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DRUG PHARMACOKINETICS IN CARDIAC AND HEPATIC DISEASE

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INTRODUCTION

The rational administration of a drug to a patient requires knowledge of the anticipated efficacy and toxicity of the drug dose that is administered. When knowledge of how a given patient will absorb and eliminate a drug is coupled with knowledge of the pharmacologic effect of a given amount of the drug, a drug dose can be selected that will result in clinical efficacy with minimal toxicity. After a dosing regimen is instituted, direct clinical observations for efficacy and toxicity and laboratory measurements of drug concentrations in plasma or blood may then be used to modify the initial regimen (1). These observations are especially important when drugs with low therapeutic indices are used.

To assist the physician in the development of a rational dosing regimen, the science of pharmacokinetics provides information about the time course of the amount of drug in the body in the expectation that this information will correlate, directly or indirectly, with the time course of drug efficacy and toxicity. Investigations of drug absorption into the body, distribution within, and elimination from the body (the latter two processes defined as drug disposition) have been performed frequently in healthy subjects on the assumption that kinetic parameters defined
individuals would apply to various patient populations (2). Although this assumption forms the basis for many pharmacokinetic investigations that are performed to evaluate drugs for clinical use, several clinical investigations have now documented that drug absorption and disposition parameters in healthy individuals may differ widely from those observed in patients

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with impairment of one or more major organ systems. In addition, it is now apparent that parameters of drug absorption and disposition may vary, not only between healthy and ill persons, but also within the same person over a period of time (3). These findings
of information that is available from clinical investigations of drug pharmacokinetics, and this complexity in turn has limited the practical application of pharmacokinetic data in many clinical settings.

For these reasons, emphasis in pharmacokinetic investigations has shifted in part from studies in healthy individuals to studies in specific populations. Furthermore, interest in purely descriptive studies of drug pharmacokinetics in healthy individuals or in specific
has expanded to include an interpretation of how physiologic variables such as blood flow, intrinsic metabolic activity of an eliminating organ, and plasma and tissue protein binding can influence drug pharmacokinetic parameters (4–7). These more recent approaches to the investigation of drug pharmacokinetics in both patient and healthy populations have resulted in a number of clinically pertinent observations. Our intent is to review some of these recent clinical studies that define
disease states on drug absorption and disposition and, when possible, to interpret the data from these studies in terms of physiologic variables that can influence
on drug pharmacokinetics is considered in a separate section of this volume, the focus of this chapter is on the influence of cardiac and hepatic disease on drug absorption and disposition.

PHYSIOLOGIC MODELS OF ORGAN ELIMINATION

Pharmacokinetic models of drug absorption and disposition are formulated in terms of one or more compartments to account for mono- or multiexponential elimination of a drug from the body (8). The compartments defined in these models do not correspond to actual anatomic spaces of the body. Physiologic (or perfusion) models of drug absorption and disposition define the pharmacokinetics of a drug in terms of physiologic parameters such as blood flow to tissues and organs of the body, protein binding of the drug to blood and tissue constituents, and the intrinsic capacity of one or more organs of elimination to remove the drug from the body. Neither model is exclusive of the other. A physiologic model of drug absorption and disposition defines
are clinically relevant and may therefore be regarded as an extension of a pharmacokinetic model.

Physiologic models, like pharmacokinetic models of drug absorption and disposition, can be highly complex, depending on the routes of absorption and elimination of a drug, its binding to plasma and tissue constituents, and

the distribution of the drug to tissues and organs of the body. A relatively simple model that defines

organ of elimination may be formulated (Figure 1). Drug enters the system in this model either before (Site I) or after (Site II) it enters the organ of elimination; this is comparable to oral or intravenous administration if the eliminating organ is the liver, or to intravenous or arterial drug administration if the eliminating organ is the lung. After the drug enters the system, it distributes both to the organ of elimination and to the remainder of the body. Drug is bound to tissues of the organ ($C_{\text{bound, organ}}$) and to tissues and fluids

to the remainder of the body ($C_{\text{bound, body}}$). Unbound drug (C_f) in the eliminating organ exists in equilibrium with unbound drug in the remainder of the body. Elimination from the organ is defined by the rate constant k. Blood from the remainder of the body flows to and returns from the organ of elimination at flow

leaving the organ at concentration C_o. Following entry of the drug into the system, the difference between C_i and C_o relative to the eliminating organ reflects

bution equilibrium has been achieved at steady state, the difference between C_i and C_o reflects

For a drug that is eliminated from the body by a single organ, as shown in Figure 1, the clearance of drug from the system (CL_{systemic}) at steady state

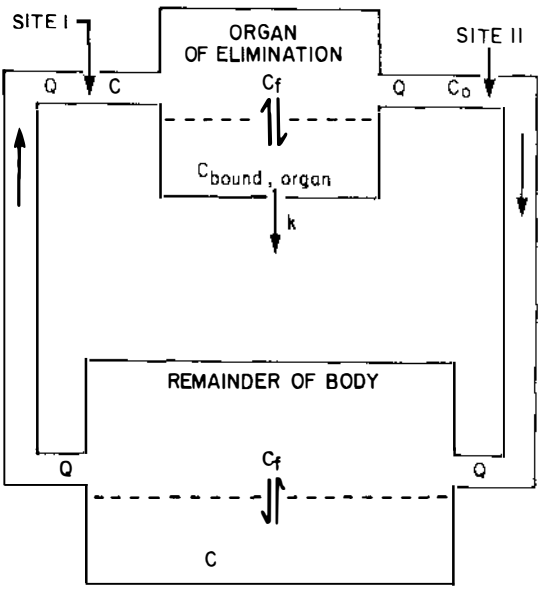

Figure 1 A physiologic model for organ elimination (see text for discussion).

is equal to clearance of drug by the organ of elimination (CL_{organ}) and is defined as the rate of elimination of drug by the organ relative to the concentration of drug entering the organ:

$$CL_{systemic} = CL_{organ} = \text{Rate of Elimination}/C_i \quad 1a.$$
$$= [Q \cdot C_i - Q \cdot C_o]/C_i \quad 1b.$$
$$= Q\,[(C_i - C_o)/C_i] \quad 1c.$$
$$= Q \cdot ER. \quad 1d.$$

