Drug-Induced Hepatotoxicity
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Willis C. Maddrey, MD

Abstract: The removal from the marketplace of several widely prescribed drugs due to hepatotoxicity has attracted considerable attention. Now under extensive review are means by which we can better identify hepatic risk prior to federal approval. Assessment of risk-to-benefit ratios regarding a novel agent with hepatotoxicity issues (especially one for a life-threatening condition) requires considerable judgment and education on the part of prescribers and patients. The spectrum of drug-induced liver injury is broad with simulation of almost all unknown liver disorders. Drug-induced liver injuries often have a somewhat characteristic signature, as regards type of injury (hepatocellular vs cholestatic) and time of onset. The diagnosis of drug-induced liver injury is often one of exclusion with initial suspicion based on circumstantial evidence. Factors affecting susceptibility to drug-induced injury include age, sex, concomitant use of other drugs, and genetic polymorphism in metabolic pathways involved in activation or disposition of therapeutic drugs. Drug-drug interactions present particular problems in patients, often elderly, who are receiving several drugs simultaneously. Mechanisms of drug-induced liver injury are many and varied. With many drugs, intermediary products produced during metabolism are highly reactive and toxic. In these situations, the balance between the rate of production of the metabolite and the effectiveness of the drug may determine whether or not hepatic injury occurs.

Key Words: hepatotoxicity, liver injury, drugs, genetic polymorphism, acetaminophen

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The removal from the marketplace of several widely prescribed therapeutic drugs has focused attention on the hepatic safety of all drugs (Fig. 1). Concepts of risk-to-benefit ratios are now being more fully discussed. Indeed, the identification of evidence of hepatotoxicity can rapidly lead to limitation of the use of a drug or, if the reaction is severe, to banning of the agent altogether.[1–6]

A significant number of drugs has been proven, or at least suggested, to cause hepatotoxicity.[1–6] It must be recognized that a drug is a chemical or biologic agent that has been found to cause a favorable effect on a symptom or disease process, has been tested for safety (relative), has been given a name, and then if approved, is widely available. Usually, the propensity to cause liver injury is identified during preapproval evaluations, especially those in large pivotal Phase 3 trials. However, some events are so rare (yet occasionally devastating) that the recognition of the hepatic problem only comes to light after release of a drug and its use in many thousands of patients in widely diverse settings. Attribution of liver injury to a specific drug in a patient may be difficult, and the difficulties are compounded if the patient has underlying acute or chronic liver disease such as chronic hepatitis C, chronic hepatitis B, nonalcoholic fatty liver disease, or alcohol-induced liver disease.

There are few clinical or laboratory manifestations which specifically suggest that a liver injury is the result of a therapeutic drug. The most important clue is often the temporal relationship between initiation of a drug (or drugs) and the appearance of the injury, and of equal importance is the resolution of an abnormality following withdrawal (deceleration).

Much attention has been given to the identification of factors that identify individuals who are at increased risk of developing an adverse hepatic reaction from a drug. There are concerns not only about the drug itself, but also about the effects of drug-drug and drug-disease interactions. In general, it appears that patients with acute or chronic liver diseases are not more likely to develop a hepatotoxic reaction of the idiosyncratic type.[7,8] However, especially in patients who have advanced liver disease, any adverse hepatic reaction that occurs is more likely to lead to clinical evidence of liver injury, in part related to decreased liver mass and decreased abilities to respond to the injury and appropriately regenerate hepatocytes.

SPECTRUM OF HEPATOTOXICITY INDUCED BY DRUGS

The spectrum of drug-induced liver injury ranges from minimal, nonspecific alterations in biochemical tests of no clinical consequence to acute hepatitis, chronic hepatitis, acute liver failure, prolonged cholestatic disease, and even cirrhosis and hepatic tumors. Furthermore, some drugs have been shown to cause fatty liver (simulating alcohol-induced liver disease) and granulomas (simulating sarcoidosis) as well as others that lead to acquired phospholipidosis or predispose to development of the Budd-Chiari syndrome.

