

SPECIAL CONSIDERATIONS FOR DRUG THERAPY IN THE PATIENT WITH LIVER DISEASE

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THE ROLE OF THE LIVER IN DRUG DISPOSITION

The liver is responsible for over 600 diverse metabolic functions. Among them are the metabolism and elimination of compounds foreign to the body. In addition to the direct role of the liver in drug disposition, the sequelae of liver disease on body fluid compartments, acid-base and electrolyte balance, and renal function can contribute to changes in drug disposition and thus the generation of toxic drug concentrations and adverse effects.

Hepatic Clearance. The volume of blood cleared drug by the liver per unit time is determined by the degree to which the drug is protein-bound; drug delivery (blood flow) to hepatocytes; and the rate and extent of hepatic drug metabolism. Once cleared by the liver, a drug or its metabolite is then eliminated from the body by either biliary or renal excretion.

Protein – binding. Many drugs are able to circulate in plasma only when bound to plasma proteins. Weakly-acidic drugs (most common) tend to be bound to albumin whereas weak bases bind to α_1 -acid glycoproteins (eg, acute phase proteins). The former tends to decrease with chronic disease; the latter may increase, particularly with acute disease. Binding of drugs to proteins impairs hepatic clearance of "capacity-limited" drugs but may actually facilitate binding of "flow-limited" drugs (by aligning the drug for extraction). The impact of protein binding is relevant only for drugs highly (> 80%) protein bound since only then can the concentration of unbound drug be effectively increased by displacement. **Hepatic blood flow.** The portal vein provides 75% of blood flow to the liver with the remaining 25% provided by the hepatic artery. Because the portal vein drains the small intestine and a large portion of the large intestine, most orally administered drug in the normal animal is circulated to the liver prior to reaching systemic circulation. Initial exposure of drugs to hepatocytes can profoundly impact the amount of drug reaching target tissues. The impact depends on the rate at which hepatocytes remove, or *extract*, the drug from the portal blood. *Flow-limited* drugs are characterized by a very high rate (> 70%) of extraction or removal of the drug by hepatocytes during a single passage through the liver. The term "first pass metabolism" is used to characterize the kinetics of such drugs because most of the drug is removed the first time it passes through the liver. First pass metabolism of flow-limited drugs can markedly decrease the systemic bioavailability of orally administered drugs. In contrast to flow-limited drugs, *capacity-limited* drugs are characterized by a very inefficient rate of extraction; less than of the drug 30% is removed with each passage through the liver. Hepatic clearance proceeds at a maximum rate for such drugs regardless of how fast the drug is delivered to hepatocytes. Changes in hepatic blood flow will minimally influence clearance of such drugs. Unlike flow-limited drugs, the hepatic clearance of capacity-limited drugs is hindered by binding to plasma proteins. **Hepatic drug metabolism.** Those drugs which require hepatic metabolism in order to be eliminated from the body tend to be lipid soluble. Hepatic metabolism is generally accomplished in two phases. *Phase I metabolism* results in a chemical in the drug molecule, thus making it more susceptible to phase II metabolism. Phase I reactions are mediated primarily by cytochrome P450 (microsomal or mixed function oxidase) enzymes. The result of Phase I drug metabolism varies. Although commonly inactivated, a drug also can be activated to a metabolite of lesser, equal or greater activity (the parent compound is referred to as a pro-drug if it is inactive and its metabolite is active); or the drug can be converted to a toxic metabolite. Phase I metabolism is susceptible to changes induced by other drugs or disease. *Phase II metabolism* is a synthetic reaction in which a large, water soluble molecule is conjugated to a drug or its phase I metabolite, thus rendering the drug water soluble. Glucuronide and glutathione are important molecules to which drugs and phase I metabolites are conjugated. Compared to phase I metabolism, phase II metabolism is less susceptible to the effects of disease and other drugs.

EFFECTS OF LIVER DISEASE ON DRUG DISPOSITION

Measurements of Drug Disposition

The effects of liver disease on drug disposition have been documented through the use of pharmacokinetic studies which have mathematically modeled the behavior of a drug in the body. Such studies depend on measurements of parameters used to estimate drug movement throughout the body. Although estimates, these parameters can be used to predict changes in disposition that will necessitate modifications in a dosing regimen in the patient with liver disease. Parameters that are most useful include volume of distribution, (body) clearance, and elimination half-life.

The *volume of distribution* (V_d) is a theoretical volume of tissue to which a known amount of drug would have to be distributed in order to generate the plasma drug concentration measured at distribution equilibrium. Simplistically, the volume of distribution of a drug is the amount of tissue that will dilute the drug. The greater the dilution, the smaller the drug concentration in the plasma and target tissue and the higher the dose necessary to achieve a target concentration. The V_d may increase with sodium and water retention in patients with liver disease. Dehydration and increased protein-binding will decrease the volume to which a drug is distributed. Changes in volume of distribution should necessitate parallel changes in the dose of drug administered. V_d also affects drug half-life. Because a drug is removed from systemic circulation as its distribution volume increases, the drug is no longer available to the organs of clearance. Thus, although clearance (the volume of blood cleared of drug) may not decrease, the rate of elimination will. Thus, as the V_d increases, drug elimination half-life also increases.

