PHARMACOKINETICS OF DRUG DISPOSITION: HEMODYNAMIC CONSIDERATIONS

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Over the past several years, the quantitative study of the time course of drug absorption, distribution, metabolism, and excretion has become an important and valuable tool in the study of the characteristics of drug action, and several pharmacokinetic texts (1–9) have become available since Wagner's review covering the literature up to 1966 (10). Because of the complexities of biological systems from the subcellular level to the entire organism, the mathematical approaches for studying the processes of drug disposition have been a compromise between hopeless complexity and oversimplification. With few exceptions, most investigators have used compartmental analysis, conceiving the body to consist of kinetically distinct compartments interconnected by, usually first-order, mass transfer constants. From a purely descriptive standpoint such an approach is frequently satisfying but, unfortunately, such empirical techniques reveal little of the underlying biological factors that control the relationship(s) between the measured input and output functions after drug administration. It is readily apparent, however, that the body is nonstationary; its response to a given input changes from moment to moment and may be modified by many factors including physiological, drug, and disease states. Classical pharmacokinetics is of little value in explaining or predicting the effects of biological perturbations and, therefore, over the past few years there has been an increased awareness of the quantitative consequences of changes in physiological parameters upon drug disposition. The purpose of this review is to highlight the role that one major physiological variable, hemodynamics, can have on the overall fate of a drug introduced into an animal or human. Awareness of the role and importance of this factor will hopefully lighten the darkness with which we perceive the black box of pharmacodynamics.

DRUG ABSORPTION AND DISTRIBUTION

In considering drug absorption and distribution, pharmacologists have to a large extent concentrated their interest on the membrane aspects of the phenomena

involved and have successfully delineated the major characteristics of a drug that determine its ability to cross a given biological membrane(s) (11). However, this largely physicochemical emphasis, and its extension to the concept of partitioning a drug between the blood and tissues, has frequently overlooked the fact that the rate of delivery and/or removal of drug is an important factor in the rate and extent of disposition within the whole animal.

Although the blood serves as the physiological medium of translocation and exchange for all tissues, each tissue has access only to a particular quota of blood. Therefore, drug uptake and washout may be at quite different rates for tissues with different blood flows, even though tissue volumes and partitioning characteristics may be identical. In his classic paper, Kety (12) recognized this phenomenon but because of the then overwhelming mathematical obstacles he was unable to integrate it into an appropriate mathematical description of anesthetic uptake. Subsequent investigators, utilizing analog and digital computers, were able to account for the differential perfusion of tissues and found that in many instances the body could be conceived as being comprised of four major lumped tissue groups differing in their perfusion and/or partition characteristics; vascular-rich group, muscle group, fat group, and vascular-poor group (13–16). For very lipid-soluble compounds, diffusion between neighboring tissues having different perfusion/partition properties could occur (17). Such models of drug distribution proved valuable to describe not only the behavior of anesthetic gases but also the action of drugs such as thiopental (13, 14) where the perfusion characteristics of the brain are instrumental in controlling the intensity and duration of action after acute administration of the drug.

The importance of perfusion on the alveolar uptake and cerebral distribution of a number of anesthetic gases has been well demonstrated by simulations (16, 18, 19). Increased perfusion of the pulmonary tissue by increasing the cardiac output leads to an enhanced uptake of anesthetic into the sytemic circulation, whereas lowering the output has the opposite effect, the changes being most pronounced with those gases exhibiting the greatest solubility in the blood. Changes in the subsequent distribution of the anesthetic to the tissues and in the induction of anesthesia depend upon the assumptions concerning the manner in which the cardiac output is distributed, tissue perfusion changing proportionally or nonproportionally with cardiac output. An excellent review of these hemodynamic and also ventilatory factors in anesthetic uptake and action has recently been published (20). The principles established by these simulations provide explanations for the observation of a more rapid increase in alveolar halothane concentration in infants and children compared to adults (21, 22) and for a similar phenomenon with various anesthetic gases in different animal species of widely divergent body weight (23): cardiac output and tissue perfusion is greater relative to body mass in the smaller animals (24, 25).

Inhalation anesthetics are a rather specialized group of drugs but the principles related to perfusion of the site of uptake appear to be valid for other routes of absorption. Since the effect of blood flow on the rate of oral (26, 27) and intramuscular (28, 29) absorption of drugs has recently been discussed, no further consideration is given to these areas except to note that at these sites the role of perfusion in drug transport is similar to that at any blood/membrane interface. Namely, the absorp-

tion of compounds with high membrane permeabilities such as very lipid-soluble or pore-diffusible substances are perfusion-limited whereas the absorption rates of drugs possessing low permeabilities are independent of blood flow.