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From the University of Texas Southwestern Medical Center at Dallas, Dallas, TX.
Reprints: Willis C. Maddrey, MD, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., M/C 8570, Dallas, TX 75390-8570 (e-mail: wcmaddrey@utsouthwestern.edu).

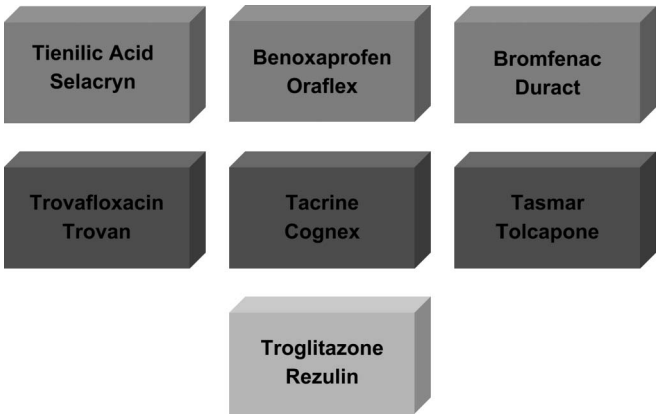

FIGURE 1. Drugs withdrawn or severely limited because of hepatotoxicity.

PREDICTIVE PARAMETERS OF DRUG-INDUCED LIVER INJURY

There are relatively few ways by which acute and chronic liver diseases become clinically manifest. Signs and symptoms of drug-induced liver disease are generally nonspecific and reflect more the extent of the liver injury than the cause. Slight elevations of aminotransferase or alkaline phosphatase levels do not of themselves cause symptoms. Subclinical liver injury induced by a drug may present only as an abnormality of one or more biochemical test detected during a random predetermined evaluation schedule. Most instances of drug-induced aminotransferase elevations are not associated with symptoms and are transient and nonprogressive.

At the other end of the spectrum are patients (fortunately rare) who develop the abrupt onset of devastating liver failure leading to death or to liver transplantation. In between these two extremes are patients who develop signs and symptoms that closely mimic those found in many liver diseases such as acute viral hepatitis, chronic viral hepatitis, or chronic cholestatic disorders.

CLASSIFICATION OF TYPES OF HEPATOTOXICITY

The major categories of drug-induced liver injuries are usually classified as predominately hepatocellular, predominately cholestatic, or mixed. With many drugs, any of these three patterns may be seen. However, most drugs have a "signature" of hepatotoxicity regarding time of onset, frequency, and type of hepatotoxicity that may be encountered.[2,4] The spectrum of recognized potential drug-induced injuries has expanded to encompass injuries in which there are autoimmune features; those that initially cause mitochondrial injury leading to interruption of oxidative phosphorylation; those that disrupt the endoplasmic reticulin or accumulate in lysosomes; and those that lead to excessive disposition of intracellular and extracellular fat. Predominately cholestatic reactions may result from injury in the subcanalicular membrane region or adverse effects on one or more of the several pumps that determines transport across the canalicular membrane into bile (eg, the bile salt excretory pump BSEP inhibition by bosentan).[9]

EVALUATION OF DRUGS BEFORE APPROVAL AND WHAT CAN BE LEARNED

The preclinical and early clinical phases of evaluation of a drug may make it clear that an agent is associated with hepatic side effects and should be abandoned. However, with many agents that later prove to be hepatotoxic, there are few if any clues found during evaluation. It is often disappointing and rather unproductive to rereview preclinical data seeking overlooked clues after a drug has been released and then has been found to be hepatotoxic. The goal is to fully understand the hepatic risk potential of a drug and to identify the type and likely extent of abnormalities before it is released. Unfortunately, the tools available for detection are often imprecise and limited, and there have been no recent meaningful advances. There is currently great interest in identifying individuals at risk based on a determination of genetic polymorphism.[10–12]

In late phase studies, we depend on observing clinical and biochemical events in a test population to identify hepatotoxic potential. However, the test population has often been carefully screened to exclude patients with any major underlying liver disease (eg, chronic viral hepatitis, alcohol-induced liver disease, fatty liver disease, or iron storage disorders to mention a few) and therefore may not reflect the broader population in which the drug is going to be used after approval and release. The full spectrum of age and types of patients likely to be treated with a drug for a commonly encountered disorder may not be included in the trials. Even one death or need for liver transplantation in a late-phase trial of a candidate agent may lead to the discontinuation of development.

