



Effect of liver disease on dose optimization

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Abstract

Many narrow therapeutic index drugs are eliminated primarily by hepatic metabolism. Selecting the proper dosing regimen for such drugs in the presence of liver disease is an important therapeutic problem. However, the effect of liver diseases on drug disposition is complex, and depends on the pathophysiology of the disease and the pharmacokinetic characteristics of the drug itself. Hepatic clearance concepts provide a general framework for understanding and predicting the changes in pharmacokinetics of drugs with high and low intrinsic clearances, but this approach is not sufficiently robust for clinical use due to difficulties in measuring patient-specific hepatocellular function and hepatic blood flow. Further complicating the ability to predict hepatic clearance in the presence of liver disease is that hepatic enzymes may be differentially affected by the presence of liver disease—glucuronidation is well-preserved even in advanced liver disease, and mild to moderate liver disease has selective effects on the catalytic activity of specific cytochrome P450 metabolizing enzymes, with CYP2C19 more sensitive to liver disease than CYP2D6. Despite considerable efforts to develop non-invasive probes of hepatic metabolic activity, there are still none that are useful clinically. Therapeutic drug monitoring may have some value, but is limited by changes in plasma protein binding that are common in liver disease. More studies are needed to develop better probes, and, in the drug development process, to provide better information on metabolic pathways and laboratory and clinical covariates that can be used to individualize dosing regimens in the presence of coexisting diseases and concurrent drug therapy. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The liver is the major site of drug metabolism and the cytochrome *P450* hemoproteins, particularly the CYP1, CYP2 and CYP3 families are responsible for the majority of drug metabolism in humans. For drugs eliminated by this system, variation in the catalytic activity of individual cytochromes *P450* may account for significant interindividual variability in drug responses. Variation in catalytic activity may be due to differences in gene expression, and genetic polymorphisms, induction and inhibition of activity by drugs, exogenous chemicals and endogenous agents, and other factors such as diet, gender, and disease [1,2]. As a result of these many influences on catalytic activity, the magnitude of variation in the rate of metabolism of drugs is substantial, with ranges of 10–30-fold the rule rather than the exception.

Liver disease might be expected to decrease the rate of metabolism of drugs eliminated by this organ, but several decades of research into the effects of liver disease on drug metabolism have largely served to indicate the complexity of this field [3–6]. The complexity is due to a number of causes, including the heterogeneity of liver disease, the differences in the rate-limiting factors determining catalytic activity, and the lack of tools for measuring metabolic clearances. This paper will briefly summarize these issues, and indicate areas in which new knowledge may assist in finding better ways to optimize therapy in patients with liver disease.

2. Heterogeneity of liver diseases

The term liver disease encompasses a wide variety of etiologies and pathophysiological changes in liver function, both catabolic and anabolic. In addition, diseases involving the liver are dynamic, with changes in severity occurring over relatively short periods in the case of acute hepatitis, and over much longer periods (months to years) in the case of diseases leading to cirrhosis and end-stage liver disease. The effects of liver diseases on hepatic drug clearance vary as a function of the etiology and stage of disease, and the intrinsic clearance [7–9] of the drug itself. Taking into account the etiology and severity of the liver disease along with intrinsic clearance and protein binding of the drug reduces some of the variability in pharmacokinetics [10,11], but very significant residual, unpredictable variability in kinetics and in pharmacological response remains.

Table 1
General classification of liver disease

Cholestasis and diseases of the biliary tract
Hepatitis
-Acute (viral and toxic)
-Chronic
Fibrosis and cirrhosis
Metabolic disorders and fatty liver
Focal lesions: pyogenic, granulomatous, parasitic, and vascular
Neoplasms: primary and metastatic

Table 2
Predominant pathophysiologic changes in various types of liver disease

Disease	Total hepatic blood flow	Hepatocellular mass	Hepatocellular function	Albumin concentration	Bilirubin
<i>Cirrhosis</i>					
Moderate	↓	↔ or ↓	↔	↔ or ↓	↔ or ↑
Severe	↓↓	↓	↓	↓↓	↑↑
<i>Acute inflammatory liver disease</i>					
Viral hepatitis	↔ or ↑	↔ or ↓	↓	↔	↔ or ↑
Alcoholic hepatitis	↔ or ↓	↑ or ↔ or ↓	↓	↔ or ↓	↑↑

↓ = Decreased ↑ = Increased ↔ = Unchanged.