As noted in Equation 1*c* and 1*d*, the term $(C_i - C_o)/C_i$ is defined the extraction ratio (ER) of the drug. According to the model depicted in Figure 1, organ (and systemic) clearance is limited by blood flow to the organ. As the extraction of drug by the eliminating organ increases ($C_o \rightarrow 0$), CL_{organ} becomes limited by the flow of blood to the organ:

$$CL_{systemic} = CL_{organ} = Q. \quad 2.$$

A fundamental objective of physiologic models of organ elimination has been to define the intrinsic clearance ($CL_{intrinsic}$) of an eliminating organ in the absence of flow (supply) limitations. At least two models have been proposed (5, 9) to define
terms of a clearance ($CL_{intrinsic}$) that relates rate of elimination to concentration of unbound drug in the organ ($C_{organ,\,free}$). Presumably this concentration represents the free drug concentration at the site or sites of elimination of drug within the organ. Because of experimental limitations in measuring $C_{organ,\,free}$, each model defines
unbound drug in the organ and the concentration of drug leaving the organ (C_o). The most straightforward and widely applied of these models of drug elimination, which has been called the Well-Stirred Model, assumes that $C_{organ,\,free}$ and $C_{o,\,free}$ are proportional (5, 10). The second model, termed the Parallel Tube Model (9, 10), assumes an exponential relationship between $C_{organ,\,free}$ and $C_{o,\,free}$. According to the assumptions of the Well-Stirred Model, and defining as equal to the fraction of drug unbound in blood (f_B) times C_o ($f_B = C_f/C_B$), the following expression for organ clearance in the absence of flow limitations has been formulated (5, 7):

$$CL_{intrinsic} = Q\,(C_i - C_o)/f_B C_o. \quad 3.$$

Through rearrangement and substitution of Equation 3 into Equation 1, the following expression for intrinsic organ clearance relative to systemic organ clearance (CL_{organ}) has been defined

$$CL_{organ} = Q\,[f_B CL_{intrinsic}/(Q + f_B CL_{intrinsic})]. \quad 4.$$

The relationships shown in Equation 4 indicate the assumptions of the Well-Stirred Model of organ elimination. These relationships emphasize the importance of organ blood flow,

tein binding to organ drug clearance and, for drugs that are eliminated by a single organ (Figure 1), to systemic clearance. For drugs that are highly extracted by an organ of elimination ($f_B CL_{intrinsic} \gg Q$), organ clearance becomes limited by organ blood flow:

$$CL_{organ} \cong Q, \quad 5.$$

whereas for drugs that are poorly extracted by the liver ($f_B CL_{intrinsic} \ll Q$), organ clearance becomes approximated by the product of f_B and $CL_{intrinsic}$:

$$CL_{organ} \cong f_B CL_{intrinsic}. \quad 6.$$

The importance of the position of the organ of elimination relative to the site of drug entry (Figure 1) has received considerable emphasis (11, 12). Drug entering the blood immediately before it enters the organ of elimination may undergo substantial metabolism in the organ before entry into the systemic circulation and the remainder of the tissues in the body (Site I, Figure 1). This "first-pass"
highly extracted by the liver after oral administration. It is also characteristic of drugs that are highly extracted by the lung after intravenous administration. No parallel exists for drugs that are highly extracted by the kidney because drugs reach this organ of elimination after entry into the systemic circulation (Site II, Figure 1).

It is difficult to obtain evidence in man that supports the assumptions of either the Well-Stirred Model or the Parallel Tube Model of organ elimination. Evidence in vitro in the isolated perfused rat liver and in vivo in the pig have supported each model (13–15). In all probability both of these models, in fact, circumscribe the range of conditions for a variety of drugs when organ elimination is investigated. Each model may be used to emphasize the difference between a physiologic description of drug elimination and the usual compartment model which is formulated on mathematical, rather than anatomical, terms. For the purpose of discussion and interpretation here, we utilize the assumptions of the Well-Stirred Model of organ elimination (hereafter referred to as the physiologic model of organ elimination). For a more thorough presentation of the two models and the evidence in support of each model, the reader is referred to Pang & Rowland (10, 13), Keiding et al (14), and Pang & Gillette (15).

CARDIAC DISEASE AND DRUG PHARMACOKINETICS

The influence of cardiac disease on drug pharmacokinetics has recently been reviewed (16); for this discussion we focus on the data that define the influence of congestive heart failure in terms of the physiologic model of

organ elimination. According to this model, at least three variables determine the clearance of a drug by an eliminating organ: flow
organ (Q), binding of the drug to blood constituents (f_B), and intrinsic capacity of the organ to remove the drug from the circulation in the absence of flow
physiologic variables. Through reduction in cardiac output because of congestive heart failure, blood flow to one or more organs of elimination may be reduced. Alteration in the capacity of an organ to eliminate a drug may occur as a result of acute or chronic congestion (17). Change in cardiac function or in the function of other organs (e.g. the liver) in individuals with congestive heart failure may alter blood and tissue concentrations of drug binding proteins, alter physiologic pH, or result in the production of endogenous displacing substances. Such changes, in turn, may influence
ing of drug to blood or tissue components. In addition, cardiac disease may alter patterns of drug absorption through changes in gastrointestinal motility, splanchnic blood flow,
tract, or change in the secretions or bacterial flora of the gastrointestinal tract (18). Although relatively few reports have defined
cardiac disease on drug absorption or disposition, a number of them have suggested that the effects of cardiac disease on the pharmacokinetics of a drug may be more pervasive than would be anticipated in an organ that does not directly participate in the process of elimination.

Cardiac Blood Flow to an Organ of Elimination

According to the physiologic model of organ elimination as shown in Equation 4, flow
minant of drug disposition for drugs that are highly extracted by the organ. For these drugs, clearance becomes limited by organ blood flow
5). For a highly extracted drug that is eliminated primarily by a single organ of elimination, both organ clearance and systemic clearance will relate directly to flow of blood to the eliminating organ. Reductions in organ blood flow
and systemic clearance. Because steady state blood concentrations of drug are inversely related to blood clearance (CL_{blood} = rate of administration/ C_B at steady state), these theoretical considerations possess clinical relevance. Drugs that are highly extracted and eliminated almost exclusively by the liver include propranolol, meperidine, lidocaine, pentazocine, dextropropoxyphene, spironolactone, and acetylsalicylic acid (19). Reduction in hepatic blood flow in individuals with congestive heart failure who receive one of these drugs will be reflected
and inversely in changes in concentrations of the drug in blood at steady state.