Often, clinically significant events that appear after release have no counterparts in a several-thousand-patient Phase 3 trial. In part, this may be related to the size of the study, the duration of observation, or newly recognized drug-drug or drug-disease interactions. In evaluating trials, it is necessary to consider the frequency, time of onset, and cause of all biochemical abnormalities, focusing predominately on the levels of aminotransferases (ALT and AST), alkaline phosphatase, and bilirubin. Gamma glutamyl transpeptidase has not added much to the evaluation process nor have measurements of serum bile acids.

Levels of aminotransferase elevations are often grouped into categories based on multiples of the upper limit of normal of:

$$>3 \times \text{ULN}$$

$$>5 \times \text{ULN}$$

$$>8 \times \text{ULN}$$

However, it is generally the presence of clinically evident liver disease that determines the fate (or if approved, the risk) of the drug. There often arises an issue as to whether all patients who entered the trial had normal aminotransferase levels before entry. In the real world, many patients have slight

elevations of aminotransferases or alkaline phosphatase from fatty liver, alcohol, undiagnosed chronic hepatitis C, or a host of underlying disorders. It may be difficult to assess whether these patients are more likely to manifest a drug-induced abnormality than a patient who has normal levels. Such is especially the case with drugs used to treat patients with chronic hepatitis, cirrhosis, cancer, or fatty liver disease. In many disorders, it may be impossible to find a large group of patients to study in whom all tests are fully within the normal range. Furthermore, it is desirable to study the effects of the drugs in patients who have varying degrees of underlying liver disease in preparation for what may happen after release.

A few broad generalizations may be drawn regarding liver injury from therapeutic drugs, especially those causing hepatocellular necrosis.

- In many (likely most) instances, a slight elevation of a serum aminotransferase is of no clinical importance and may well resolve through poorly understood adaptive mechanisms that develop with continued drug use.
- The combination of elevated aminotransferase (at least $>3 \times$ ULN) and clinically evident jaundice (>3 mg/dL) identifies patients at heightened risk of developing severe injury.
- There may be few clinical signs suggesting liver injury, even in a patient who has biochemical and histologic evidence of considerable damage.
- Early symptoms associated with drug-induced liver injury are usually nonspecific and include loss of appetite, lassitude, and occasionally a dull discomfort in the right upper quadrant of the abdomen.
- With a few drugs, there is the presence of fever, rash, or eosinophilia: the hallmarks of immuno-allergic reactions. These reactions may (or may not) be important in the pathogenesis of the liver injury.

RISK-BENEFIT CONSIDERATIONS IN DRUG EVALUATIONS

With some conditions, the decision is made by the regulatory agencies and then by physicians to accept some hepatic risk to favorably treat a serious health problem, especially if there are few, if any, effective alternatives. There is considerably more leeway in approving drugs for cancer, HIV, Alzheimer's disease, and rare fatal disorders than for those agents directed against nonthreatening problems.[9,13] These considerations are important to the clinician who must determine if abnormalities in biochemical tests or a clinically apparent liver injury in a patient has resulted from an adverse drug reaction or is the result of the underlying medical problem and whether the drug-related risk is worth taking. Sorting out the likely role of a drug in liver injury is especially difficult in patients who are receiving many drugs. The astute clinician must become aware of possible risks to the liver from the specific drugs or combinations of drugs used in an individual's practice.