Once within the body the distribution of a drug may depend upon tissue perfusion, although the ability to recognize such a phenomenon is impaired by the inadequacy of the assessment of distribution to the various tissues by the kinetic constant, volume of distribution. Nevertheless, profound changes in distribution have been reported to be associated with alterations in hemodynamics. Patients with congestive heart failure have almost double the plasma concentration of lidocaine than normal subjects receiving the same intravenous dose, and this is associated with a decreased initial distribution space and volume of distribution at steady-state (30, 31). Altered perfusion of the body tissues via a reduced cardiac output appears to play a dominant role in these observations as subsequent studies in the rhesus monkey, hemorrhaged to reduce tissue perfusion, produced similar results and, more significantly, pretreatment of the animals with isoproterenol increased cardiac output and led to an increase in the volume of distribution (32). Cardiac failure produces a similar decreased distribution of procainamide (33), and higher than usual blood levels of quinidine have been reported after administration of standard doses of this drug to these patients (34, 35). Differences in circulation velocities (cardiac output/blood volume) also account for the large interspecies differences in the disposition of methotrexate where distribution and elimination are predominantly perfusion-limited (36, 37). Thus, from a pharmacokinetic standpoint, one minute in the life of a mouse is equivalent to about 8 minutes for man and 16 minutes for the sting ray. An interesting possibility arises if a drug has cardiovascular activity leading to alteration in tissue perfusion, because with increasing dose, and thus effect, there is the potential for the drug to influence its own distribution. Such a mechanism has been postulated to explain the dose-dependent distribution of oxotremorine and the absence of this phenomenon if the peripheral cholinergic effect, predominantly the profound hypotension, are blocked (38). A similar feedback control of drug uptake and distribution based upon the effects on cardiac output and distribution of organ blood flow produced by halothane anesthesia (39) has been investigated (40–43).

DRUG METABOLISM

Clearance Concepts

Removal of a drug from the circulation by an organ such as the liver and its subsequent conversion to another chemical entity is generally referred to as drug metabolism, despite the fact that the actual biochemical transformation may not be rate-limiting in the overall process. The in vivo quantification of drug metabolism has been a long-standing problem. Use of a first-order rate constant, or its equivalent half-life, as estimated from the terminal portion of plasma concentration or urinary excretion time profiles, even if corrected for multicompartmental distribution of the drug (3, 5), is entirely empirical, and dependent upon drug distribution as well as elimination. Because of this, an increasing emphasis has been placed upon the

estimation of the mean hepatic clearance of a drug (44, 45) as this value, equivalent to the volume of blood or plasma from which drug is completely removed in unit time (46), is considered a measurement of the physiological efficiency of the liver to irreversibly remove drug, independent of other disposition processes. For example, good agreement was found between the in vitro clearance of a number of drugs in the isolated perfused rat liver and their in vivo clearance whereas significant differences were apparent in the half-lives; even better correlations might have obtained if earlier in vitro samples had been taken and the blood/plasma concentration ratio determined (47).

Many investigators measure the plasma concentrations of a drug and therefore estimate plasma clearance; however, the question of plasma versus blood clearance must always be raised. Generally, the choice largely depends on the ultimate use of the information (27, 44) but blood clearance seems the more appropriate parameter for physiological interpretation of clearance. This is because drug is delivered to the clearing organ by the blood which, from a mass transfer standpoint, usually functions as a single compartment; drugs equilibrate sufficiently rapidly between the erythrocytes and the plasma so that any drug in the red blood cells is available for clearance. Thus, propranolol (48, 49) and nortriptyline (50) are almost completely extracted by the liver despite their extensive distribution in the erythrocytes. Also, the clearance of certain amines by the kidney (51) and the gastric excretion of others (52) exceeds their rate of drug delivery by the plasma. For compounds which distribute poorly, if at all, into the erythrocytes, e.g. highly bound drugs, an estimated plasma clearance may be related to plasma flow through the clearing organ(s), and when a drug partitions equally between the plasma and the red blood cells, plasma clearance is as valid as blood clearance, although the latter is still the parameter that must be compared to organ blood flow. In general, however, it is incorrect to relate plasma clearance to plasma flow; blood clearance must be used, necessitating either direct determination or knowledge of the plasma clearance and the blood/plasma concentration ratio over the plasma concentration range studied. Glomerular filtration of drug is a special case as this process occurs without disturbing the equilibrium of drug between plasma water, binding sites, and erythrocytes.