Several in vivo and in vitro investigations in animals have documented the theoretical assumptions of the physiologic model of organ elimination relative to organ blood flow. Shand et al (6) demonstrated that clearance of the highly extracted drug lidocaine, as represented by steady state drug concentration, was directly related to the perfusate flow in the isolated perfused rat liver when the drug was administered into the reservoir (Site II, Figure 1). At a perfusate flow of 10 ml/min, steady state blood concentrations of lidocaine equalled 7.66 ± 0.38 μg/ml, falling to a mean of 3.51 ± 0.17 μg/ml at a perfusate flow of 20 ml/min (Figure 2). In the dog, clearance of both *d*-propranolol and *dl*-propranolol has been shown to correlate directly with blood flow to the liver (20). In the rhesus monkey, *dl*-propranolol, but not *d*-propranolol, produced β-adrenergic blockade and reduced cardiac output. Systemic clearance of the racemate was reduced significantly (14.1 ± 0.7 ml/kg/min), in comparison to the clearance of the *d*-isomer (18.3 ± 1.0 ml/kg/min). These observations support not only the theoretical assumptions of the physiologic model shown in Equation 4, but also demonstrate a unique form of drug interaction in which the disposition of a drug is influenced by its own pharmacologic effect, which is decreased blood flow to the eliminating organ (21). A similar interaction between *dl*-propranolol, but not *d*-propranolol and lidocaine, has been

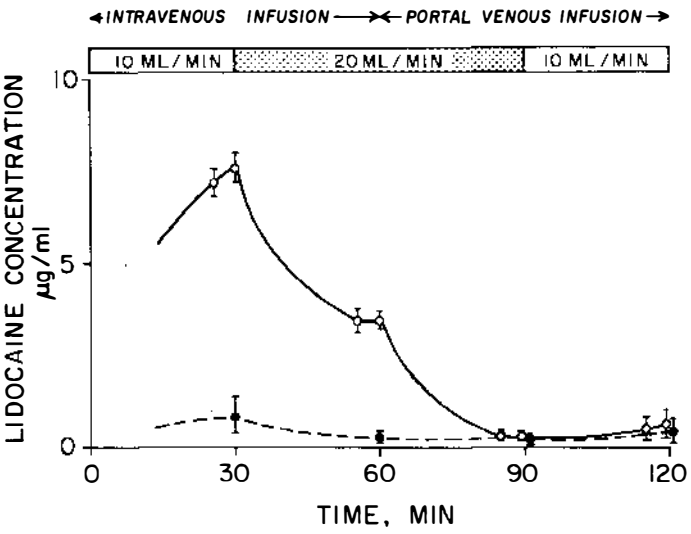

Figure 2 Lidocaine concentrations in blood flowing to the isolated perfused rat liver from the reservoir (*open circles*) and in the venous effluent (*closed circles*) during administration of drug into the portal system (58 μg/min) at constant blood flows of 10 and 20 ml/min. Each point represents the mean ± SEM of five experiments.

demonstrated in the anesthetized dog (22). In the rhesus monkey, Benowitz et al (23) observed that isoproterenol increased and norepinephrine decreased total liver blood flow. After infusion of lidocaine to steady state, isoproterenol infusion was associated with a fall in lidocaine concentration and increased drug clearance, while norepinephrine (NE) produced a rise in lidocaine concentration and a corresponding fall in clearance (Figure 3).

Investigations in humans to document the assumptions of a physiologic model of organ elimination are not readily available because of the difficulty in measuring both blood flow to an organ of elimination and the extraction ratio of a drug by this organ. Despite these limitations, several investigations in man have indicated that cardiac output is an important determinant of drug clearance for drugs that are highly extracted by an organ of elimination. In studies performed during cardiac catheterization in individuals with varying degrees of cardiac impairment, Stenson et al (24) demonstrated that hepatic blood flow and cardiac index correlate directly with one another and that each is inversely related to steady state arterial concentrations of lidocaine. In subsequent studies, Thomson et al (25, 26) confirmed that

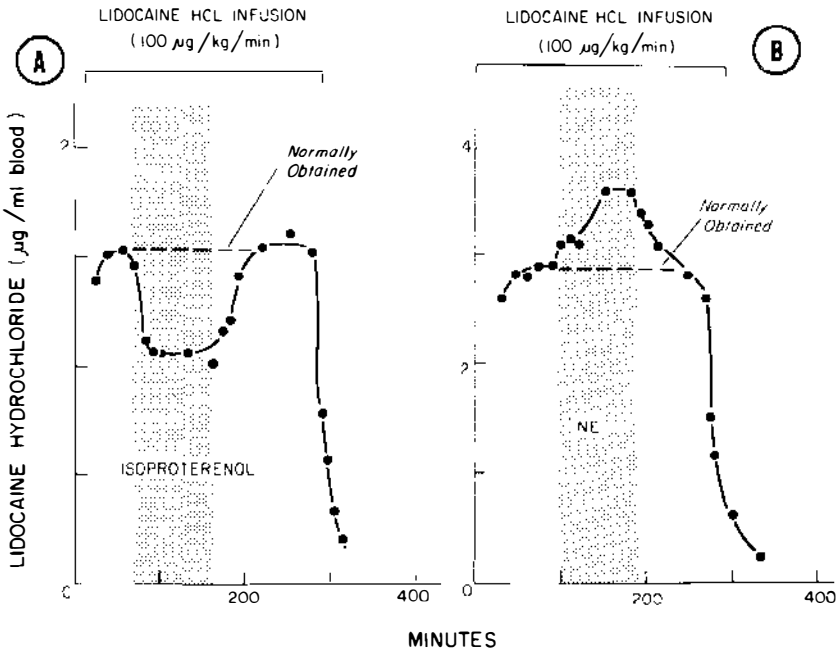

Figure 3 Arterial lidocaine blood concentrations in the rhesus monkey: The effect of isoproterenol infusion (*A*) and norepinephrine infusion (*B*) on steady-state lidocaine levels during constant infusion (100 µg/kg/min).

lidocaine clearance is reduced in patients with congestive heart failure in comparison to healthy control subjects and that clearance of this drug in the patient group correlated significantly with cardiac output. In these individuals, the change in lidocaine clearance occurred in association with a reduction in both the central volume into which the drug appeared to distribute, as well as the volume of distribution at steady state. No change in lidocaine half-life was observed in the subjects with congestive heart failure. In a more recent study, Zito et al (27) found that lidocaine clearance was reduced in patients with impaired cardiac output. These authors also found that the clearance of indocyanine green, a compound which is also highly extracted by the liver in individuals with normal hepatic function, correlated significantly with lidocaine clearance. Zito et al suggested that the determination of indocyanine green clearance is a simple test that can be used to predict the clearance of lidocaine in individuals with congestive heart failure.

