REVIEW ARTICLE

MEDICAL PROGRESS

Drug-Induced Hepatotoxicity

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In the past five years, two drugs have been withdrawn from the market by the Food and Drug Administration (FDA) for causing severe liver injury, a potential danger that had not been fully recognized in the course of the preapproval clinical trials. Reports of adverse drug reactions of any type engender fear and skepticism in the public about the actions of the pharmaceutical industry and the FDA.[1] Drug-induced hepatic injury is the most frequent reason cited for the withdrawal from the market of an approved drug, and it also accounts for more than 50 percent of the cases of acute liver failure in the United States today. More than 75 percent of cases of idiosyncratic drug reactions result in liver transplantation or death.[2] Recent efforts by the National Institutes of Health and the FDA have been directed toward a better understanding of these occurrences in order to improve the outcomes.[3,4] In this article, I will review the pathogenesis of drug-induced liver injury, the common adverse drug reactions that involve the liver, and the process of drug approval.

Hepatic Biotransformation

The liver, located between the absorptive surface of the gastrointestinal tract and drug targets throughout the body, is central to the metabolism of virtually every foreign substance. Most drugs and xenobiotics are lipophilic, enabling them to cross the membranes of intestinal cells. Drugs are rendered more hydrophilic by biochemical processes in the hepatocyte, yielding water-soluble products that are excreted in urine or bile.[5] This hepatic biotransformation involves oxidative pathways, primarily by way of the cytochrome P-450 enzyme system.[6] After further metabolic steps, which usually include conjugation to a glucuronide or a sulfate or glutathione, the hydrophilic product is exported into plasma or bile by transport proteins located on the hepatocyte membrane, and it is subsequently excreted by the kidney or the gastrointestinal tract.

Types of Drug Reactions

Most drugs cause liver injury infrequently. These reactions are considered idiosyncratic, occurring at therapeutic doses from 1 in every 1000 patients to 1 in every 100,000 patients, with a pattern that is consistent for each drug and for each drug class. Idiosyncratic reactions are characterized by a variable delay or latency period, ranging from 5 to 90 days from the initial ingestion of the drug, and are frequently fatal if the drug is continued once the reaction has begun. In contrast, with a drug such as isoniazid, mild injury may disappear despite continued use. Rechallenge is typically met with a more severe reaction regardless of whether the initial reaction was severe or mild. A few drugs such as acetaminophen injure hepatocytes in a dose-dependent fashion, so that the administered dose is a stronger determinant of the likelihood of a reaction than the host's metabolic constitution. In addition to the dose received, the patient's age,[6] sex,[7] and body-mass index affect metabolism and, therefore, outcomes, as do the simultaneous

use of other foods and drugs and physiologic changes such as pregnancy and renal[8] or liver disease.

For reasons that are unclear, women generally predominate among patients with drug-induced liver injury, as illustrated in a recent study in which women accounted for 79 percent of reactions due to acetaminophen and 73 percent of idiosyncratic drug reactions.[2] Substances such as phenobarbital, phenytoin, ethanol, cigarette smoke, and grapefruit juice that induce hepatic enzymes may alter plasma drug levels; such alteration, in turn, can result in extrahepatic adverse effects (e.g., torsade de pointes and drug interactions).[6,9] Enzyme inducers have a dynamic role in enhancing hepatotoxicity, as exemplified by the interaction of ethanol with acetaminophen (Fig. 1), in which ethanol (the inducer) enhances liver injury.[10] Substrate competition occurs when ethanol and acetaminophen are taken simultaneously; the combination actually decreases the speed of the metabolism of acetaminophen to its harmful byproduct. However, ethanol simultaneously slows the degradation of the 2E1 isoform of cytochrome P-450, thus increasing the availability of the enzyme and enhancing the formation of the toxic metabolite once ethanol is withdrawn.

TARGETS OF CELL INJURY

At least six mechanisms that primarily involve the hepatocyte produce liver injury, and the manner in which various intracellular organelles are affected