Consideration should also be given to the source of any drug cleared by an organ. It is well accepted that glomerular filtration is limited to substances present in the plasma water whereas the active processes in the proximal renal tubule are capable of secreting drug originally bound to various plasma macromolecules (11). Similarly, drug metabolism is generally regarded as being limited to the unbound fraction of the drug, and hence the blood clearance of a compound should be equal to the rate of delivery of unbound drug to the metabolizing organ(s). Although there are a number of examples where this situation exists (53), it is becoming apparent that plasma binding of a drug may not limit its removal by the liver. A hepatic blood clearance exceeding the delivery rate of unbound drug implies that some fraction of the bound drug must dissociate during passage through the liver. Propranolol (54), bromosulfophthalein (55), meperidine (56), lidocaine (30, 31), and probably chlorpromazine and nortriptyline (54) are among those drugs with this characteris-

tic. The relative contribution of the various free and bound moieties has not been extensively investigated; with propranolol (54) and meperidine (56) the data are consistent with almost complete hepatic extraction of all delivered drug irrespective of binding. On the other hand, the splanchnic uptake in sheep of hydrocortisone, 80% of which is attributable to the liver (57), appears to be derived of 42% from unbound, 31% from albumin-bound, and 27% from transcortin-bound steroid (58). This type of information may contribute to the clarification of the effects of alterations in binding on drug disposition in general. When clearance is restricted to the unbound drug then increasing this fraction will lead to an increase in metabolic clearance and a shortening of the elimination half-life, e.g. diphenylhydantoin (59) and warfarin (60), although distributional changes may offset the latter change (61). On the other hand, for a drug where both bound and unbound moieties are completely extracted, a decrease in the extent of binding should have no effect on the metabolic clearance, and the half-life may increase since distribution is often a function of plasma binding, e.g. propranolol (54). If only a fraction of the bound drug is cleared then the changes in clearance and elimination rate resulting from altered binding will be more difficult to predict and will depend on the relative contribution of each moiety.

Clearance and Blood Flow

Despite the value and importance of the clearance concept in understanding the control of blood/plasma concentrations after drug administration there has been increasing awareness of its limitations as an index of the functional competence of an organ, the liver in particular. The rate of drug delivery to the organ is also involved in clearance since the latter reflects both removal of drug, expressed by the term extraction ratio, and the blood flow to the organ.

The physiological literature contains early references to the role of hepatic circulation in controlling removal of substances from the bloodstream by the liver, and in fact most of the pertinent principles were defined by these investigators. In the isolated perfused rat liver preparation, the clearance of chromic phosphate colloid (62–64) and bromosulfophthalein (64, 65) was found to be a function of the rate of organ perfusion. Dobson (66) suggested a role for hepatic blood flow in controlling the clearance of vasopressin, adrenoglomerulotropin, and aldosterone, and evidence in man for the latter has been presented (67). The application and relevance of these findings to the disposition of therapeutically useful drugs has been limited. In the dog the elimination half-life of hydrocortisone was significantly affected by the degree of hepatic arterialization (68) and the hepatic clearance in the sheep was a function of liver plasma flow (57). A positive relationship was also found between the liver blood flow and the hepatic removal rate of oxyphenbutazone (69). It was suggested that the profound decrease in the plasma clearance of lidocaine in patients with heart failure (30, 31) was a result of diminished hepatic blood flow. This was supported by the finding in such patients of a reduction in this value proportional to the decrease in cardiac index, resulting in increased steady-state arterial concentrations of the drug (70). Some of the above investigators (57, 62–65, 69, 71) also

noted that changes in hepatic perfusion led to varying alterations in the efficiency of organ uptake, the extraction ratio decreasing as a consequence of increased blood flow.

A few limited theoretical analyses have attempted to evaluate the role and importance of liver blood flow in the hepatic clearance of exogenous compounds (61, 64, 72–74), but only recently has a useful, general unifying concept been postulated. Based upon a perfusion model with first-order elimination and distribution equilibrium of drug between the emergent venous blood and the tissue, Rowland et al (45) showed that the interrelationships between organ blood flow, clearance, and extraction ratio could be described by equation 1.

