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Special Article

Antecedent liver disease and drug toxicity

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One of the more common questions asked of hepatologists concerns the risks and proper use of potentially hepatotoxic drugs in patients with underlying liver disease. A typical example is a patient with tuberculosis and abnormal liver tests (perhaps due to alcohol and/or hepatitis C) who requires treatment with isoniazid, rifampicin and/or pyrazinamide. Should all these drugs be used, should the combination be modified, and/or should the dosages be changed? Are there special monitoring considerations in such a patient? At what level of increased liver test abnormality should the drugs be stopped? The purpose of this illustrative case is not to focus on this specific patient, but to provide a forum for a general discussion of this dilemma.

While it is generally known that most drugs are metabolized by the liver and many are excreted by it, and thus liver dysfunction may require adjustment of drug dosage in such patients, the implications of this for overall drug hepatotoxicity have not been formalized. This is, perhaps, best explained by the lack of meaningful published data. Nevertheless, in a number of instances involving the use of therapeutic agents with potential liver toxicity (pyrazinamide, tolcapone, troglitazone), prior liver dysfunction has been cited as a contraindication. Our aim in this article is to amalgamate and interpret available information on this topic.

A number of key concepts serve as guidelines for this analysis. These can generally be catalogued under the headings of mechanisms of drug-induced liver injury, summation of toxic effects and difficulties in early diagnosis.

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Mechanisms of Drug-Induced Liver Injury

Dose-dependent hepatotoxicity

First, hepatotoxic drug reactions can be divided into those which are predictable (i.e., dose-dependent) and those which are idiosyncratic (i.e. dose-independent) (1). The predictable group is small, inasmuch as the dose of the drug recommended on the basis of initial studies is aimed at achieving concentrations of the agent (or its toxic metabolites) below (and ideally well below) the dangerous level. Where such precautions may break down is when due to age, genetically altered metabolism, interaction with another drug or with underlying liver disease, normal removal of the drug is impaired, resulting over a period of time in toxic concentrations. Such alterations in drug disposition are termed pharmacokinetic changes. Some examples of this are seen in Table 1, as with perhexiline maleate

TABLE 1

Dosage-dependent drug-induced liver disease

Drug	Risk factors
Acetaminophen	total dose*, toxic derivative+
Tetracycline	total dose (renal dysfunction)
Methotrexate	total dose*, alcohol, diabetes, prior liver disease*
Perhexiline	total dose*, slow hydroxylator**
Amiodarone	drug levels over time*
Cyclosporine	drug levels*, P450 3A phenotype**
Cyclophosphamide	total dose*
Valproic acid (?)	total dose*, toxic derivative**+, young age
Oral contraceptives	total dose* (adenomas)
Aspirin	drug level*, rheumatoid diseases
Niacin (?)	total dose
Pyrizinamide (?)	total dose, ? drug/drug interaction
Bromfenac	total dose
Naltrexone	total dose*, prior liver disease*

* abnormal hepatic metabolism.
** genetic effects.
\+ induction.

(Modified (with permission) from Farrell GC. Management of drug-induced liver disease, Chap 8. In: Drug Induced Liver Disease, Churchill Livingstone, London, 1994, pp 163).

whose toxicity is seen primarily in slow hydroxylators (a genetic effect) or with acetaminophen or other agents in chronic alcoholic patients in whom there is enhanced metabolism to a toxic derivative of usually safe doses of the drug. It should be appreciated that dosage and duration of therapy are not the only factors in drug toxicity of such predictable toxins, and that other individual metabolic variations must also play a part. These metabolic aberrations (a form of superimposed idiosyncracy) probably account for the infrequent clinical manifestations of toxicity with these drugs. A more comprehensive list of agents which may accumulate in the body in the presence of liver disease and which require dosage adjustment to prevent toxic effects has been compiled (2). The presence of underlying liver diseases may indeed predispose to greater dose-dependent drug toxicity, if the drug dosage is not appropriately adjusted downward, and if the margin of safety between therapeutic and toxic concentrations (the toxic threshold) is small. This effect of antecedent liver disease presupposes that the drug is eliminated primarily by the liver, that it is the parent drug or one of the early metabolites that is toxic, that the liver is sufficiently damaged to impair drug elimination and that the injury affects the metabolic pathway relevant to the drug in question. Otherwise, if a distal metabolite is toxic, liver dysfunction may actually be protective in this type of drug-induced liver injury by decreasing the formation of such a derivative. Thus, underlying liver disease would be conceptually anticipated to enhance drug-induced liver disease only for dose-dependent liver toxins with a low therapeutic index and only under special clinical/pharmacokinetic circumstances. This may partly account for the lack of reports of drug-induced liver injury in patients with prior stable hepatic damage. The paucity of such reports may be related also to the instinctive reluctance to prescribe potentially hepatotoxic drugs to patients with liver disease