Cardiac Disease and Intrinsic Metabolic Capacity of an Eliminating Organ

Although cardiac disease might theoretically alter the intrinsic ability of an organ to eliminate a drug, relatively few studies have assessed this possibility. In a study of individuals immediately after acute myocardial infarction, Hagemeijer (28) reported that the half-life of aprindine, an antiarrhythmic agent which is similar to lidocaine in pharmacologic effect but which is slowly cleared from the plasma, was markedly extended in comparison to healthy control subjects. Jackson et al (29) also reported a marked prolongation in the elimination of canrenone, a slowly cleared metabolite of spironolactone, in patients with cardiac failure. In this study, half-life of canrenone ranged between 32 and 105 hr (mean: 59 hr) in individuals with congestive heart failure, while values in individuals without evidence of cardiac impairment varied between 13.5 and 24 hr. Aminopyrine is a drug that is poorly extracted by the liver. In contrast to aminopyrine clearances of 125.1 $\pm$ 21.5 ml/min (mean $\pm$ SD) in healthy control subjects, Hepner et al (30) observed that clearance of this drug was reduced to 43.6 $\pm$ 16.9 ml/min in patients with congestive heart failure. This change in clearance was associated with an increase in apparent volume of distribution of aminopyrine (patients: 66.6 $\pm$ 14.0 L; healthy controls: 43.1 $\pm$ 7.1 L) and with prolongation in drug half-life (patients: 23.3 $\pm$ 16.9 hr; healthy controls: 4.2 $\pm$ 1.5 hr). Minimal elevations in bilirubin or serum glutamic oxalacetic transaminase were noted in six of the nine subjects in this study, suggesting that hepatic impairment, perhaps secondary to chronic passive congestion of the liver, contributed to the observed alteration in aminopyrine disposition parameters.

Koch-Weser & Klein (31) stated that the absorption of procainamide was delayed and peak plasma drug concentrations were lower in patients with congestive heart failure. However, Giardina et al (32) reported that peak plasma concentrations of this antiarrhythmic drug after oral administration were higher and that drug half-life was prolonged in five individuals with congestive heart failure but with normal indices of hepatic function in comparison to five healthy control subjects. Peak plasma drug concentrations in the patient group in this study were 7.1 ± 1.4 μg/ml (healthy subjects: 4.2 ± 0.3 μg/ml); drug half-life in the patient group was 5.5 ± 0.9 hr (healthy subjects: 2.9 ± 0.5 hr).

Prazosin is an antihypertensive drug that is undergoing trial in the therapy of persons with congestive heart failure because of its potential ability to reduce both cardiac pre- and afterload (33). Baughman et al (34) and Jaillon et al (35) have reported that peak plasma concentrations of this drug were higher and plasma decay of prazosin was delayed in patients with chronic congestive heart failure, even in the presence of hepatic function tests that were within normal limits (Figure 4). In the absence of data from intravenous dosing of this drug, it is not possible to determine whether these changes occurred because of a change in the fraction of drug absorbed from the gastrointestinal tract or because of a change in drug clearance. Andreasen & Mikkelsen (36) reported that furosemide plasma clearance decreased and terminal half-life increased when values in three groups of

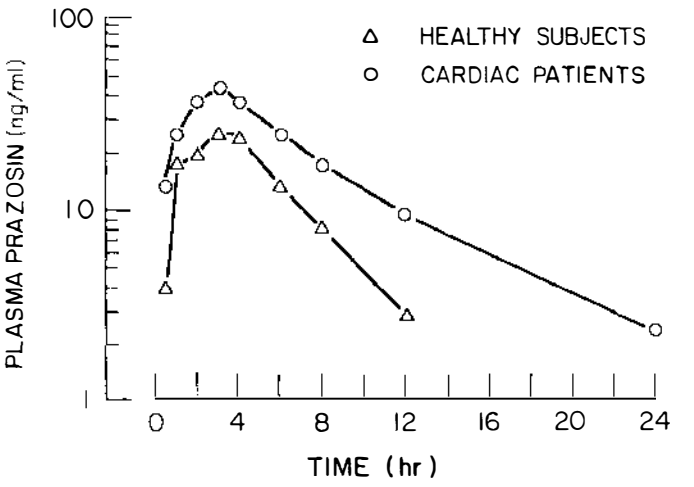

Figure 4 Mean plasma prazosin concentration versus time in five healthy individuals (triangles) and nine patients with Class III or IV (New York Heart Association) congestive heart failure after a single 5 mg dose of the drug that has been administered orally (34).

patients with cardiac decompensation were compared to those found in normal volunteers.

Additional data suggest that clearance of a poorly extracted drug by the liver may be changed, not through changes in the eliminating capacity of the liver, but through changes in drug volume of distribution. Using data of Bellet et al (37), Crouthamel (38) reported that the volume of distribution of quinidine was decreased in patients with congestive heart failure in the absence of change in the elimination half-life of the drug. This observation for quinidine has been confirmed by Ueda & Dzindzio (39) and by Kessler et al (40). These observations are not strictly in accord with the theoretical assumptions of the physiologic model of organ elimination as defined in Equation 4, and may be attributed to changes in drug protein binding in the absence of change in metabolic function or organic perfusion.