$$\text{organ clearance} = \left[Q \frac{C_{\text{intrinsic}}}{Q + C_{\text{intrinsic}}} \right] \qquad 1.$$

where Q indicates the organ blood flow and $C_{\text{intrinsic}}$ refers to intrinsic maximal capacity of the organ to remove drug by all pathways in the absence of any flow limitations. This parameter, a distinctive characteristic for any particular drug in a given situation, reflects 1. the partitioning of the drug into the organ from the blood, 2. the size of the organ, and 3. The intrinsic overall rate of elimination by the biochemical processes, i.e. V_{max}/K_m. The fractional term of equation 1 is equivalent to the extraction ratio; thus, actual organ clearance and extraction are dependent on both independent variables: $C_{\text{intrinsic}}$ and organ blood flow. As flow increases, the measured drug clearance increases in a fashion analogous to a cumulative exponential with an asymptote equivalent to $C_{\text{intrinsic}}$ (75). However, with respect to the liver, physiological limitations exist on the range and magnitude of the hepatic blood flow. Accordingly, the behavior of a particular drug will depend on the relative values of $C_{\text{intrinsic}}$ and the in vivo flow (Figure 1). When $C_{\text{intrinsic}}$ is very large compared to the flow, equivalent to an extraction ratio >0.8, actual clearance does not reflect the activity of the drug-metabolizing enzymes but rather the blood flow rate to the liver, and changes in this rate will produce almost proportional alterations in the measured clearance. On the other hand, when hepatic blood flow is much greater than $C_{\text{intrinsic}}$, equivalent to an extraction ratio <0.2, clearance is approximately equal to this parameter and is essentially independent of flow. For intermediate conditions, clearance is partly flow-dependent. For drugs of the former type, alteration in hepatic blood flow leads to relatively small but proportional changes in the extraction ratio, whereas in the case of drugs with low $C_{\text{intrinsic}}$ values, changes caused by flow tend to be compensated by an opposite and larger curvilinear alteration in the extraction ratio (Figure 2). The above concept appears to be entirely consistent with the limited published data in the drug literature and more recent experiments (cited herein) provide additional verification and illustrate the value of this approach to drug elimination studies.

VARIATION IN HEPATIC BLOOD FLOW The potential importance of liver blood flow in the hepatic clearance of drugs, particularly those with high extraction ratios, suggests that consideration of those factors involved in the control and magnitude of this parameter might clarify their respective roles in drug metabolism. Total

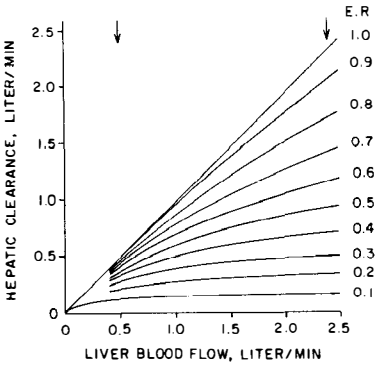

Figure 1 Relationship between liver blood flow and hepatic clearance for drugs with varying extraction ratios (ER). The arrows indicate the normal physiological range of liver blood flow in man and the extraction values refer to a normal flow of 1.5 liter/min.

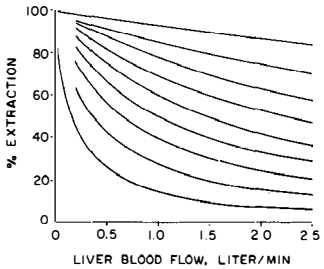

Figure 2 The effect of liver blood flow on hepatic drug extraction. The individual curves reflect 10% stepwise changes in extraction at a normal flow of 1.5 liter/min and therefore each is complimentary to the equivalent curve in Figure 1.

hepatic blood flow in most animal species is generally considered under resting conditions to approximate 25% of the cardiac output and of this 25–30% is supplied by the hepatic artery and the remainder by the portal vein (76). Furthermore, the total splanchnic circulation is quantitatively the major site of redistribution of blood flow during metabolic stress (77). Thus, changes in cardiac output and/or distribution of the output to the liver are responsible for the wide variations that occur in the blood flow to this organ. Factors regulating both values are generally extrahepatic and have recently been summarized (25, 77); hence, mention is made only of some for which correlative drug metabolism information is available.

Physiological variations Exercise and thermal stress both can produce large increases in cardiac output, but fractional redistribution usually leads to a reduction in hepatic blood flow (77). In humans, both stresses lead to a 40–60% impairment in the hepatic removal of indocyanine green and, as only insignificant drug distributional changes occur, this leads to an approximate doubling of the elimination

half-life (78, 79). In addition, the effects are additive (79). A similar situation should apply to any drug with a comparably high extraction ratio despite the fact that the hepatic removal of this dye reflects uptake by the binding protein, ligandin (80), and subsequent biliary excretion (81). On the other hand, the plasma clearance of antipyrine is unaffected by a combination of these stresses (79), an expected finding as the hepatic extraction of the drug is low. Changes in the distribution of antipyrine (79) are probably related to shifts in body water and perhaps hemodynamic redistribution (see above).