Second, chronic liver disease often results in a low serum albumin concentration. Inasmuch as many drugs in serum are highly protein bound, a lower protein with decreased drug binding may result in greater distribution of free (unbound) drugs to their target organs with subsequent tissue toxicity (3). An example of such adverse effects may be the greater sedative effect of diazepam in cirrhotic patients (4), in part at least, due to a greater penetration of the free drug into the brain (5). Similar observations have been reported for triazolam (6). Thus, decreased protein binding of drugs may be another adverse effect of underlying chronic liver disease on predictable drug toxicity. However, although the greater concentrations of unbound benzodiazepine may affect cerebral function adversely, there is only scanty evidence that such a process with other drugs contributes to damage of hepatocytes.

Thus, in patients with liver disease, hypoalbuminemia may play a role in aspirin-induced hepatic damage. In patients hospitalized with alcoholic liver disease, the unbound plasma salicylate concentration after a single oral dose of aspirin (1.2 g) was increased (7), while the urinary excretion of total or unbound aspirin was not affected. There was no comment as to whether the liver disease became worse. Another study confirmed the increase in unbound plasma concentration of aspirin, in inverse proportion to the serum albumin, in patients with acute rheumatic fever. The ratio of unbound to bound salicylic acid was directly related to the rise in transaminases (AST, ALT) (8). Moreover, others have shown that aspirin, through activation of its metabolite into salicyl-CoA, leads to sequestration of extra mitochondrial CoA and eventual impairment of beta oxidation of fatty acids to produce hepatic microvesicular steatosis (9). Thus, hypoalbuminemia in liver disease increases the risk of aspirin hepatotoxicity. We are unaware of other drug-induced liver damage related to drug binding. It is conceivable that a similar adverse phenomenon may affect patients with other causes of hypoalbuminemia as occurs in malnutrition and chronic protein loss through the kidneys or the intestine.

Toxicity by altered pharmacodynamics

In contrast to altered drug removal or binding, some drug toxicity may be exerted at the tissue (receptor) level. Such effects may be caused by altered pharmacodynamics. For instance, in the presence of chronic liver disease, it is known that the brain is more sensitive to the sedative effects of benzodiazepines, morphine and possibly other soporific agents (4). Moreover, the kidney in such individuals is more sensitive to prostaglandin depletion from non-steroidal analgesics (10,11), and to aminoglycosides, which tend to be more toxic to renal tubules of cirrhotic patients (12). The precise mechanisms of these adverse effects are not clear. While these effects of drugs in cirrhosis are not exerted on the liver, they still fall into the category of adverse drug effects in the presence of underlying cirrhosis. A general compilation of these agents has recently been published (2).

A similar type of hepatic sensitivity to toxins may be seen also in patients with liver disease. This is most likely to be in the realm of hepatic response to potential toxins. Although little studied, conceptually, a diseased liver may exhibit impaired Kupffer cell function in detoxifying endotoxin, may have aberrant intercell

TABLE 2

Drug pharmacodynamics in liver disease

- Sensitivity of brain in chronic liver disease to benzodiazepines, morphine, etc.
- Sensitivity of kidneys to prostaglandin depletion and to aminoglycosides
- ? Sensitivity of diseased liver to respond to "toxins"
  - ? Endotoxin
  - ? Kupffer cell function (tumor necrosis factor)
  - ? Intercell signaling
  - ? Cytokines
  - ? Mitochondrial integrity (GSH)