Protein Binding

According to the physiologic model of organ elimination described in Equation 4, binding of drug to plasma or blood components may be an important determinant of drug clearance. For drugs that are poorly extracted by an eliminating organ (Equation 6), changes in clearance may be directly proportional to changes in the fraction of drug bound in blood. Only minimal information is available to document the influence of cardiac disease on drug protein binding, although the extensive physiologic changes that may occur in individuals with acute and chronic congestive heart failure suggest that drug binding changes frequently occur in these patients. Yacobi et al (41, 42) observed that over time, protein binding of warfarin varied widely between, but not within, individuals with congestive heart failure. As predicted by Equation 6 for poorly extracted drugs such as warfarin, the difference in individuals was correlated with plasma drug clearance. The reason for the wide variation in protein binding in individuals with cardiac disease was not apparent, although displacement of warfarin from plasma protein binding sites may have occurred because of additional medications received by the individuals in the study.

Drug Absorption in Cardiac Disease

From a pharmacokinetic standpoint, the gastrointestinal tract may be perceived as an organ of elimination that removes drug from the lumen of the gut into the body. Based on this perception, models of gastrointestinal drug absorption may be used that are analogous to the physiologic model of organ elimination from the body (Equation 4). Drugs may be rapidly absorbed (extracted) from the gastrointestinal tract because of small molecular size and the resulting freedom from pore-size restrictions, because of high lipophilicity, or because of active gastrointestinal transport processes

(43, 44). For these drugs, absorption from the gastrointestinal tract may be influenced by changes in splanchnic blood flow. For drugs that are poorly extracted from the lumen of the gut by the gastrointestinal tract, extraction of drug from gastrointestinal fluids may be sensitive to changes in intraluminal processes or to changes in binding of the drug to gut contents. Theoretical models that define the influence of splanchnic blood flow, drug concentrations in gut and blood, and gastrointestinal permeability factors have been described (45, 46) and reviewed (18).

Early studies of the influence of cardiac disease on drug absorption documented malabsorption of both neutral fat and fatty acids from the gastrointestinal tract of individuals with chronic congestive heart failure (47). The malabsorption of fat in these studies was attributed both to the passive congestion of bowel wall and to decreased exocrine function of the pancreas.

More recent studies have documented that cardiac disease may impair gastrointestinal absorption of drugs. Tilstone et al (48) reported that the bioavailability of metazolone in individuals with congestive heart failure was reduced by approximately 50% in comparison to individuals with normal cardiac function. Anderson and co-workers (49) reported that maximum concentrations of hydrochlorothiazide in plasma after administration of radiolabeled drug were lower in individuals with congestive heart failure. The fraction of drug excreted into the urine in 24 hr in these individuals was also substantially less (42%) in comparison to healthy controls (62%). Both Koch-Weser & Klein (31) and Crouthamel (38) suggested that the absorption of antiarrhythmic drugs such as quinidine and procainamide may be delayed in individuals with cardiac disease. More equivocal data are available regarding the oral absorption of furosemide and digoxin in individuals with cardiac dysfunction. Greither et al (50) reported that although the absorption of furosemide was erratic and incomplete both in healthy individuals and in individuals with congestive heart failure, there was no significant difference in the extent of availability of the drug in these two groups of individuals. Although Oliver et al (51) described decreased absorption of digoxin tablets in a single individual with congestive heart failure, Doherty et al (52, 53), Ohnhaus et al (54), and Meister et al (55) reported no apparent influence of cardiac failure on the absorption of this digitalis glycoside.

While Meister et al (55) did not find significant changes in digoxin absorption in patients with heart failure, marked changes in other pharmacokinetic parameters were noted in patients who experienced clinical improvement with digoxin dosing. For example, the following changes were observed in a 58-year-old, 87-kg male whose condition improved after receiving daily doses of digoxin: Total plasma clearance increased from 92 ml/min to 132 ml/min; of this total, metabolic clearance increased from

23 to 43 ml/min and renal clearance from 69 to 89 ml/min; the half-life decreased from 60.6 hr to 36.9 hr; oral availability increased only slightly from 61 to 68%.

HEPATIC DISEASE AND DRUG PHARMACOKINETICS

On the assumption that a diseased organ functions less effectively than a healthy organ in the process of drug removal, physicians are generally advised that if the liver is impaired the elimination of drugs that are removed from the body primarily by hepatic biotransformation or excretion is retarded (56, 57). Advice to physicians also has generally included the warning that patients with hepatic impairment may be unduly sensitive to the effects of certain drugs in the absence of changes in drug absorption and disposition (58–60). A substantial amount of information regarding the influence of hepatic disease on drug pharmacokinetics and pharmacodynamics has become available in the last decade. Although much of these data support these general admonitions, it is now apparent that the influence of hepatic disease on drug absorption and disposition parameters may be highly variable. Diminished, unchanged, and even accelerated drug elimination has been reported in patients with liver impairment. Irrespective of the presence of a significant change in drug pharmacokinetics, there is usually a wide overlap in the range of values of absorption and disposition parameters between normal individuals and patients. The pharmacokinetic or pharmacodynamic consequences of a specific hepatic disease may differ between individuals, or even within a single individual over a specific period of time. Different forms of hepatic disease may produce different alterations in drug absorption and disposition and pharmacologic effect. Because of this variability, the use of drugs in patients with hepatic impairment would be aided considerably if a simple, rapid, and safe test of the capacity of the liver to eliminate a drug were available. Several investigators in the last decade have attempted to develop useful clinical correlates between the concentration of endogenous compounds, such as bilirubin or serum transaminase concentrations, or between the pharmacokinetic parameters of exogenous model compounds (such as indocyanine green or antipyrine) and one or more pharmacokinetic parameters of a specific drug. Although an occasional correlation is observed which is statistically significant, none of these attempts have proved clinically useful. At this time there is no generally available test that indicates the degree of hepatic impairment relative to drug absorption and disposition.