Decisions regarding attribution of an hepatic injury to a drug is especially difficult in patients (often elderly) who are receiving many drugs (occasionally from several physicians) and in patients who are receiving multiple drugs for complex underlying conditions, such as cardiopulmonary disorders, HIV infection, systemic infections, or cancers.

DIAGNOSIS OF DRUG-INDUCED HEPATIC INJURY

The diagnosis of hepatic injury caused by a drug is often based on circumstantial evidence.[1,4,14] It depends on suspicion (the prepared mind) by the clinician who recognizes that the time of onset of liver injury is possibly related to the introduction of a therapeutic agent. Resolution of manifestations of liver injury (deceleration) following withdrawal of a drug may provide the strongest supportive evidence implicating a drug. Rechallenge with a suspected drug to establish a diagnosis is seldom necessary and, if the initial reaction was clinically apparent, may not be safe. Even histologic evaluation of the liver only allows recognition of what type and how much injury is present, rather than clearly indicating that the liver injury is from a specific drug.

FACTORS THAT AFFECT SUSCEPTIBILITY TO DRUG-INDUCED LIVER DISEASE

Age, sex, and the concomitant use of other medications are important factors to consider in assessing an individual patient's susceptibility to drug-induced liver disease, as is weight and a history of previous reactions to drugs. For some drugs, there is a well-established increase in the risk of adverse reactions with age, especially for individuals who are older than 50 years For example, whereas older patients (>50 years) are quite likely to have some evidence of hepatic toxicity from isoniazid (up to 2%), few reactions have been reported in patients who are younger than 20 years.[1,15] There are a few agents, among them valproic acid and erythromycin estolate, which predominantly cause adverse hepatic reactions in children. Valproic acid-induced hepatotoxicity is also more prevalent in patients who have inherited mitochondrial disorders.[1] Duration of therapy before a reaction occurs is an important part of the "signature." Phenytoin rarely causes significant hepatic toxicity after 6 weeks of therapy, whereas liver injury from nitrofurantoin-induced hepatotoxicity may appear after many months of therapy.[4] For many drugs, females are at an increased risk of developing an adverse hepatic reaction, far exceeding that found in males.

MECHANISMS OF HEPATOTOXICITY

Several mechanisms, some proven and others suggested, may be involved in producing drug-induced injuries.[1,16–18] Some chemical compounds are established hepatotoxins (eg, carbon tetrachloride) and are readily detected as such in preclinical evaluations. With many drugs, intermediary products produced during metabolism prove to be highly reactive and toxic. Potentially injurious metabolic products may be present only transiently and are rapidly metabolized further into harmless substances, thereby avoiding injury. The cytochrome P450s, a family of enzymes largely involved in initial oxidative (Phase 1) reactions of drug metabolism, have established roles in the production of highly reactive

intermediates as well as established roles in further metabolism and disposition. Recognition and characterization of the various cytochrome P450 subspecies involved in metabolism of a drug allow predictions to be made regarding the likelihood of production of reactive intermediates and may focus assessment of the potential for drug-drug interactions if two or more agents are used in combination. For a growing number of drugs, there is evidence that genetic polymorphism in metabolic pathways are important in determining which individuals are likely to have an adverse reaction.[10–12]

Immunologic reactions of the immuno-allergic type appear to play less important (or at best augmenting) roles in the production of most drug-induced injuries. Haptens formed by a drug product and a cellular constituent may provoke formation of antibodies to the neo-antigen and add to injury. Reactions to several drugs, including halothane, diphenylhydantoin, and sulindac, occur in settings suggesting roles for immunologic processes often superimposed on metabolic injury.

Furthermore, some patients with drug-induced liver injury develop autoantibodies. The formerly used (and now withdrawn) uricosuric diuretic tienilic acid occasionally led to hepatic injury in a setting in which there was development of anti-LKM2 autoantibodies.[19] These antibodies were targeted against the cytochrome P450 enzyme that catalyzes the hydroxylation of tienilic acid.