Change in posture from the supine to upright position may decrease cardiac output 5–20%, which leads to a significant reduction in hepatic blood flow (82). A twofold difference exists in the metabolic clearance of aldosterone between these two positions when they have been established for several hours. Also, adaptation to the supine position is not rapid (67). Of interest to all pharmacokinetic studies is the finding of smaller interindividual variation in clearance in the upright position compared to an overnight supine state. The pharmacokinetic implications of bed rest have been briefly alluded to previously (83) but greater attention may need to be given to the matter if a drug has a high hepatic clearance.

Ingestion of food can significantly increase the total splanchnic blood flow (84) and the direct effect of this on drug absorption has been indicated above. However, a further complicating factor arises because the systemic availability of a drug after oral administration depends on its hepatic extraction ratio (44, 85). Consequently, increasing or decreasing the hepatic blood flow by food intake, which then leads to alterations in extraction, may cause changes in the amount of drug escaping the first-pass effect, and the greater the extraction ratio, the larger this effect.

The fractional organ composition of the body is remarkably constant throughout the mammalian kingdom, but biochemical and physiological functions are frequently a function of body weight less than unity (86). Consequently, values such as cardiac output and organ perfusion rates are greater in small animals than large, when compared on a body weight or organ basis (87–89). Hence, for a drug whose hepatic clearance is flow-dependent, the difference in physical size of an animal may account, in part or in full, for intra- or interspecies variations in the rate of drug metabolism rather than the often invoked reason of differences in the reaction velocities of enzymatic processes (90). Some examples of this concept with respect to various anticancer agents have been presented (91). The differences in the total body clearance of propranolol in human and dog (49) can be explained on the basis of hepatic perfusion, and undoubtedly many other examples exist. Consideration should therefore be given to the organ perfusion characteristics in comparative drug metabolism studies. Reference has already been made to the concept of an equivalent time-scaling factor, and use of body surface area may be of value in this regard (36, 91).

Pathological variations A number of different pathological conditions are known to alter cardiac output and/or blood distribution leading to changes in hepatic blood flow (25, 77, 89) but definitive data on the effects of these changes on drug metabolism is limited. Most information concerns factors leading to an impairment of organ

perfusion presumably because this leads to unexpected drug accumulation and toxicity.

Evidence exists that congestive heart failure results in a decreased hepatic clearance of a number of compounds, and this is probably related to the perfusion changes that occur in the splanchnic circulation (77). The plasma clearance of lidocaine in patients with cardiac failure is reduced to about 50–60% of the value determined in normal volunteers (30, 31). Because the distribution of the drug is also altered (see above) no significant change is seen in the terminal elimination half-life after intravenous administration, an excellent example of the limitation of this parameter to measure hepatic drug removal and metabolism. Similar effects on the clearance of another highly extracted compound, aldosterone, have also been reported (92). The latter study provides a cautionary reminder that a decrease in clearance may also arise from an impairment in hepatic extraction, a phenomenon that may also be associated with congestive heart failure.

The same problem of separating the relative contributions of flow and extraction in an observed impairment of hepatic clearance also exists when considering the effects of liver disease(s) on the metabolism of drugs that normally have a high extraction ratio, for example lidocaine (31) and meperidine (56). Damage to the liver may well lead to an impairment of the intrinsic drug-metabolizing activity, reflected by $C_{\text{intrinsic}}$, but the alterations in total hepatic blood flow and the presence of portasystemic shunting (93, 94) considerably complicate the assessment of the biochemical change; in the presence of decreased blood flow, clearance considerations overestimate the actual impairment.

A reduction in blood volume as a result of shock of varying etiology has a profound effect on hemodynamics (25, 76, 95), and drastic alterations in hepatic clearance can occur. Again problems arise in attributing the latter to perfusion changes, which alter drug delivery and extraction, or to reduced oxygen supply to the liver and the mixed function oxidase system(s). The latter was suggested to explain the effect of hemorrhage on the rate of hexobarbital metabolism in the dog (96). On the other hand, the hepatic clearance of indocyanine green is decreased in patients with circulatory shock (97),and 30% hemorrhage in the rhesus monkey leads to a 46% decrease in the clearance of lidocaine (32).