signaling and abnormal cytokine release or may have depleted mitochondrial reduced glutathione (GSH) stores with adverse effects on mitochondrial integrity and function (Table 2). Examples of this are the enhancement of acetaminophen, alcohol, endotoxin and tumor necrosis factor toxicity to mitochondria depleted of antioxidants (GSH, S-adenosyl methionine), a condition which may prevail in patients with chronic alcoholic liver disease (13–18). The possible contribution of malnutrition (i.e., with acetaminophen toxicity) (19), or of increased hepatic iron stores (favoring oxidative stress) (20) in such patients needs investigation. Increase in hepatotoxicity due to endotoxin (a possible mediator of alcoholic liver disease) by estrogen may be another example of such enhanced sensitivity of the liver to ethanol in women (21). Data regarding this aspect of drug toxicity with underlying liver disease are surprisingly scanty and are needed.

Idiosyncratic (unpredictable) injury

The overwhelming majority of drug-induced liver injury is not dose-dependent. It appears to occur in highly selected individuals with a genetic proclivity for generating an unusual metabolite and/or who develop an allergic response to such a derivative (1,22). Such reactions cannot be anticipated in preclinical studies and the susceptible individuals cannot be identified *a priori*. It is usually only in post-marketing surveys, which target larger populations, that the problem is detected. Inasmuch as the toxic effect is not dependent on intact (normal) hepatic metabolism, impairment of it is unlikely to promote drug toxicity. Thus, the presence of prior hepatic dysfunction would not be expected to induce or worsen idiosyncratic liver damage by drugs, unless the liver is more susceptible (more sensitive) to the process of damage as a result of decreased defense systems due to the liver injury (Table 2). The issue has not been adequately studied experimentally, but is conceptually attractive. On the other hand, it is of interest that increased problems with halothane anesthesia have not been reported in patients with prior liver disease undergoing portal systemic shunt operations. The rarity of this idiosyncratic reaction, however, makes interpretation of such lack of data difficult. Other research is also needed to determine if prior liver damage may actually decrease the formation of some toxic metabolites and thus be protective.

Summation of Toxic Effects

Another aspect of this problem is the incremental effect of drug-induced liver injury added to antecedent hepatic damage. Clearly, such a summation needs to be avoided, or at the least diagnosed early enough to minimize cumulative injury. The same principle guides the current recommendation that patients with chronic hepatitis C be vaccinated for hepatitis A and B, if not already immune to these infections (23).

Diagnostic Difficulty

Usually the development of drug-induced liver injury is heralded by the onset of new symptoms (fatigue, myalgias, nausea, abdominal pain and, eventually, jaundice) and abnormal liver tests (2). This provides an opportunity to stop a potentially offensive drug and watch for diagnostically helpful resolution of these findings. With the presence of underlying liver disease such monitoring may be more difficult. Only detection of incremental symptoms and/or laboratory tests is helpful. Hence, recording of a good baseline and more frequent than customary clinical and biochemical follow up of the patient may be needed to detect early drug-induced injury.

Drug Metabolism in Underlying Liver Disease

A quantitative assessment of this problem is clearly relevant to proper drug dosing in patients treated with agents that exhibit dose-dependent drug toxicity. The subject of drug elimination (hence, possible dosage adjustments) in chronic liver disease has recently been reviewed (2) and will be commented on here only briefly.

In general, hepatic drug elimination depends on drug binding to plasma protein, hepatic blood flow (including capillarization) and hepatic metabolism. Each of these factors may have a bearing on drug hepatotoxicity, but this will vary with the nature of the drug. For example, some agents with low protein binding (i.e. acetaminophen) will not be influenced by a low serum protein or the presence of other drugs which may compete for *a priori* lower protein binding reserve. Highly bound (>90%) agents with a low clearance, on the other hand, may exhibit greater penetration to receptor sites in the presence of decreased binding. Normally, high clearance drugs depend primarily on liver blood

flow and those with a low extraction on hepatic biotransformation (intrinsic clearance). In the presence of chronic liver disease, on the other hand, metabolism may become rate-limiting (2). High extraction agents, however, may be particularly affected by liver disease when the drugs are given orally. The removal of such a drug by the chronically diseased liver is often markedly decreased due to portosystemic shunting of blood (spontaneous or surgical), resulting in a high concentration of the drug in blood (reduction in first-pass effect). An example of this is the greater analgesic/sedative effect of oral demerol (meperidine) in patients with cirrhosis as compared to individuals with a normal liver (24).