SPECIFIC DRUGS OF SPECIAL INTEREST

Acetaminophen

Acetaminophen-induced hepatic injury is the most common form of drug-induced liver disease and more particularly of acute liver failure in the United States, accounting for nearly 50% of all cases.[5,20,21] Acetaminophen is likely the most widely used drug in the United States and is found in a remarkable number of prescribed and over-the-counter single and combination products, including cold remedies and medications for pain (eg, Vicodin) with names that in no way indicate acetaminophen is a component. Acetaminophen is an established dose-related hepatotoxin.[5,20] In healthy individuals, there is apparently a considerable therapeutic range between harmless and harmful doses of acetaminophen. In therapeutic doses (<3 g/day), the drug is usually quite safe and well tolerated. Ingestion of excessive amounts of acetaminophen (>10–15 g), often in suicidal attempts, predictably leads to liver injury and occasionally death. The issues lie in assessing the risk of patients receiving acetaminophen of 3 to 10 g/day, and whether there are settings in which liver injury is more likely to occur when the patient has not taken a large amount of the drug with a suicidal intent (so-called "therapeutic misadventures").[20]

Hepatic injury from acetaminophen is caused by the effects of a highly reactive metabolic product, N-acetyl-benzoquinone-imide (NAPQI) (Fig. 2).

Acetaminophen is predominantly metabolized by conjugation reactions to form sulfate and glucuronide metabolites, which are excreted in the urine. A lesser amount of the drug is metabolized by cytochrome P450 2E1 to form NAPQI,

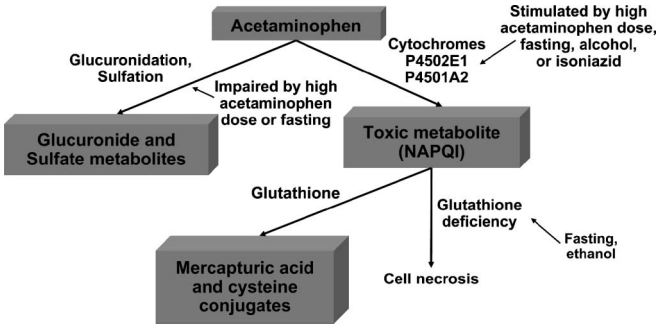

FIGURE 2. Potentiation of acetaminophen hepatotoxicity.

which is rapidly bound to intracellular glutathione and excreted in the urine as mercapturic acid. When excessive amounts of acetaminophen are ingested, the ability to conjugate is overwhelmed and metabolism by cytochrome P450 2E1 becomes of much greater importance. In these situations, the capacity of glutathione to serve as an effective hepatoprotectant may be overwhelmed, and the hepatocyte becomes relatively defenseless against attack by the reactive intermediates.

Two important factors determine the likelihood of production of hepatic injury by acetaminophen: the amount of NAPQI produced by P450 2E1 and the availability of glutathione as a hepatoprotectant. The intracellular concentration of NAPQI and dose of acetaminophen ingested are clearly associated. However, there is more to the story than simply dosage. Factors that affect the production of cytochrome P450 2E1 and of glutathione are of importance. With chronic ingestion of alcohol, doses of acetaminophen near or even with the suggested therapeutic range may lead to liver injury, promoted by an alcohol-induced decrease in intracellular glutathione and possibly an increase (actual or relative to GSH) of cytochrome P450 2E1. The end result is overproduction of NAPQ1 relative to the dispositional pathway of GSH leading to a heightened likelihood of liver damage.

It must be noted that there continues to be controversy regarding the risk of acetaminophen use in patients who drink alcohol.[22–24] Many discussions have occurred at the U.S. Food and Drug Administration regarding labeling and the need for increased awareness of risks by the public. There is general agreement that an overdose of acetaminophen is more likely to cause liver injury in a patient who is a chronic alcoholic. The debate is the definition of overdose and the amount of alcohol ingestion needed to predispose the patient to injury.[22,23] N-acetylcysteine, now available in both oral and intravenous formulations, has proven effective when given early in the course of minimizing acetaminophen-induced injury.