Assessing the etiology and especially the severity of liver disease is often difficult. Table 1 provides a general, working classification of liver diseases. The pathophysiology varies widely with the different etiologies and with the severity. Table 2 presents the predominant pathophysiological changes associated with cirrhosis and acute inflammatory liver diseases. These differences in pathophysiology are important, since there is an interaction between these changes and the intrinsic clearance of a drug, to be discussed below.

3. Pharmacokinetics versus pharmacodynamics

Much of the focus on dosage optimization in patients with liver diseases has been on alterations in the pharmacokinetics of drugs eliminated largely by hepatic metabolism. Less consideration has been given to changes in the plasma concentration–response relationships (pharmacodynamics) associated with liver diseases. Two organs are especially prone to manifesting pharmacodynamic changes: the central nervous system [12] and the kidney. The drugs listed in Table 3 are well documented as having pharmacodynamic changes in liver disease, but it is conservative to assume that patients with advanced stages of hepatic insufficiency due to any cause will be more sensitive to agents with

Table 3
Drugs for which there is evidence of altered sensitivity in liver diseases

Increased sensitivity.

- Diazepam
- Chlorpromazine
- Diuretics (untoward effects)
- Narcotics
- Barbiturates
- Gentamicin (untoward effects)
- Clofibrate

Decreased sensitivity.

- Diazepam (acute alcohol withdrawal)
- Paraldehyde (acute alcohol withdrawal)
- Azathioprine

primary or secondary actions on the central nervous system, as well as to assume that the effect will last longer. Often overlooked are adverse CNS effects due to administration of two or more drugs, each of which has minor CNS depression in patients without liver disease, but when given concurrently, produce significant sedation or agitation. The mechanism for the increased sedation produced by a variety of agents in patients with liver disease is unknown, but it is instructive to note that in the circumstance of agitation associated with alcohol withdrawal, there is a decrease in sensitivity to benzodiazepines [13], while sensitivity is increased when the acute episode resolves [14]. Less intuitive is the interaction between diuretics and liver diseases. Diuretic resistance in patients with cirrhosis is well established [15], as is the development of hepatorenal syndrome with the use of diuretics in patients with ascites. However, less well known is that the presence of liver disease predisposes patients to the development of renal insufficiency when treated with aminoglycoside antibiotics [16]. The cause of the increased risk of renal insufficiency with aminoglycosides is unknown.

4. Interactions between pathophysiology and drug disposition

It has been recognized for a number of years that the effect of liver diseases on drug disposition was dependent on the intrinsic clearance (CL_{int}) and protein binding of the drug. The hepatic clearance concepts formulated about 25 years ago [7,9] predict that drugs with low intrinsic clearance will be sensitive to changes in hepatocellular function while drugs with high intrinsic clearance will be sensitive to processes that alter hepatic blood flow. Binding to plasma proteins and the presence of porto-systemic shunting are other drug and disease factors which must be considered when creating a physiologically based pharmacokinetic model for the effects of liver disease [10,11]. As shown in Table 2, acute inflammatory liver disease is associated with declines in synthetic and metabolic hepatocellular activity, and the decline is related to the severity of the liver injury. Mild or even moderate liver injury due to viral hepatitis appears to have minimal impact on hepatocellular metabolic function. Williams et al. showed that acute viral hepatitis had minimal effects on the disposition of warfarin [17], a drug with low intrinsic clearance (Table 4). The interpretation is made more complex, however, by the fact that decreased synthetic activity and a decline in albumin concentrations may lead to an increased free fraction, which in turn may cause an apparent increase in total plasma clearance in this setting [18]. Available data would appear to show that mild to moderate hepatitis leads to clinically insignificant changes in drug disposition, and dose modifications are usually not necessary. However, in the presence of severe hepatic injury due to viruses or alcohol, significant impairment of hepatic clearance may be present.

Changes in hepatic perfusion have their greatest effect on drugs with high intrinsic clearances. The hepatic clearances of such compounds are blood flow limited, and diseases that alter hepatic blood flow can have substantial impact on their disposition. High intrinsic clearance drugs, when given by the oral route, also undergo substantial first-pass metabolism and have low oral bioavailability. In the presence of porto-systemic shunting, characteristic of advancing cirrhosis, both the bioavailability and the systemic clearance may be dramatically increased. This phenomenon occurs for a number of

Table 4
Characteristics of certain drugs

High intrinsic clearance ($CL_{int} > Q$)	Low intrinsic clearance ($CL_{int} < Q$)
Propranolol	Warfarin
Lidocaine	Diazepam
Nortriptyline	Chlordiazepoxide
Desmethylinipramine	Phenytoin
Metoprolol	Tolbutamide
Alprenolol	Antipyrine
Propoxyphene	
Meperidine	
Pentazocine	
Morphine	
Saquinavir (and other HIV protease inhibitors)	

important therapeutic agents, some of which are shown in Table 4. A helpful review of the effects of liver disease on the disposition of many drugs can be found in the review by Howden et al. [19].