Clearance is the volume of blood irreversibly cleared of drug per unit time. As with volume of distribution, drug clearance affects drug half-life. The smaller the volume of drug cleared by the liver per unit time, the longer the drug remains in the body and thus the longer the elimination half-life. The *elimination half-life* of a drug is the time necessary for 50% of the drug to be eliminated from the body. It is a hybrid parameter that varies proportionately and directly with V_d and inversely with clearance. Because drug elimination half-life is the major determinant of dosing interval, the frequency of drug administration should decline as drug half-life increases. Thus both an increase in the volume to which a drug is distributed and a decrease in the volume cleared per unit time should necessitate an increase in the dosing interval of a drug. However, unless the drug accumulates, or changes have occurred in distribution volume, the dose of the drug may not change. Drug half-life can also effect the dose if the drug is characterized by a long (> 12 hrs) half-life, particularly if administered at a dosing interval smaller than its elimination half-life (eg, phenobarbital, selected non-steroidal anti-inflammatories). Such drugs accumulate peak drug concentrations may increase. Additionally, the time to steady-state also increases and maximum response may take longer. Both prolonged clearance and increased volume of distribution will prolong half-life.

Changes in drug disposition induced by liver disease

Liver disease is heterogenous in nature. Likewise, its effects on drug disposition are complex and varied. Not only is each determinant of clearance (protein-binding, blood-flow and metabolism) likely to be affected, but subsequent changes in fluid compartments, acid/base and electrolyte imbalances and effects on renal function can alter drug disposition. Protein-binding. Changes in f_u , parallel changes in plasma-protein concentrations. Albumin changes both quantitatively (usually decreased) and qualitatively, due to changes in molecular conformation. In addition, drugs must compete with endogenous substrates (ie, bilirubin and bile acids) which can accumulate in liver disease for the same protein-binding sites. Increased f_u of a drug has several effects. The concentration of pharmacologically active drug in the blood increases as the drug becomes unbound. Minimal changes in the binding of a highly protein-bound drug can result in marked increases in the concentration of active drug. For example, nonsteroid antiinflammatories are 99% bound. A decrease in protein binding to 98% will double the concentration of free, pharmacologically active drug. This sequelae may, however, be minimized if the drug is capacity-limited because hepatic clearance increases. Adverse reactions are thus more likely to persist for flow-limited drugs. For flow-limited drugs, severe hepatic disease may decrease extraction to <70. Changes in protein binding which accompany hepatic disease exemplify why half-life often may not reflect changes in drug movement. The V_d of a highly protein-bound drug will increase as protein-binding decreases and freed drug leaves the circulation to be distributed to tissues. Plasma drug concentrations consequently decrease and the drug cannot reach the liver. Note that clearance does not necessarily change in

this scenario, however. Drug half-life will be prolonged despite normal clearance. If clearance increases (ie, with capacity-limited), then the volume of drug cleared increases and drug half-life may be normal, despite changes in the parameters of disposition. The effects of changes in body fluid compartments in patients with liver disease (ie, ascites, edema) can have the same effect as decreased protein binding since drugs are likely to be distributed to a larger extracellular volume.

Hepatic blood flow. Changes in hepatic blood-flow in the patient with hepatic disease can be profound. The progressive nature of hepatic disease is accompanied by progressive decreases in hepatic blood flow. Inflammation accompanies most hepatic diseases and is followed by proliferation of new blood vessels and collagen deposition by activated fibroblasts. With progression to chronic disease, collagen matures, and organized fibrous tissue within sinusoidal spaces contracts around functioning hepatocytes. Collagen and fibrous tissue serve as mechanical barriers to blood able to reach hepatocytes ("capillarization") so that substrate delivery to metabolic sites is delayed. Delayed substrate delivery to hepatocytes will affect both flow-limited and capacity-limited drugs. Viable hepatocytes regenerate but the new hepatic parenchyma is nodular. The marked alteration of normal hepatic architecture which accompanies most progressive liver disease alters the intricate relationship between blood supply and hepatocytes. Blood supply from the portal vein and hepatic artery is disturbed as is passage of blood from hepatic sinusoids to hepatic veins. The portal veins become grossly distorted and tributaries to functional hepatocytes are lost. Regenerating hepatocyte nodules may be perfused only by branches of the hepatic artery and fistulae between the portal and hepatic veins may bypass the hepatocytes. Thus only a portion of total hepatic blood flow ("true hepatic blood flow") may reach hepatocytes. Distortion of vascular beds increases hepatic vascular resistance and increased portal pressure. Collateral veins may divert up to 60% of blood away from the liver. Changes in the clearance of flow-limited drugs parallels changes in hepatic blood flow. Clearance of capacity-limited drugs may also decrease in cirrhotic liver disease because substrate delivery is decreased due to capillarization of the vasculature.