Drug interactions A variety of mechanisms may be responsible for alteration of a drug's elimination by a second drug (98), and changes in the rate of delivery of a drug to its site of elimination, producing a hemodynamic interaction, may play a significant role in certain drug/drug interactions. In the dog a 50% increase in the half-life of lidocaine was noted when *dl*-propranolol was administered (99). No discernible change occurred in the extraction ratio but hepatic clearance, cardiac output, and liver blood flow were significantly reduced. Since the pharmacologically inactive *d*-isomer caused no change in any of the above parameters, the prolongation of the half-life was ascribed to the alterations in hemodynamics. The same explanation was suggested to explain the results of a similar study in the dog with oxyphenbutazone (100). In this case, prolongation in half-life and impairment of clearance were smaller and accompanied by an increase in hepatic extraction; obser-

vations entirely predictable from equation 1 as the extraction ratio was between 0.1 and 0.2. A unique example of a hemodynamic interaction leading to an impairment of clearance appears to result from the pharmacological effect of *l*-propranolol upon its optical isomer. In the monkey, the clearance of *dl*-propranolol is about 25% lower than that of *d*-propranolol and there are small, but borderline, differences in the extraction ratios (101). The difference in clearance is accompanied by an almost identical difference in hepatic blood flow attributable to the selective β-adrenergic blocking action of the *l*-isomer, which causes a reduction in cardiac output and decreased blood flow to all organs except the brain (102). It was suggested, therefore, that the elimination of *l*- and *dl*-propranolol reflects drug clearance under the hemodynamic influence of the *l*-isomer. In other animal species including human, where the hepatic extraction approaches 90–100% (49), the hemodynamically produced differences in elimination should be greater. Significantly, after oral administration, *d*-propranolol has a shorter half-life than either *l*- or *dl*-propranolol (103), and hepatic blood flow considerations offer an attractive and quantitatively consistent alternative to the previously suggested explanation invoking stereospecific metabolism (103).

A drug's clearance may also be enhanced by changes in hemodynamics. Thus glucagon causes dose-related changes in cardiac output and total liver blood flow in the monkey which lead to an increase in the clearance of *d*-propranolol (104). The rather specific effect upon splanchnic blood flow led to the suggestion that glucagon might have clinical possibilities in the treatment of drug intoxication by drugs exhibiting blood flow-dependent elimination such as the tricyclic antidepressants. Similar studies with dopamine demonstrated inconsistent changes in hepatic hemodynamics but renal blood flow increased (105). Interestingly, dopamine causes an increase in the renal excretion of phenobarbital in the intoxicated dog (106). The importance of the extraction ratio upon the magnitude of changes in clearance associated with alterations in blood flow is well demonstrated by consideration of the effect of phenobarbital pretreatment upon the elimination of antipyrine and *d*-propranolol in the monkey (107). Pretreatment leads to an increase in clearance and a decrease in the half-life of both drugs, an observation normally attributed to enzyme induction (108). While this does indeed occur, the contribution of this mechanism to the overall changes varies since phenobarbital also causes significant increases in hepatic blood flow (107, 109). Accordingly, only 43% of the increase in the clearance of *d*-propranolol, initial extraction ratio 0.56, could be attributed to an increase in $C_{\text{intrinsic}}$, a direct measurement of induction. The majority of the change (57%) resulted from an increase in the rate of drug delivery to the liver. On the other hand, the latter factor played a minor role (15%) in the changes observed with antipyrine since its initial extraction was only about 25%. Consequently, the effects of phenobarbital cannot always be attributed to enzyme induction; whether this is the dominant mechanism will depend on the initial ability of the liver to extract the drug.

The above investigations illustrate the principles and potential importance of hemodynamic interactions in disposition studies and, as many drugs have similar vasoactive characteristics, it is an area towards which greater consideration should

be given. In particular, the general anesthetics widely used in pharmacological investigations frequently affect organ perfusion rates (110). Mention has been made of the effect of halothane upon its own disposition (40–43) and presumably these changes would influence the pharmacokinetics of a concomitantly administered drug. In a similar fashion, the splanchnic and total metabolic clearance of hydrocortisone in the sheep is reduced by more than 50% during pentobarbital anesthesia (57). Hence, pharmacokinetics in an anesthetized animal or human may be considerably different from those established in conscious animals.

DRUG EXCRETION

The kidneys receive about the same fraction of the cardiac output as the liver but, because of autoregulatory mechanisms, total renal blood flow and glomerular filtration rate are maintained much more constant than is the hepatic blood flow. Nevertheless, changes in these parameters can markedly affect the excretion rate of drugs in a fashion similar to that described for the metabolic route of elimination. These effects will be more significant for drugs that are actively secreted and have a high renal clearance than for those that are simply filtered at the glomerulus. However, since the concepts and principles of altered hemodynamics and clearance are generally similar irrespective of the specific organ, no attempt is made to review specific examples.