Isoniazid (INH)

Isoniazid has been the mainstay therapeutic agent for the treatment of tuberculosis for more than 50 years. Combination therapies anchored by INH are generally used to prevent the development of resistance to a single therapeutic agent. In the 1960s, INH was used as a single agent in patients who were found to be at risk for developing tuberculosis because of the

findings of a positive tuberculin skin test. INH given alone often leads to elevations of aminotransferase and occasionally to overt liver disease.[15,25] When INH was used as a sole agent, instances of hepatotoxicity appeared suggesting that when given in combination therapies (especially with PASA) the combination of drugs may have been associated with a reduced production of intermediate metabolites of INH.

Elevations of aminotransferase levels from INH usually appear within several weeks following initiation of treatment and are found in 10% to 20% of patients. Usually, these elevations are modest and not associated with signs or symptoms suggestive of liver disease. In many (likely most) patients, continued use of INH is well tolerated and often the aminotransferase levels return to or near normal. If INH is discontinued when the elevations are noted, the aminotransferase levels generally return to normal within 1 to 4 weeks. However, a few patients receiving INH develop significant clinical hepatitis, and drug-induced hepatic failure may occur (0.1%–2.0%) (Fig. 3). Patients older than 50 years are at an increased risk of developing clinically evident hepatitis from INH. Children rarely manifest any clinically evident liver disease from INH. Women are more likely to be severely affected than men. Presently, patient-monitoring schedules with discontinuation of treatment in those in whom there are significant or rising levels of aminotransferases are recommended and appear to be effective. The liver injury from INH appears to be mediated by toxic metabolic products, including hydrazine and monoacetyl derivatives formed during metabolism. There are generally no signs or symptoms suggestive of hypersensitivity. INH is metabolized by N-acetyltransferase and CYP 2E1 to form reactive intermediates.

In the first phase, isoniazid is metabolized by N-acetyltransferase (NAT2) to acetylisoniazid, which is then hydrolyzed to acetylhydrazine.[26,27] Acetylhydrazine is further metabolized by CYP 2E1 to produce hepatotoxic derivatives. In a study from Taiwan of 318 patients who had tuberculosis and were receiving INH, the genotypes of CYP 2E1 and NAT2 were determined by a restriction fragment length polymorphism method.[26] Forty-nine (5.4%) of the patients showed some evidence of hepatotoxicity. The risk of hepatotoxicity based on CYP 2E1 activity and the acetylator status (rapid or slow) was analyzed. The wild-type allele for CYP 2E1 is c1. The risk of hepatotoxicity was 3.94 for CYP 2E1 c1/c1 with rapid acetylation status to 7.43 for CYP 2E1 c1/c1 with slow acetylation. Even after adjustment for acetylation status, CYP 2E1 c1/c1 was an independent risk factor for hepatotoxicity ($P = 0.017$). Volunteers who were CYP 2E1 c1/c1 had higher CYP2E1 activity than those with c1/c2 or c2/c2, suggesting accelerated production of hepatotoxins. Possible induction of CYP 2E1 by alcohol may explain the increases in INH hepatotoxicity seen in regular to heavy users of alcohol. Based on these studies, determination of the CYP 2E1 phenotype before institution of isoniazid therapy may prove clinically useful.

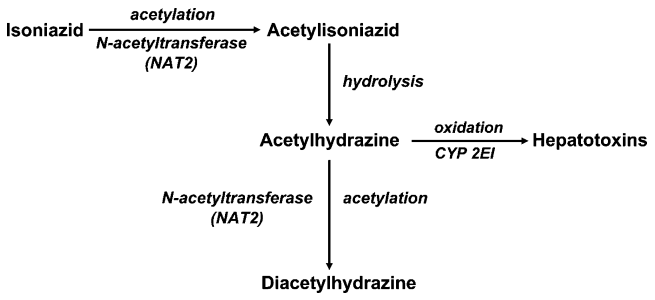

FIGURE 3. Metabolism of isoniazid in the liver.[26]