Despite the complexity of the influence of hepatic disease on drug disposition and the absence of clinically useful correlates to predict this influence, in the last decade several carefully controlled and well-designed investiga-

tions in humans have clarified the influence of hepatic disease on the disposition of several drugs. Although earlier studies on drug kinetics in hepatic disease states focused almost exclusively on drug half-life as the parameter of interest, these more recent investigations at least have included estimates of clearance, one or more volumes of distribution, and one or more drug half-lives. In some instances, these studies have included a determination of drug binding to plasma or blood components and measurement of the blood to plasma drug ratio. The importance of these latter determinations can be seen in Equations 4 through 6 which define the influence
ologic variables such as blood flow and protein binding on drug disposition.[1]

Because of the complexity of the influence of hepatic disease on drug disposition, physiologic models of hepatic drug elimination have been especially useful. By defining
intrinsic hepatic clearance, and protein binding, physiologic models of organ elimination, such as that defined
understanding of the influence of these variables on drug disposition. Although the application of this knowledge to patients in clinical settings with hepatic disease has not yet been accomplished, investigators of drug disposition in individuals with impaired liver function now have a more thorough understanding of important parameters of drug disposition in patients with acute and chronic liver disease and can design clinical experiments accordingly. Physiologic models have been used to develop noninvasive methods for determining hepatic blood flow
have even formed the basis for estimating intrahepatic shunting of blood in the liver (62).

Hepatic Blood Flow, Drug Absorption, and Highly Extracted Drugs

In terms of drug absorption and disposition, the liver occupies a unique position both functionally and anatomically. Not only is it a primary organ of elimination for many drugs that are introduced into the body, it is also positioned between the systemic circulation and the vasculature that drains

[1]Concentrations of drug are frequently determined in plasma rather than blood. Conversion of plasma clearance to whole blood clearance can be performed if the blood to plasma drug ratio is known and is stable over the concentration range of the drug that is encountered clinically. It is also possible to use plasma clearance data to estimate intrinsic hepatic clearance (see Equation 6) for drugs that exhibit low plasma clearances. However, it is not possible to do this with drugs that exhibit high plasma clearances because concentration of drug in red blood cells could occur. In these cases, it is possible for plasma clearance to exceed plasma or blood flow to the eliminating organ because drug is being removed from both the plasma and the red blood cell.

the absorptive areas of the gastrointestinal tract. Therefore, drugs that are introduced into the body orally reach the liver before entering the systemic circulation. For drugs that are slowly cleared by the liver, the position of the liver between the portal and systemic circulations is of minimal importance: The availability of a drug is not altered appreciably if it is poorly extracted by the liver. For drugs that are highly extracted by the liver, the position of the organ relative to drug absorption is crucial: Entry into the systemic circulation may be negligible for drugs that are highly extracted by the liver. Furthermore, minor alterations in the ability of the liver to extract a drug can have a major influence on the bioavailability of a drug because of the relationship between the extraction ratio (ER) and the fraction of a drug (F) that traverses the liver ($F = 1 - ER$). A small reduction in the extraction ratio for a highly extracted drug (for example, from 0.95 to 0.90) may double the fraction of drug available from the gastrointestinal tract (F changes from 0.05 to 0.10). The relationship between extraction ratio and bioavailability is thought to account for the highly variable plasma or blood drug concentrations that are observed following the oral administration of a drug that is highly extracted by the liver (63). This variability may be accentuated in patients with hepatic impairment because the blood is shunted past functioning hepatocytes. The degree of shunting varies widely in individuals with acute and chronic hepatic disease, but it can be substantial. Using a selective percutaneous catheterization technique, Groszmann et al (64) reported that shunting of blood from the mesenteric vasculature in patients with hepatic disease averaged 61.9%, while blood from the splenic vasculature was shunted an average of 80.1% past the liver.

Although it is generally thought that hepatic blood flow is reduced in patients with hepatic disease, the data in Table 1 suggest that the influence of acute and chronic hepatic disease on hepatic blood flow is not readily predictable. Using clearance of galactose to estimate hepatic blood flow, Tygstrup & Winkler (65) reported that apparent liver blood flow was increased on average in a small number of individuals with either acute hepatitis or cirrhosis in comparison to healthy controls. Pessayre et al (66) reported opposite findings in individuals with chronic stable cirrhosis when they used hepatic extraction of indocyanine green to estimate liver blood flow. Other reports based on indocyanine green clearance measurements have generally confirmed these observations (67). However, both Lundbergh & Strandell (68) and Preisig et al (69) have reported that hepatic blood flow may be increased in individuals with acute viral hepatitis (Table 1). Using indicator dilution techniques, Cohn et al (70) demonstrated a statistically significant increase in hepatic blood flow in individuals with acute alcoholic hepatitis and chronic cirrhosis with and without enceph-

alopathy. The studies cited in Table 1 suggest that the influence of acute and chronic hepatic disease on hepatic blood flow may be highly variable and may, in turn, account for the high variability in clearance of drugs that are efficiently removed from the blood by the liver.

The reduction in clearance of drugs that are highly extracted by the liver may be attributed not only to alterations in hepatic blood flow, changes in $CL_{intrinsic}$. Drugs and other compounds that are highly extracted by the liver in healthy individuals may be poorly extracted in individuals with reduced hepatic function. This has been demonstrated for both indocyanine green and for the model drug *d*-propranolol (66, 77). Pessayre et al (66) suggested that the change in hepatic clearance of *d*-propranolol in individuals with cirrhosis could be attributed primarily to a reduction in $CL_{intrinsic}$ of the drug rather than to a reduction in hepatic blood flow. Changes in intrinsic eliminating capacity for drugs that are highly extracted by the liver must be substantial to be reflected in changes in systemic clearance (Equation 5). The finding

extracted drugs may be significantly correlated with clearances of poorly extracted drugs in both healthy individuals and patients with chronic liver disease suggests that hepatic disease may affect the intrinsic eliminating capacity of the liver for highly extracted drugs more profoundly than for drugs that are poorly extracted (72–75). One explanation for these observations, termed the intact hepatocyte hypothesis, is that hepatic disease reduces the total mass of functioning hepatocytes, but that these hepatocytes are normally perfused and function normally (75). According to this hypothesis, the reduction in clearance of highly extracted drugs may be attributed to blood that is shunted past normally functioning hepatocytes,

Table 1 Hepatic blood flow in acute and chronic hepatic disease

Disease	Hepatic blood flow (ml/min)		Reference
	Patients	Controls	
Hepatitis/ cirrhosis	1,695 (990–2,557)[a]	1,520 (670–3,100)	Tygstrup & Winkler (65)
Acute viral hepatitis	1,510 (890–2,430)	(930–2,130)[b]	Preisig et al (69)
Acute viral hepatitis	2,210 (± 340 SD)	1,440 (± 210 SD)	Lundbergh & Strandell (68)
Cirrhosis	980 (469–1,771)	1,750 (966–2,688)	Pessayre et al (66)
Cirrhosis	1,658 (586–3,090)	1,352 (1,120–1,552)	Cohn et al (70)
Alcoholic hepatitis	2,288 (1,050–3,380)	1,352 (1,120–1,552)	Cohn et al (70)
Cirrhosis/ hepatic coma	1,812 (825–3,340)	1,352 (1,120–1,552)	Cohn et al (70)

[a] Mean (range).
[b] Mean not provided.

while the reduction in clearance of poorly extracted drugs is attributable to the reduced mass of functioning hepatocytes. Because there may be a relationship between the degree of shunting and the reduction in functioning hepatocyte mass (62), a correlation may be observed between clearances of drugs that are highly and poorly extracted by the liver.