Intrinsic metabolism. In both cirrhotic and non-cirrhotic liver disease, decreased cytochrome P-450 content and hepatocyte mass reduces clearance of capacity-limited drugs. Clearance of capacity-limited drugs declines with changes in cytochrome P450 enzyme activity. Drugs normally characterized by a high E may also be affected by profound changes in intrinsic clearance and thus may behave more like capacity-limited drugs. The effects of liver disease on hepatic metabolism and thus drug clearance may vary with the location of the histologic lesion and the microcirculatory pattern. Hepatocytes located in zone 1 contain beta glucuronidases responsible for phase II endogenous and exogenous substrate metabolism. Hepatocytes in zone 3 are characterized by large amounts of endoplasmic reticulum containing cytochrome P-450 as well as cofactors for P450-mediated drug metabolism. Zone 2 represents a transition between zones 1 and 3. Zone 3 cells are probably more susceptible to drug-induced hepatotoxicity because of the high concentration of drug metabolizing enzymes which can convert otherwise innocuous compounds into toxic metabolites. Theoretically, lesions of zone 3 should result in more profound changes in the clearance of capacity-limited drugs.

First-pass metabolism. Gastrointestinal absorption should decline for some drugs in the presence of portal hypertension or profound ascites due to congestion and decreased mucosal blood flow. However, oral bioavailability is likely to be greater for drugs which are absorbed from the gastrointestinal tract but are characterized by first-pass metabolism in the liver (Table 1). Increased bioavailability may reflect both a decline in the metabolic capacity of the liver as well as shunts that allow portal blood to bypass the liver. This effect can be profound even if there is only a modest decrease in the extraction of the drug. Plasma drug concentrations may also double, which increases the likelihood of an adverse reaction to the drug. Extraction can decrease due to changes in metabolism or due to shunting of blood. Shunting of portal blood from the liver will have the same effect. Increased bioavailability parallels the fraction of portal blood shunted around the liver. In fact, changes in systemic bioavailability of an orally administered drug normally characterized by first pass metabolism can be used to evaluate the fraction of portal blood shunted past the liver in human patients with liver disease.

CLINICAL IMPLICATIONS

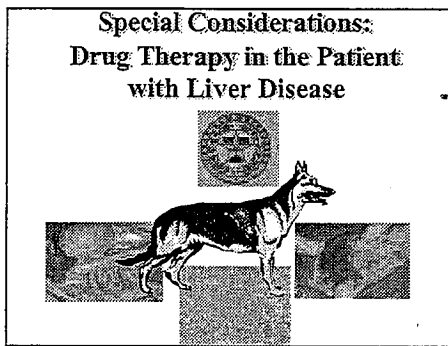
The disposition of many drugs is altered in the patient with liver disease. Although drugs metabolized by the liver are most likely to be affected, hepatic disease can effect the disposition of drugs not cleared by liver due to effects on Vd and

protein binding. The oral bioavailability of many flow-limited drugs is also increased in these patients. Although changes in drug volume of distribution in patients with liver disease are less predictable, most often they reflect an increase. Increased volume of distribution results from both water and salt retention (increased extracellular fluid and total body water) and, for protein-bound drugs, decreased plasma proteins. The effect of hepatic disease on protein binding of drugs in dogs has not been studied in depth. The effect on drug response depends in part on whether or not the drug is distributed to the ascitic compartment. Dosing on a mg/kg basis will minimize underdosing a patient if the drug is distributed to the ascitic compartment, but will overdose a patient if the drug is not distributed to the ascitic compartment. In dogs with experimentally induced liver disease, the ascitic compartment represents up to 30% of total body weight, yet mean Vd of some drugs does not change if animals are dosed on a mg/kg basis. The effect of liver disease on drug elimination half-life is dependent on both changes in volume of distribution and clearance. If clearance decreases and volume of distribution increases, then drug elimination half-life will be prolonged. If both volume of distribution and clearance decrease, changes in drug elimination are less predictable.