There are several major concerns in using dose-dependent hepatotoxic drugs in patients with liver disease. The first problem is our inability to define, with precision, the degree of impairment of liver function relevant to elimination of a particular drug in a given patient. There is, at present, no single equivalent of the creatinine clearance-like test (as for renal disease) in patients with liver disease. It is generally appreciated that the severity of liver disease correlates roughly with the Child-Pugh classification or Maddrey's Discriminant Index, but these are gross indices for any one patient. Similar considerations apply to pharmacokinetic measurements of liver function (antipyrine, aminopyrine, galactose clearances) (25). Second, different forms of liver disease vary appreciably in their effects on drug handling. For instance, acute liver disease often affects drug elimination less than chronic disease (cirrhosis) of apparently similar severity (25). Cholestasis also tends to decrease drug biotransformation more (for many agents), as compared to hepatocellular disease. Finally, oxidative processes are generally more deranged than conjugation, especially with mild or moderate liver disease (25–29), and oxidative detoxification varies substantially with the severity and type of liver disease and with the cytochrome isozyme needed for a particular drug biotransformation (30–32) (Table 3).

TABLE 3

Selective effect of liver disease on hepatic cytochrome P-450

	P-450 2c19 S-Mephentoin Clearance (ml/min)	P-450 2D6 R-Mephentoin Clearance (ml/min)
Control (8)	1987	24
Mild liver disease (9)	745*	21
Moderate liver disease (9)	72*	25

* $p<0.05$

Arns PA, Adedoyin A, DiBisceglie AM, Waggoner JG, Hoofnagle JH, Wilkinson GR, Branch RA. Mephenytoin disposition and serum bile acids as indices of hepatic function in chronic viral hepatitis. Clin Pharm Ther 1997; 62: 527–537 (*with permission*).

Accordingly, it is a challenge to adjust dosages of such drugs in patients with both acute and chronic liver disease. In mild acute disease, no change or only a modest alteration may be needed. In chronic hepatic disease, the general rule is to employ an arbitrarily selected dose (often one half), depending on Child-Pugh classification of severity of disease, observe for specific end points (if present), i.e., lower heart rate with propranolol or increased pulse rate with theophylline and/or measure drug blood levels (as with propranolol or theophylline) (25,29). For example, acetaminophen is a safe analgesic in patients with modest liver disease (without chronic alcohol abuse), as its metabolism is generally well preserved in patients with mild/moderate liver impairment (33). With severe hepatic dysfunction, acetaminophen metabolism was decreased significantly in one study (34). In this study, using a single dose of acetaminophen, patients with severe liver disease (cirrhosis characterized by hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time, ascites, varices), but not those with milder disease, had significantly longer acetaminophen half-life and greater ratio of acetaminophen/glucuronide and acetaminophen/sulfate conjugates than healthy controls. However, their urinary excretion of cysteine and mercapturic acid conjugates – metabolites that reflect conversion of acetaminophen to reactive hepatotoxic compounds – were normal. The excretion of cysteine and mercapturic acid rises with increasing doses of acetaminophen (35,36). Therefore, there is no evidence to support the interdiction of acetaminophen in patients with chronic liver disease, provided low therapeutic doses (2 g/d) are not exceeded and alcohol is avoided. Nonetheless, it is prudent to monitor the patients' clinical course and liver tests because the effect of long-term acetaminophen dosing is unknown.

Special attention must be paid to the effects of enzyme induction or decrease in drug metabolism by other agents in the presence of liver disease. An example of induction is the effect of chronic ethanol use on the formation of a toxic metabolite of acetaminophen in liver and kidney (37). Since such effects are seen in patients with alcoholic liver disease, it is evident that the process of induction is not vitiated by the presence of cirrhosis. Again the use of only 2 g acetaminophen/day is felt to be safe in such patients (13,38). An example of impaired degradation (which could also be caused by liver disease) is the effect of ketoconazole on the metabolism of cisapride with accumulation of the parent drug, sometimes to cardiotoxic levels (39). The effects of liver damage on induction and inhibition of

drug metabolism, however, appear to have been little studied, so far.