5. Selective effects of liver disease on hepatic enzymes

It has been known for a number of years that glucuronidation and other phase II reactions were relatively well preserved in patients with advanced liver disease [3,20,21]. As the understanding of the cytochrome *P450* superfamily of enzymes has advanced with the use of molecular biological techniques, it has been possible to apply these techniques to studying the effects of liver disease on these enzymes. This field is still at an early stage, but already some interesting observations have emerged. George et al. [22] have shown disease-specific alterations in cytochrome *P450* activities by measuring activity in livers from patients with end-stage cirrhosis with and without cholestasis undergoing transplantation. They further showed that pre-translational mechanisms were likely responsible for the changes [23]. In an *in vivo* study in patients with mild to moderate cirrhosis (using the Pugh–Child classification [24]) given racemic mephenytoin and debrisoquin simultaneously, Adedoyin et al. [25] showed selectivity in the effect of liver disease on activities of specific CYP enzymes, CYP2C19 being more sensitive than CYP2D6. The magnitude of the decrease in CYP2C19 activity depended on the severity of the disease. Studies such as these would seem to suggest that dosage adjustments in patients with liver disease should depend on which enzyme is responsible for the metabolism of the drug, and on the severity of the liver disease. However, much more data are needed for other specific enzymes and etiologies of liver diseases before clinically useful guidelines can be proposed.

6. Probes of drug metabolizing activity in liver disease

For several decades the goal of many laboratories has been to find a relatively simple biochemical measurement or test which would have a clinically useful correlation with

hepatic clearance in a variety of settings, including patients with or without known liver disease, patients receiving concurrent drugs which could affect hepatic metabolism, and seriously ill patients with multiorgan or multisystem dysfunction. Despite a considerable effort, there is still no such test available, and, as our understanding of the complexity of the regulation of the *P450* system increases, it is clear that more complicated models involving biochemical and physiological pharmacokinetic models [26] will be necessary for useful predictions. Advances in genomics offer some optimism that predictions of individual metabolism may ultimately be made on the basis of a person's genetic makeup, but this approach is also well in the future.

Efforts to develop probes of hepatic metabolic activity have been well summarized in a number of papers and reviews [19,27–30], and will not be discussed in detail here. Biochemical markers in plasma have not proved useful in predicting hepatic clearance in individual patients, with the notable exception that hyperbilirubinemia, hypoprothrombinemia and hypoalbuminemia are generally associated with significant reductions in hepatic clearance and in the binding of drugs to plasma proteins. Hepatically cleared drugs should be used cautiously if at all and at much lower doses in such patients [19]. Similarly, assessment of severity with the Child–Pugh clinical scores is at best roughly correlated with hepatic clearance, and not useful for individual patients, many of whom have other factors affecting metabolism, such as concomitant drugs or nutritional status.

The most extensively studied model substrates or probe drugs are antipyrine, aminopyrine, trimethadione as non-selective probes and caffeine, chlorzoxazone, erythromycin, lidocaine, and midazolam as selective probes. A summary of the features of these probes can be found in the review of Tanaka and Breimer [28]. Another approach has been the use of drug “cocktails” [31–41]. A recent, promising cocktail is one designed to probe the activities of five specific cytochrome *P450* enzymes (CYPs 1A2, 2C19, 2D6, 2E1 and 3A4) and *N*-acetyltransferase enzymes using a five-drug cocktail of caffeine, mephenytoin, debrisoquin, chlorzoxazone and dapsone, respectively [42]. While some of these approaches appear promising for studying selective effects of liver disease on drug disposition [25] and have been applied to investigating drug interactions [43,44], more research is needed before probes can be applied to predicting drug disposition in specific patients.

7. Pharmacogenomics

There has been much enthusiasm about the prospects for using genomic information to individualize treatment regimens, reducing the variability in outcomes. While this holds substantial promise in drug selection, the many factors that regulate the expression of *P450* enzymes and the non-genetic factors that affect hepatic metabolic activity and clearance will likely limit the value of this approach as a clinical tool in patients with liver disease. Along with *in vitro* studies, it does have a very important early role in understanding and predicting the effect of disease states and the potential for significant drug interactions *in vivo* [27], and will become an important component of the drug development process.