Troglitazone

Troglitazone, a thiazolidinedione agent that is a PPAR-γ agonist used in the treatment of diabetes, was withdrawn from the market after early extensive use when several instances of acute liver failure leading to death or the need for liver transplantation were identified.[28–31] A vigorous debate has ensued as to whether there was a signal in the prerelease clinical trials, which indicated likely major hepatotoxicity. In the trials, 2510 patients received the drug.[32] Two developed jaundice and 1.9% had aminotransferase elevations of >3 times ULN as compared with 0.6% in patients who received placebo. The hepatic injury in patients who developed liver injury was predominantly hepatocellular. The mechanism for troglitazone-induced liver injury has not been established. Other PPAR-γ agonists (rosiglitazone and pioglitazone) have been associated with hepatotoxicity in rare instances.[33]

Statins

Few drugs have been as widely prescribed as the statins. There have been lingering concerns regarding statin-induced hepatotoxicity from the time of introduction in 1987 of lovastatin, the first member of the class.[34–36] Millions of patients have now received these drugs. Asymptomatic increases in aminotransferase levels develop frequently. Elevations to >3 times upper limit of normal occur in 1% to 3%. In one study, 127 of 6,605 patients treated with lovastatin had ALT elevations of 1.5 to 3 times the upper limit of normal.[37] The elevations in ALT generally return to or toward normal despite continued therapy. There have been remarkably few well-documented instances of statin-induced severe liver injury. There is evidence that suggests the increases in aminotransferases may represent a pharmacologic effect associated with lipid lowering. An intracellular accumulation of precursors following HMG-CoA reductase inhibitors may lead to enlargement of hepatocyte and to ALT increases. Exactly how lowering cholesterol or favorably affecting the lipid profile is associated with aminotransferase elevations remains unknown.

There is no evidence that patients who have elevated baseline ALT levels associated with diabetes, steatohepatitis, or chronic hepatitis C are at increased risk.[38] Therefore, present evidence supports the concept that statins are hepatically safe agents despite the rather frequent elevations of ALT. Again, this supports the concept that mild to moderate elevations of ALT do not equate to liver injury. There is scant support for following a regular biochemical monitoring schedule in patients receiving statins.

Minocycline

Minocycline, a semisynthetic derivative of tetracycline that has been widely used in the treatment of acne, has been reported to cause acute hepatitis, a chronic hepatitis with autoimmune features, and a systemic lupus erythematosus syndrome.[39–43] Several deaths from liver disease have occurred. Positive rechallenges with recurrence of liver disease have been observed. Particular attention has been directed to the autoimmune hepatitis syndrome, which is more frequently observed in females who have received the drug for months to more than a year and is characterized by the presence of fever, arthralgias, hyperglobulinemia, antinuclear antibodies, and a liver biopsy indistinguishable from classic type autoimmune hepatitis.[39,41–43] It is important for the clinician to recognize the role of minocycline and withdraw the drug, which usually leads to rapid improvement. If the patient is considered to have Type 1 autoimmune hepatitis and is treated with corticosteroids while minocycline is continued, there is a risk of partially masking the drug-induced injury. This masking was the case with methyldopa-induced chronic hepatitis and oxyphenistatin-induced chronic hepatitis.[44] The mechanism of minocycline-induced liver injury is unknown.

Patients with the minocycline-induced hypersensitivity syndrome present within a few weeks of initiating therapy with a Stevens-Johnson syndrome, characterized by eosinophilic exfoliative dermatitis and lymphadenopathy.[45]

HEPATOTOXICITY FROM HERBAL COMPOUNDS AND VITAMIN A

There has been increasing recognition that herbal products of many types can cause hepatotoxicity. Patients who have underlying liver disease often use a variety of herbals as alternative medicines. Milk thistle (silymarin) has been widely embraced by patients with hepatitis C, despite lack of extensive controlled studies supporting benefit. Fortunately, there is equally scant evidence of any hepatotoxicity from the compound.