Studies which have characterized the disposition of drugs in the small animal patient with liver disease are limited. The elimination of flow-limited drugs such as bromosulphophthalein and lidocaine are decreased up to 50% or more in dogs, depending upon the severity of disease. The elimination of capacity-limited drugs such as antipyrine and caffeine (both binding-insensitive) also progressively. In dogs with severe experimentally-induced disease, clearance of antipyrine decreased to less than 75% of control animals. Recommendations regarding dosing regimens in the patient with liver disease are difficult to make since the sequelae on disposition are as varied as the diseases and the drugs administered. The magnitude of changes in hepatic function can not be quantitated as easily as changes in renal function. Although several drugs have been studied in both spontaneous (humans) and experimental disease (animals), none has been used for a basis of drug modification in patients with liver disease. However, the traditional tests of hepatic function can be used to estimate the severity of liver disease. These tests include the static tests such as albumin and blood urea nitrogen and dynamic tests such as serum bile acid and bilirubin concentration. Changes in the static tests indicate profound changes in hepatic function including metabolism. Profound changes in serum bile acid concentrations indicate changes in hepatic blood flow, and thus changes in the clearance of flow-limited drugs. In general, drug doses should be reduced for drugs characterized by extraction greater than 0.7. In humans, doses are generally reduced by 50%, particularly for orally administered drugs. In patients with severe disease, prolonging the dosing interval of both flow-limited and capacity-limited drugs up to 50% or longer is probably indicated, although this method of compensation has not been documented in clinical patients with spontaneous disease. If the drug is a pro-drug, therapeutic failure due to inadequate metabolism of the pro-drug to its active form should be anticipated and increased dosing may be indicated.

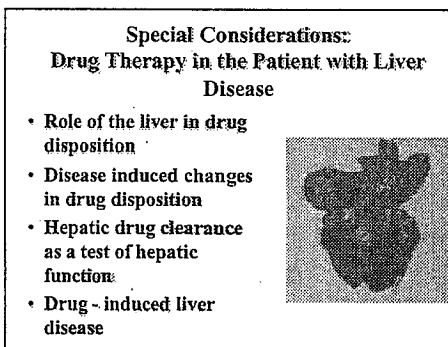
SPECIAL CONSIDERATIONS: DRUG THERAPY IN THE PATIENT WITH LIVER DISEASE

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Our next speaker this morning is Dr. Dawn Boothe. I am sure many of you know Dr. Boothe, she got a DVM at Texas A&M, and her Phd. there too, completing that in 1989. She has done a small animal internship at Auburn and is a diplomate of both the ACVIM as well as the ACVCP. She currently serves as associate professor in the department of veterinary physiology and pharmacology at Texas A&M. Dawn is an expert in many areas. One of those has to do with the effect of liver function on drug action and pharmacokinetics, and as far as I can recall, that indeed was the subject of her dissertation research, so you have certainly more than 10 years experience in this area. So you are, indeed, very welcome this morning.

Thank you, I shudder to hear the word expert. Being an expert in liver disease and drug disposition is really a difficult thing if not impossible.. Before we get started, I am going to take 30 seconds of my precious time; if you know me then you know I have a lot to say. I am from Texas, and most Texans think of it as a separate country. Well, we know better now, because we gave you our president. I never lose an opportunity to poke a little fun at our president, who I didn't vote for. You may be aware that he is very excited to be president, and has been known to state that he is having the time of his life driving around in the presidential limousine with all its the flags, and flying around in Air Force One. Well, he brought a little bit of his own Texas flavor to those modes of transportation, and I thought you might like to see them, just in case you have not had an opportunity. This is the new Air Force One, and then the presidential limousine. Okay, so no more laughing, now we have to get down to work. So I am going to talk about the pharmacokinetics of drug therapy in liver disease, and not just liver failure, but one of the reasons I went into clinical pharmacology was as an internal medicine resident I was so frustrated with trying to approach the treatment of a patient with chronic progressive liver disease. And I came to the realization that we know very little about what the liver does to drug disposition. So I am going to tell you right up front that there is surprisingly little information both in people as well as animals, dogs in particular, about the effect of liver disease on pharmacokinetics. One of the reasons for that is when you look at the modeling potential, in contrast to renal disease where there are some pretty good models that can be used experimentally to describe the effect of changes in renal function experimentally, the same is not true for liver disease. In fact, we are frequently limited to studying the spontaneously diseased patient, and you know as well as I do that the complexities associated with liver disease are enormous. Trying to wade through those complexities is very difficult. So, I am going to share with you what I know, but the approach that I am going to use is to back up and look at a little basics, then apply it to the patients. Then perhaps we can go to the clinical floor and decide what we can do to accommodate each patient's disease as we reach for drugs.



So if we are going to talk about the role the of the liver in drug disposition, and we have to do that to understand how it changes in liver disease, we have to understand what the liver does to drugs. Then we have to turn around and decide what the various diseases do to the liver before we can understand how that disposition is going to change. Then I would like to talk a little bit about the use of drug clearance by the liver as an indicator for hepatic function (that was indeed the topic of my dissertation research) and then I will going finish up with just a word or two about drug induced liver disease in order to make sure that, in treating these patients, we don't contribute to the disease process.