H = hepatic extraction, (in–out)/in
G = drug input rate
Q = blood flow
C_{art} = arterial blood concentration
C_{PV} = pulmonary vein blood concentration
C_{PA} = pulmonary artery blood concentration
C_{HV} = hepatic vein blood concentration
K_M = half-saturating concentration (Michaelis constant)
V_{max} = maximal drug elimination capacity of whole organ
f = fraction of cardiac output which perfuses liver
co = cardiac output
P = pulmonary
H = hepatic
ia = intraarterial
iv = intravenous
po = oral

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Comparison of Serum Bilirubin Levels in Humans and Two Monogastric Animal Species After a Single Administration of Sulfisoxazole

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Abstract □ Administration of sulfonamides during periods of hepatobiliary failure or hepatic immaturity increases the toxic potential of unconjugated or indirect bilirubin. A small but statistically significant increase of indirect, or unconjugated bilirubin was noted in dogs after oral administration of sulfisoxazole (100 mg/kg). A similar increase was not observed in swine after oral or intravenous administration of sulfisoxazole (100 mg/kg) or in humans (~28 mg/kg) after oral administration or in dogs (100 mg/kg) after intravenous administration. Total and conjugated bilirubin showed small but statistically significant increases and were significantly correlated in dogs after oral and intravenous administration of sulfisoxazole (100 mg/kg) and in swine after oral administration of sulfisoxazole (100 mg/kg). There was a significant negative correlation between conjugated and indirect bilirubin, while total bilirubin increased in dogs after oral and intravenous administration of sulfisoxazole. These data illustrate a difference in species and administration route when attempting to assess the potential toxicity of bilirubin.

Keyphrases □ Sulfisoxazole—comparison of serum bilirubin levels after a single administration, dogs, pigs, humans □ Bilirubin—serum levels after a single administration of sulfisoxazole, dogs, pigs, humans □ Toxicity—potential, indirect bilirubin serum levels after a single administration of sulfisoxazole

Sulfisoxazole [4-amino-*N*-(3,4-dimethyl-5-isoxazolyl)]-benzenesulfonamide is a white-yellowish, odorless, slightly bitter, crystalline powder with a pK of 4.9 (1). It is distributed in the extracellular fluid and fails to enter cells (2–5) resulting in a plasma concentration which is three times higher than that produced by an equal quantity of sulfanilamide (4). Sulfonamides, as a class of chemotherapeutic agents, are considered to be toxic since they may precipitate in the kidney, producing crystalluria (5). The infrequency of renal toxicosis (crystalluria) with sulfisoxazole is due to the exceptionally high water solubility of the free and conjugated (acetyl) fractions within the physiological pH range (6, 7).

Clinical toxicities have been induced by sulfisoxazole competing for the same binding sites as warfarin (8) and furosemide (9, 10), inducing hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency (11), inhibition of anticoagulant factor VIII (12), hypersensitivity (13), anorexia (14), agranulocytosis (14), and aplastic anemia (14). A case of myocarditis, myositis, and vasculitis associated with severe eosinophilia following sulfisoxazole therapy has been reported (15). Kernicterus has been reported in premature infants with increased levels of serum bilirubin after treatment with sulfisoxazole (4, 16, 17).

Kernicterus occurred when unconjugated or indirect bilirubin was less than 20 mg% in 24 infants, less than 17 mg% in 15 infants, and less than 15 mg% in 11 infants. These occurrences were enhanced by prior acidosis, hypercapnia, and hypothermia (4).

Plasma samples from six adult patients showed that sulfisoxazole concentrations above 5 mg/100 ml had a significant displacing effect on bilirubin *in vitro* (18). When comparing the displacing effects of salicylic acid, salicyluric acid, and aspirin at sulfisoxazole concentrations of 10 mg/100 ml, the most pronounced effect was observed when sulfisoxazole displaced bilirubin from plasma sam-

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