The changes in drug metabolism caused by liver disease are an extension of the large genetic variability (polymorphism) of drug metabolism in normal man (40). Testing of various population groups for drug toxicity prior to drug distribution is a safety valve in defining drug dose and lack of toxicity, even over a wide range of metabolic activity of the liver.

Idiosyncratic Drug Hepatotoxicity with Prior Liver Injury

As commented on earlier, this is the most common type of drug toxicity to the liver and it is believed to depend on the presence of an unpredictable metabolic pathway with the generation of a toxic metabolite, which, by itself or by serving as a haptene for an immune response, induces liver injury. It seems evident that the presence of underlying liver disease should not promote this mechanism of injury which is likely genetically/immunologically determined. In fact, liver injury theoretically could interrupt the metabolite-generating pathway. As conceptualized earlier, it is possible that the idiosyncratic drug toxicity process may be enhanced by the presence of prior liver disease. To our knowledge, however, there are no clinical examples of such reactions. Possible exceptions are the apparently increased hepatic injury with methotrexate in individuals with diabetes, obesity and alcoholism (41), and those given niacin with prior liver disease (42). These, however, are examples of possible potentiation of dose-dependent toxins. Another example is the worsening of liver damage in hepatitis C patients with alcohol consumption. More data in this area are needed, but will be difficult to obtain, as there are no animal models for idiosyncratic toxic drug reactions, and for most of these precise mechanism(s) of injury are uncertain.

A more productive approach would be the development of techniques which can identify susceptible individuals. This would require prior knowledge of the metabolic pathways for each drug that causes this type of injury and the use of surrogate markers for assessing this. This approach has been utilized with dose-dependent hepatotoxic drugs, such as perhexiline maleate using debrisoquine as a metabolic marker (43), and with cyclosporine employing labeled erythromycin (44). When isoniazid toxicity was felt to depend fully on rapid acetylator status, this too could be assessed using other agents. This mechanism is now in doubt, however (45,46). The rarity of the idiosyncratic reactions renders genetic testing, at present, cost-ineffective. However, in patients with such reactions there may be merit in studying *in vitro* drug toxicity in relatives.

Summation of Effects – the Role of Monitoring

Since it is not possible to predict when idiosyncratic hepatotoxins may cause liver damage, and patients with underlying liver disease may require such medications, early detection of such added injury is needed. This usually implies patient monitoring. There are 2 types of surveillance – symptoms/signs and laboratory tests.

Hepatotoxicity is often (but not always) accompanied by symptoms of malaise, anorexia, abdominal pain and fever (25,47). While non-specific, these symptoms should precipitate a prompt patient evaluation for drug hepatotoxicity. This is especially true in the first 6 months of drug use, when such reactions are much more likely (47). Such patient-generated reporting involves the patient, is inexpensive and efficient, and should be mandated. Detection of injury prior to the development of jaundice is especially useful, as onset of hyperbilirubinemia with hepatocellular injury implies a more serious prognosis (25,48). This is especially likely with underlying liver injury.

The use of liver tests for monitoring drug hepatotoxicity is more controversial. While often advocated by drug manufacturers (perhaps partly for legal reasons), such an approach has a number of difficulties. First, mild increases in aspartate and alanine aminotransferase (AST and ALT) may be seen with the use of a number of therapeutic agents, i.e. propylthiouracil (49), isoniazid (25), tacrine (50), without evidence of progressive liver disease and with eventual normalization of results while remaining on the drug. It is difficult, therefore, in the absence of symptoms to determine which abnormal results are clinically important. The usual cut off for concern in patients with previously normal tests is a three-fold increase in AST and ALT, and this mandates close follow up of tests, and often a decision about stopping the drug (51). However, this is an arbitrary number and must be used in the clinical context with each individual. In patients with *a priori* elevated transaminases, there are no guidelines as to what constitutes a significant increase. Extrapolating from data in patients with no liver disease, an increment of about 50–100 IU/l above a verified baseline, especially if sustained or actually rising, would be a logical cause for concern. Concomitant clinical symptoms would be a reinforcing argument. The degree of increase for stopping the drug will depend on the baseline values, and will logically be lesser with higher initial values and impaired clinical condition of the patient. Too many individual factors enter into such equations to permit dogmatic recommendations at

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