8. Conclusions

There have been significant advances in our understanding of the biochemical processes which affect hepatic drug metabolism, especially the genetics and regulation of the cytochrome *P450* system. Elegant physiological modeling of the relationships between intrinsic clearance, blood flow and plasma protein binding in the past two decades has helped explain many of the observations that have been made for drug disposition in the presence of liver disease, but have not had value in terms of predictions for individual patients. Most drug development programs now include studies in patients with liver disease, as part of special population studies. Despite all this new knowledge and understanding of the processes, little progress has been made in providing guidelines for tailoring doses for individual patients with liver disease, and adjustments are usually made only when the severity of illness is major. As with all drugs, individual titration to a pharmacological surrogate or clinical endpoint is the best approach, including in patients with liver disease. When this is not possible, the best hope appears to be the use of single or multiple probes, although success has been limited thus far when applied to the individual. Therapeutic drug monitoring may also have a role, but the extensive protein binding and effect of liver diseases on binding limit application in this setting. The differences in sensitivity in patients with liver disease must always be considered, as kinetic changes will not account for all of the increase in variability. The studies which are needed are difficult, and progress in this field will be gradual.

Appendix A. Discussion 19

L. Sheiner: What can we learn about hepatic failure and drug metabolism from observing patients with hepatic transplant?

T. Blaschke: Hepatic transplantation has certainly been a source of good information about the role of the liver. Bob Branch has done much more on this area, being located at the home of the liver transplant at Pittsburgh, and has done some very interesting studies in anhepatic patients. However, I think there are so many changes occurring in the acute post-transplant period that I don't know that one could get much information out of that period. I certainly didn't come across any helpful information in the post-transplant patient. Beyond the acute recovery phase they behave much more like patients with relatively normal liver function.

M. Reidenberg: On your slide on drug resistance in liver disease you included diazepam and paraldehyde. I'd always thought that was related to alcoholism but not liver disease. Do you want to expand on that a little bit?

T. Blaschke: Resistance to these drugs is seen mostly in the presence of acute alcohol withdrawal, and that's why diazepam was shown on both slides, the increased and decreased sensitivity slides. It's a very interesting story, and one that we encounter on the wards because the house staff often overdoses the patients initially with diazepam because they don't quite know how to use the drug properly to prevent withdrawal. Then, starting about 3 days later, the patient becomes unconscious for a week or two. It's a phenomenon that's not very well understood by house staff.

N. Holford: You showed a “bee in my bonnet” slide with that triangle thing because it’s the wrong way up because it implies that the clearance of drugs is unchanged by protein binding with high extraction ratio drugs, which is true for total clearance but exactly the opposite way round for unbound clearance. In fact for drugs, which have low extraction ratios, the unbound clearance doesn’t change with protein binding, and for drugs that have high extraction ratios, the unbound clearance does change with protein binding. If what you are interested in is what happens to unbound drug concentration, which is what causes effects, you have to reverse that diagram. Do you actually believe that slide? I think you should throw that slide away and draw an unbound clearance slide.

T. Blaschke: I think it’s a good idea. You’re absolutely right. In fact, I’ve been talking about protein binding and unbound clearance a lot recently, because it’s very important in the HIV protease inhibitor area. It’s a key point for protease inhibitors, not so much because of liver disease, but because of the drug interactions. But you’re absolutely right about the slide I showed, and I’ll redraw it.

P. Morgan: You didn’t mention what may happen to hepatic transporters in liver disease. Some of the probe substrates that you talked about, such as erythromycin, while it may be selective for CYP3A4, is also a substrate for PGP and other hepatic transporters. So obviously the hepatic handling of those compounds is going to alter if something happens to the transport proteins.

T. Blaschke: That’s another major topic that’s got to be added to this whole issue of effects of liver disease. We are just getting started in that and it is at a point where there’s very little data yet. We can’t just look at the CYP enzymes in liver disease. We’ve also got to look at the transporters, we’ve got to look at phase II reactions, but there’s just not much of anything in the literature yet.

A. Breckenridge: One of the most useless bits of information a drug regulator is confronted with, is the effect of liver disease in drug handling, and based on the need to give advice on how you optimise dose. Would you give drug regulation authorities any advice on how they should reformulate the requirements for licensing a new drug with respect to liver disease and its effects on dosing?