The data in Table 2 present the results of clinical studies of drug disposition in individuals with acute and chronic hepatic disease in comparison to control populations. Although numerous investigations have defined influence

inclusion in Table 2 represent those that provide at least estimates of clearance, volume of distribution, and half-life. The data in this table are presented as the ratio between the mean value for the pharmacokinetic parameter observed in the patient study population (numerator) to the mean value for the kinetic parameter observed in the control study popula-

Table 2 The influence of hepatic disease on drug pharmacokinetics[a]

Drug	Disease[b]	*n*	Half-life ratio	Volume ratio	Clearance ratio	Reference
Highly extracted drugs						
Lidocaine	C	8	3.17[c]	1.31 ($V_{d\beta}$)	0.57[c]	Thomson et al (26)
Lidocaine	AVH	6	1.78	1.30 (V_{dss})	0.65	Williams et al (78)
Meperidine	C	10	2.19[c]	1.38 (V_{dss})	0.50[c]	Klotz et al (76)
Meperidine	AVH	14	2.07[c]	0.94 (V_d)	0.51[c]	McHorse et al (77)
d-Propranolol	C	14	2.66[c]	1.0 ($V_{d\beta}$)	0.38[c]	Pessayre et al (66)
Poorly extracted drugs						
Ampicillin	C	9	1.45[c]	3.03 (V_{dss})	0.82	Lewis & Jusko (86)
Amobarbital[d]	C	5	1.87[c]	1.0 (V_{dss})	0.45[c]	Mawer et al (85)
Antipyrine	C	5	1.90[c]	0.90 (V_d)	0.59	Branch et al (89)
Diazepam	C	9	2.27[c]	1.53 (V_{dss})	0.52[c]	Klotz et al (79)
Chlordiazepoxide	C	8	2.63[c]	1.45 (V_{dss})	0.50[c]	Roberts et al (80)
Hexobarbital	AVH	13	1.88[c]	1.00 (V_{dss})	0.54[c]	Breimer et al (84)
Hexobarbital	C	8	1.49[c]	0.91 (V_{dss})	0.57[c]	Zilly et al (83)
Lorazepam	AVH	9	1.13	1.19 ($V_{d\beta}$)	0.99	Kraus et al (82)
Lorazepam	C	13	1.44[c]	1.57[c] ($V_{d\beta}$)	1.08	Kraus et al (82)
Oxazepam	AVH	7	1.04	1.08 ($V_{d\beta}$)	1.21	Shull et al (81)
Oxazepam	C	6	1.04	1.00 ($V_{d\beta}$)	1.14	Shull et al (81)
Prednisolone	CAH	6	0.91	0.99 (V_d)	1.10	Schalm et al (88)
Theophylline	C	9	3.82[c]	1.54 (V_{dss})	0.68[c]	Piafsky et al (90)
Theophylline	C	8	4.67[c]	1.17 (V_d)	0.29[c]	Mangione et al (91)
Tolbutamide	AVH	6	0.68[c]	1.00 (V_d)	1.44[c]	Williams et al (92)
Warfarin	AVH	6	0.92	0.90 (V_d)	1.00	Williams et al (87)

[a] Numerals indicate the ratio between the mean value of a pharmacokinetic parameter in individuals with a specific hepatic disease to the mean value observed in healthy control subjects.

[b] C = cirrhosis; AVH = acute viral hepatitis; CAH = chronic active hepatitis.

[c] Difference between mean values in the pharmacokinetic parameter between the patient and control study populations was statistically significant ($p < 0.05$).

[d] Values based on unbound drug concentration.

tion (denominator). In the first part of Table 2, data for three highly cleared drugs in individuals with acute viral hepatitis or cirrhosis are presented. It is apparent from these data that the influence of both acute and chronic hepatic disease on the disposition of meperidine, lidocaine, and *d*-propranolol is remarkably consistent. In each instance the clearance of drug is reduced by approximately 50% (38–65% range) while drug half-life increases two to three times. No consistent or statistically significant changes in the volume of distribution of these highly cleared drugs were observed in these studies. With a single exception, the changes in clearance and half-life are statistically significant. In the study of Williams et al (78), the clearance of lidocaine was reduced in four of six individuals during the acute phase of viral hepatitis in comparison to values observed during the recovery phase. Clearance of the drug did not change in one individual and actually increased in another individual during the acute period. Because of the small number of individuals in this study, these alterations in drug clearance in two of six individuals was sufficient to preclude statistical significance, although the trend in the data is consistent with the studies reported for meperidine, *d*-propranolol, and lidocaine (Table 2).

Hepatic Eliminating Capacity and Poorly Extracted Drugs

Most of the therapeutically administered drugs that are eliminated from the body by the liver are slowly cleared from the blood. Data for the disposition of these drugs in individuals with acute and chronic hepatic disease are shown in the remainder of Table 2. It is again apparent from these data that both acute and chronic hepatic disease may alter significantly the disposition of drugs that are poorly extracted by the liver. Furthermore, it is apparent that this influence is similar to that observed for drugs that are highly extracted by the liver (Table 2). For diazepam, chlordiazepoxide, hexobarbital, amobarbital, antipyrine, and theophylline, the presence of acute and chronic hepatic disease appears to reduce plasma clearance by approximately 50% (29–68% range) without significantly altering volume of distribution. The change in clearance without apparent change in volume of distribution results in a prolongation of half-life for these drugs. For oxazepam, lorazepam (in acute viral hepatitis), warfarin, and prednisolone, hepatic disease did not produce alterations in drug disposition. When lorazepam and ampicillin were administered to individuals with chronic liver disease, drug volume of distribution increased without a corresponding change in drug clearance, producing a prolongation in drug half-life. Tolbutamide clearance increased and half-life diminished without change in volume of distribution in individuals with acute viral hepatitis (see below).