PHYSIOLOGICAL MODELING

The effect of altered perfusion on drug uptake and/or clearance by a particular organ may be appreciated fairly readily and in isolation from the other disposition process occurring in different parts of the body. However, the underlying and causative factor for the change in perfusion may well have repercussions at these other sites. Integration of the overall in vivo response to hemodynamic changes is therefore difficult to conceptualize on an intuitive basis. Because of this, there has been increasing interest in the development and testing of mathematical models that permit investigation of the role of physiological factors in drug disposition and often lead to a better understanding of the biological factors controlling these processes. These models consist of anatomical and physiological parameters of organ size, blood flow, physicochemical plasma and tissue binding values, and kinetic constants for enzymatic processes such as metabolism and active transport. Simultaneous solution of the mass balance equations for each appropriately interconnected compartment provides various tissue concentration/time profiles after drug administration. As all of the model parameter values are physiologically meaningful, the model should *a priori* predict the in vivo situation.

Physiologists have long used such models for studying blood flow rates and volumes in the circulatory system, and the exchange of materials in capillaries (111–113). However, attention has been mainly directed towards the dispersion of an indicator within a particular vessel or organ in the absence of recirculation of the compound. Early attempts to develop a dynamic description of blood flow

distribution in the entire circulation have been reviewed (114) and useful models of varying sophistication described (114, 115). There is, however, one major distinction between these models and those subsequently developed to describe drug disposition; in the latter the time scale is often several orders of magnitude greater. As a consequence, the sophistication and complexity of the model can be considerably reduced but, more important, mass transfer resistance within the vascular beds can be considered to be negligible and flow-limited mass transport can be assumed. Expressed somewhat differently, effluent blood from an organ and the tissue may be regarded as being in equilibrium with respect to the diffusible drug moiety. Those drugs whose disposition has been modeled—anesthetic gases (16, 18, 19, 40–43), thiopental (13, 14, 116, 117), propranolol (118), ethanol (119), lidocaine (32), 1-β-D-arabinofuranosylcytosine (120), and methotrexate (36, 37, 87, 121–123) —are fairly lipid-soluble and therefore this assumption is probably valid, at least for the major organs. However, in the case of methotrexate, the transport of drug from the blood into the bone marrow, spleen, and small intestine is much slower than the rate of tissue perfusion and thus significant membrane resistance exists (123). This observation has been explained by the presence of a saturable membrane transport phenomenon and so a similar situation may apply to other drugs at other active uptake sites. Other assumptions implicit in physiological modeling include the constancy of organ flow rates and binding parameters, and a uniformity of the model compartments representing various individual or lumped organs as well as an absence of intertissue diffusion (17).

Parameter Values

Ideally, all of the values of the various model parameters are independently estimated; however, in practice, the precise information on the values is frequently deficient, and confidence in the data decreases in the order of organ size and perfusion characteristics, drug binding to the plasma and tissue, and enzyme kinetics.

With few exceptions, there is considerable anatomical regularity both within and between various species of mammals and, consequently, the volume fraction of the body occupied by individual organs is essentially independent of body size. Mapleson summarized the data on the tissue volumes in humans (15) and an updated collation of similar information has been published (124). Adolph's study provides considerable data on organ size in various other animals (86). As mentioned previously, organ perfusion rates as a function of organ or body weight usually decrease with increasing size, and reasonable information is available for various organ blood flows in humans (15, 124) and animals (87). It should, however, be realized that such values apply to an average resting animal and may not necessarily apply to a given individual or group of animals under the experimental conditions employed. Nevertheless, the remarkable predictive capabilities of the perfusion-limited model to describe the blood and tissue levels of methotrexate in a variety of species (36, 37, 122) and lidocaine in the monkey and human (32) attest to the general validity of the physiological parameters and the overall modeling philosophy.

Drug distribution to the various organs involves multiple factors including binding to macromolecules in the blood and tissues that may be nonlinear, i.e. saturable,