T. Blaschke: You are reminding me of the Chester meeting not too long ago, and I think the response that I had then is still the one that I would stick with right now. I still don’t think we have a good approach. Because we don’t have any way of adequately classifying different types of liver disease. I think the best we can do is through phase IV studies, using observational data, and special population pharmacokinetics. FDA has a guideline coming out, but I think it’s still in draft form, as a guidance for testing drugs in liver disease. I don’t think it helps the practitioner, because the guidelines define a few things in terms of some studies to do in patients with cirrhosis, define liver disease by the Child–Pugh scores, and the companies complete the check the box on the NDA at the time of submission. I don’t think that’s particularly helpful to anyone, and we need more sophisticated ways of looking at this.

L. Sheiner: I think the situation is similar between adjusting therapy for children and those with disease states: Where there is not a lot of money to be made, I think the manufacturers in general would rather simply say, for example, “Don’t give the drug to people with elevated transaminase”, and be done with the problem. From an economic perspective the gain in revenue from access to the liver-disease market cannot offset the

cost of the studies required to get approval for such access. Those costs of course do not disappear: if the public so chooses, it may bear them in the form of subsidies for the study of drug disposition in liver disease patients, or if not, then the costs will be borne by the liver disease patients themselves in the form of increased risk of inefficacy or toxicity when receiving drugs whose disposition has not been adequately studied in them.

K. Park: The changes in cytochrome *P*450 are really quite interesting, because on your first slide you suggest that enzyme induction could actually compensate, and then you show the differential effects between CYP2C19 and CYP2D6. Is there anything known about the mechanism? Is there actually down regulation of these enzymes, over and above the cellular injury?

T. Blaschke: In the one study that looked at the biochemical pharmacology of this it looked like, in fact, there may be a dual effect. One on transcription and decreased synthesis, but also increased breakdown of the mRNA. It's not clear because the mechanism for those two compounds looked like it was different.

P. Joubert: In my 10 years of experience in the pharmaceutical industry, we have done a number of hepatic impairment studies. They have all been useless, of no value, they have not given the practitioner any guidance, they were done to simply appease the regulatory authorities and they, in my opinion, unnecessarily exposed patients to a drug in a situation that gave us no useful information. The liver is a very efficient eliminator of drugs by metabolic processes. By the time the liver is impaired to the extent that it affects drug metabolism there are much more serious problems with the patient: the patient has a bleeding tendency, jaundice and hypo-albuminaemia and they are seriously ill. Getting back to phase IV, what I would like to see, is that we look at how important a co-variate hepatic impairment is in terms of a problem in relation to adverse drug reactions. The only exception I see is that you need guidelines for people in terms of drugs that are hepatotoxic, and how to use them in patients that already have liver disease. If, on the other hand you look at renal disease, it is a tremendously important co-variate in general terms of producing adverse events for drugs eliminated predominantly by the kidney. I'm not convinced that hepatic impairment is an important factor clinically speaking.

T. Blaschke: I think we have a problem expressing it as a covariate. Hepatitis, as it turns out, has relatively limited clinical effects, at least in any study that I've seen, on drug metabolism. I think as liver disease progresses there is a state between hepatic failure and early stages of fibrosis, at which there are probably some changes that do need to be made, and some differences in dosing and sensitivity.

M. Ingelman-Sundberg: I would just like to stress the results of some of our own studies, and other studies which really implicate that the expression of the phase I enzymes do go down quite tremendously on the RNA and protein level during liver fibrosis. The mechanisms are unknown, but likely candidates to mediate the effect are the inflammatory cytokines, which are known to down-regulate most of the phase I enzymes quite tremendously, and quite fast.

T. Blaschke: Related to what Pieter Joubert was challenging me about earlier, I think it's important to really have some mechanism for at least staging the severity of the liver disease. We all have seen studies and had examples ourselves where patients with what I would call moderate cirrhosis, if we use the Child–Pugh scores, have shown relatively little impairment of hepatic metabolism or hepatic clearance. There does appear to be a

tendency for hepatic clearance to fall off fairly precipitously at some point. Where that point is, of course, is not clear. I think it would be nice if we had some covariates to help—the only ones we do have are albumin and bilirubin; when the albumin start falling and bilirubin starts going up, everything falls apart. But, there is relatively little evidence that there is much of any effect of mild to moderate liver disease on drug metabolism, and the value of measuring the enzyme levels appears to be small.

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