Acute hepatitis and acute liver failure have been reported with a number of compounds including kava. There are special difficulties in associating an herbal product with hepatic injury. These include problems in obtaining an accurate history of ingestion and often an unwillingness of the patient to fully disclose what has been ingested. Traditional and alternative treatment regimens abound throughout the world. These products may vary from lot to lot and are not manufactured to approved standards.

Kava

Extracts of kava-kava, a plant in the pepper family, has been used as a beverage for centuries by South Pacific islanders for reducing anxiety and as a remedy for sleeplessness and menopausal symptoms. More recently, standardized extracts of kava-kava containing concentrated extract have been produced in Europe and subsequently introduced into the United States. Instances of acute hepatic failure and death have been attributed to kava-kava.[46–52] The commercially available standardized extracts that have caused liver injury contain 30% to 70% lactones. Hepatotoxicity is possibly related to the methods of extraction of kava lactones from the roots of the plants.[51] Traditionally kava-kava extracts were prepared by maceration of roots in a water and coconut milk solution. Commercial extracts now use ethanol or acetone as extraction solvents. It has been suggested that glutathione is found in 25% ethanol extracts and plays a role in the Phase 2 conversion of lactones into excretable waste products. It has been determined that glutathione binds irreversibly with kava lactones. Hepatotoxicity in the most highly extracted lactones may in part relate to the concentration of kava and to glutathione depletion. In contrast to the crude extract, standardized extracts contain scant amounts of glutathione relative to the concentration of kava lactones. Signs and symptoms suggestive of liver disease usually appear within several weeks to several months after starting the use of kava-containing preparations. In many patients, only asymptomatic elevations of aminotransferases have been found. However in some, acute liver failure, death, and necessity for liver transplantation have been reported.

Vitamin A (Retinol)

Excessive ingestion of vitamin A is an established cause of liver disease leading to cirrhosis with ascites and portal hypertension.[53–55] Chronic ingestion of large amounts of vitamin A often used as part of the megavitamin generalized health protection programs can lead to chronic intoxication and liver injury.

Hypervitaminosis A most often results from self-medication. The usual recommended dose of vitamin A for adults is 5,000 IU per day. Hepatic injury has been seen in patients who received 15,000 to greater than 40,000 units a day for a period of years.[54] Even higher doses may produce signs of intoxication within several months. The liver is a principal storage site for retinol and, more specifically, the stellate cells bear the brunt of the attack. Many patients with liver injury from ingesting excessive vitamin A go unrecognized, and only an astute clinician is likely to make the association between chronic ingestion of vitamin A and otherwise unexplained advanced hepatic disease with cirrhosis, ascites, and portal hypertension.

The clinical picture most often is one of insidious onset of cirrhosis. Elevations of aminotransferases are found in over 70% of patients with vitamin A-induced liver injury, along with slightly elevated levels of alkaline phosphatase and occasional minimal to modest elevations of serum bilirubin. In patients with advanced vitamin A intoxication, hypoalbuminemia and hypoprothrombinemia are present.

Vitamin A is stored in stellate cells. A syndrome of hepatoportal sclerosis with portal and perisinusoidal fibrosis as well as sclerosis of terminal venules and atrophy of zone 3 of the hepatic lobule are characteristic findings. Portal hypertension results from the compromising of sinusoids by the enlarged stellate cells as well as by fibrous tissue deposited in the sinusoids and the sclerosis of the terminal venules. Occasionally microvesicular steatosis is found.

Vitamin A-induced hepatic injury apparently results from the intrinsic toxicity of vitamin A, and the extent of the injury depends on the dose and duration of exposure. The increased levels of vitamin A in stellate cells lead to

multiplication of the cells and conversion to myofibroblasts. Alcoholic patients appear to be unusually susceptible to vitamin A intoxication. Alcohol potentiates the toxicity of vitamin A in experimental situations. The treatment is withdrawal, and the diagnosis depends on careful history taking and awareness.

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