or the binding capacity may be so high that linear partition occurs. Considerable data exist, or can be easily generated, with respect to drug binding in the plasma (125). Both linear (13, 14, 16, 18, 19, 36, 37, 40–43, 87, 121–123) and nonlinear binding with multiple sites (116, 117) have been successfully incorporated in the model, with the unbound drug being the diffusible moiety. On the other hand, little information is usually available on the kinetics of drug binding to tissue constituents, particularly over a wide concentration range. In general, linear binding has been assumed for the anesthetic gases (16, 18, 19, 40–43), thiopental (13, 14), lidocaine (32), ethanol (119), and 1-β-D-arabinofuranosylcytosine (120) based upon experimentally determined blood/tissue equilibrium concentration ratios generally obtained after a single acute dose of the drug. Initially, linear tissue binding was assumed for methotrexate (121) but further studies (87, 123) indicated the presence of a specific binding site in certain tissues that dominated uptake at low plasma concentrations. A similar situation was modeled for the tissue uptake of thiopental (116, 117) and for the hepatic extraction of propranolol by the isolated perfused rat liver (118). Quantifying tissue binding is difficult, and inter- and intraspecies differences may be present. Where such information is not available, the use of an empirical effective protein fraction has been advocated to produce the measured tissue concentration (116, 117).

Much of the success of the previously cited interspecies disposition correlations of methotrexate is due to the fact that the drug is cleared almost entirely by glomerular filtration, a process reflective of renal perfusion. When drug metabolism occurs an extra dimension is added to the problem. Although in vitro metabolic kinetic constants can be generated, their relevance to the in vivo situation is questionable as they may not be the rate-limiting factor (see above). The few studies involving significant metabolism have generally used an empirical approach in adjusting the appropriate model parameters to give good agreement between the model and experimental data (116–118). Reasonable in vivo kinetics are, however, predicted from the in vitro data for ethanol (119) and 1-β-D arabinofuranosylcytosine (120), but this is probably because of the insensitivity of the model to these parameters. Clearly, much more effort is required to delineate the quantitative aspects of in vivo drug metabolism.

Perspectives

Physiological modeling of the type reviewed above is a relatively new and different approach to the study of drug disposition and relevant information exists for only a few drugs. Further experience must be gained, particularly with respect to the validity of the frequent assumption of flow-limited transport, and to the sensitivity of the models to parameter perturbations, before the capabilities and limitation of the approach become adequately defined and appreciated. Most applications have been simulations using independently determined or assumed values for the model parameters. Attempts should be made to estimate some of the more critical values, such as in vivo Michaelis–Menten constants or binding parameters, by best-fit analytical solutions. Such information would be extremely valuable in establishing the validity of in vitro/in vivo correlations for the appropriate processes. Emphasis has also been placed on the use of average parameters determined independently and

often by other investigators. There is a need to investigate interindividual variability and determine the cause(s) of this. It may well be that only one or a few parameters are responsible for this variation, which would considerably simplify the prediction of a drug's pharmacokinetics in a given individual. A particularly useful application of physiological models is their ability to assess the contribution and importance of various complex and interrelated anatomical, physiological, physicochemical, and biochemical factors to the overall disposition of a drug. The self-depression of the uptake and distribution of halothane (40–43) is an excellent example of such an application and it provides information which would otherwise be almost impossible to obtain. In a similar fashion, a perfusion-limited model of the distribution and elimination of lidocaine has permitted investigation of the role of cardiovascular function on these processes (32). It would be useful to extend this approach to other physiological or pathological situations where biological properties may be altered.

Although there is frequently no necessity for such detailed information on drug disposition, and the classical pharmacokinetic approach is probably sufficient, physiological modeling has contributed and will continue to contribute to our understanding of the principles and concepts underlying the processes controlling the time course of drug distribution and elimination in animals and humans.

CONCLUSIONS

The history of pharmacokinetics is in many respects one of rediscovery of principles, concepts, and techniques attributable to a variety of disciplines. Thus it is not surprising that the role of hemodynamics in the body's handling of various substances is not conceptually new. However, its specific application to drugs and therapy has only recently begun to clarify certain aspects of our understanding of pharmacodynamics and to delineate more clearly the factors responsible for the sojourn of a drug in the body. This review has attempted to summarize the pertinent data available to illustrate how and why considerations of blood flow, particularly to sites of metabolism such as the liver, must be taken into account when investigating the disposition of a drug. Evidence exists to demonstrate that the clearance of highly extracted drugs is essentially perfusion-limited and even less efficiently extracted substances may well exhibit some flow-dependence. Definitive data upon the particular drugs that manifest these properties is slowly accumulating, and the routine estimation of hepatic blood clearance values, preferably after intravenous drug administration, would be of great value in this area. Our understanding of the quantitative role of hemodynamics in the other disposition processes such as drug distribution is less clear, and this may be an area where physiological modeling can make a significant contribution. In any case, a greater understanding and appreciation of the biological mechanisms and principles involved in experimentally determined phenomena, such as the various drug disposition processes, would appear mandatory if the interpretations that are placed upon values generated from a series of mathematical equations are to have any basis in reality.

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