The data in Table 2 for poorly extracted drugs are not as consistent as the data for highly extracted drugs. Because plasma clearance for poorly extracted drugs may be used to estimate intrinsic hepatic clearance

($CL_{intrinsic}$), the data in Table 2 suggest that the influence of hepatic disease on the intrinsic capacity of the liver to eliminate a drug may be highly variable.

Protein Binding and Hepatic Disease

The importance of drug protein binding on the pharmacokinetics and pharmacodynamics of drugs in patients with hepatic impairment has recently received particular emphasis as a consequence of physiologic models of organ elimination. According to the physiologic model described in Equation 4, the fraction of drug unbound in blood or plasma will be directly related to the hepatic clearance of drugs that are slowly cleared from the blood by the liver. In the absence of changes in clearance based on unbound drug concentration (equal to intrinsic hepatic clearance), increase or decrease in the fraction of drug unbound in blood will produce corresponding changes in drug clearance. Although total blood (or plasma) clearance will change with changes in protein binding, the concentration of unbound drug in blood or plasma theoretically should not (100,101). Assuming that free rather than total drug concentration determines pharmacologic effect, changes in protein binding for drugs that are poorly extracted by the liver will be manifested by a change at steady state in total blood drug concentration but not in unbound drug concentration or in pharmacologic effect. Conversely, for drugs that are highly extracted by the liver, changes in protein binding should not result in changes in blood clearance (Equation 5), but may result in changes in free drug concentration in blood. Changes in protein binding for these drugs may therefore result in changes in pharmacologic effect, which will be manifested as a change in sensitivity at a given blood drug concentration.

The data in Table 3 (102) summarize the influence of hepatic disease on drugs that are highly and poorly extracted by the liver and are eliminated from the body primarily by this organ. It is apparent from these data that acute and chronic liver disease may substantially alter the binding of drug to plasma and tissue components. The protein binding data for tolbutamide, from the study of Williams et al (92) (see Table 3), relates to the observed change in clearance of this drug in individuals with acute viral hepatitis, as shown in Table 2. In this study, when clearance based on unbound drug concentration was calculated, no significant change in this pharmacokinetic parameter was observed in the participants during the acute, compared to the recovery, phase of illness. This finding
clearance of tolbutamide in individuals with acute viral hepatitis may be attributed solely to the change in plasma protein binding. The importance of changes in drug binding to plasma or blood constituents, relative to changes in clearance and volume of distribution, has been the subject of several recent reviews (100, 101, 103, 104).

Table 3 Hepatic disease and drug protein binding[a]

Drug	Disease[b]	Percentage increase in fraction unbound	Reference
Highly extracted drugs			
Lidocaine	AVH	No change	Williams et al (78)
Meperidine	AVH	No change	McHorse et al (77)
Morphine	AVH/C	15	Olsen et al (94)
Propranolol	AVH/C	38	Branch et al (93)
Poorly extracted drugs			
Amobarbital	AVH/C	38	Mawer et al (85)
Diazepam	C	210	Klotz et al (79)
Diazepam	C	65	Thiessen et al (95)
Phenylbutazone	C	400	Wallace & Brodie (98)
Phenylbutazone	AVH/C	500	Held et al (99)
Phenytoin	AVH	33	Blaschke et al (96)
Phenytoin	C	40	Affrime & Reidenberg (97)
Quinidine	C	300	Affrime & Reidenberg (97)
Tolbutamide	AVH	28	Williams et al (92)

[a] Adapted from Blaschke (102).
[b] AVH = acute viral hepatitis; C = cirrhosis.

SUMMARY AND CONCLUSIONS

Clinical pharmacokinetic studies have now documented that the influence of cardiac and hepatic disease states on drug absorption, distribution, and protein binding may be substantial. These observations, together with the information that has been found using physiologic models of organ elimination, have greatly increased our understanding of drug pharmacokinetics in disease states. The development of physiologic models of organ elimination has served to identify the importance of specific physiologic variables of drug absorption and disposition. Although the data concerning the influence of cardiac disease are somewhat preliminary, evidence now available suggests that the influence of hepatic disease on drug disposition may be more consistent than has been previously recognized. For several drugs, clearance is approximately halved in individuals with either acute or chronic hepatic illness, while half-life is prolonged. Volume of distribution of these drugs does not change. For other drugs, there may be no apparent influence of hepatic disease on drug disposition, or the influence is not easily predicted. The data in Table 2 permit the clinician to choose drugs and dosing regimens for patients with hepatic impairment with greater confidence. These data, however, represent only guidelines. The high degree of variability in pharmacokinetic parameters between individuals (or even

within a single individual over time) requires that close patient observation and performance of plasma or blood drug concentration determinations be maintained after a dosing regimen has been instituted in patients with hepatic disease. Because half-life of many drugs is prolonged in individuals with both cardiac and hepatic impairment, the time for close monitoring of patients should be extended to allow achievement of steady state blood-drug concentrations.

Despite the information that is now available regarding the influence hepatic and cardiac disease on drug absorption and disposition, the data base for drug pharmacokinetics in individuals with cardiac or hepatic disease should be extended. Further research is necessary to understand why the influence of hepatic disease may vary not only between different drugs, but also between individuals receiving the same drugs. The influence of a hepatic disease over time in a single individual also requires further investigation. Studies of the influ

must be coupled with carefully performed pharmacokinetic investigations. Adequate pharmacokinetic description of a drug in individuals with cardiac or hepatic disease requires determination of drug clearance and one or more volumes of distribution and half-lives. Determinations of drug protein binding in serum or plasma, as well as blood-to-plasma drug ratios, may be necessary. Because of the influence of age, sex, smoking, diet, and other factors on drug absorption and disposition, study and control populations must be carefully matched to achieve valid conclusions.

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