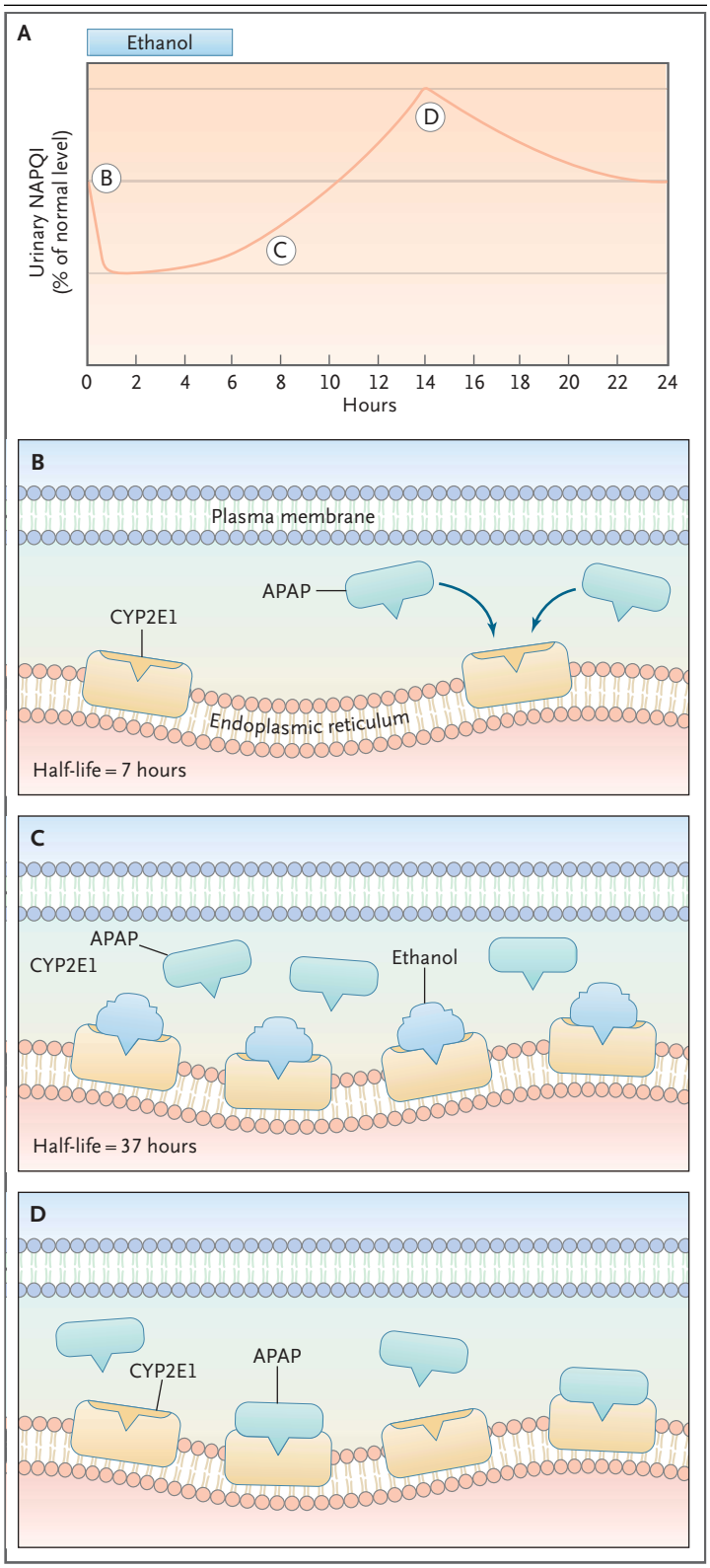


Figure 1. The Role of Ethanol in the Formation of *N*-acetyl-p-benzoquinone-imine (NAPQI), the Toxic Metabolite of Acetaminophen (APAP), and the Dynamics of Enzyme Induction.

Panel A depicts the variation in urinary levels of NAPQI over time, when ethanol competes with acetaminophen for cytochrome P-450 2E1 (CYP2E1). Panels B, C, and D depict three phases of this process. During the metabolism of acetaminophen, NAPQI formation is diminished when alcohol is present, and although the rate at which CYP2E1 degrades is slowed, the half-life of the enzyme increases, from 7 hours (Panel B) to 37 hours. As long as ethanol remains in the body, there is competition between acetaminophen and ethanol for CYP2E1, which is temporarily more available (Panel C). As Panel D shows, once ethanol is removed, NAPQI formation is enhanced, resulting in increased hepatic injury in the 24 hours after the cessation of alcohol consumption. Adapted from Thummel et al.[10]

defines the pattern of disease (Fig. 2). If high-energy reactions involving cytochrome P-450 enzymes lead to covalent binding of drug to intracellular proteins, intracellular dysfunction is apparently produced that results in the loss of ionic gradients, a decline in ATP levels, and actin disruption, cell swelling, and cell rupture (Fig. 2A).[15,16] Drugs that affect transport proteins at the canalicular membrane can interrupt bile flow. Certain drugs, for example, bind to or disable the bile salt export protein. This process causes cholestasis; however, little cell injury occurs (Fig. 2B).[11] Genetic defects in transporters, as in the multidrug-resistance–associated protein 3, in combination with hormones may promote cholestasis during pregnancy or during treatment with estrogen-containing medications. In mixed forms of hepatic injury, the combined failure of canalicular pumps and other intracellular processes allows toxic bile acids to accumulate, causing secondary injury to hepatocytes. If cells of the bile ducts are injured, a likely outcome is protracted or permanent cholestasis, a disorder that has been termed the "vanishing bile duct syndrome."

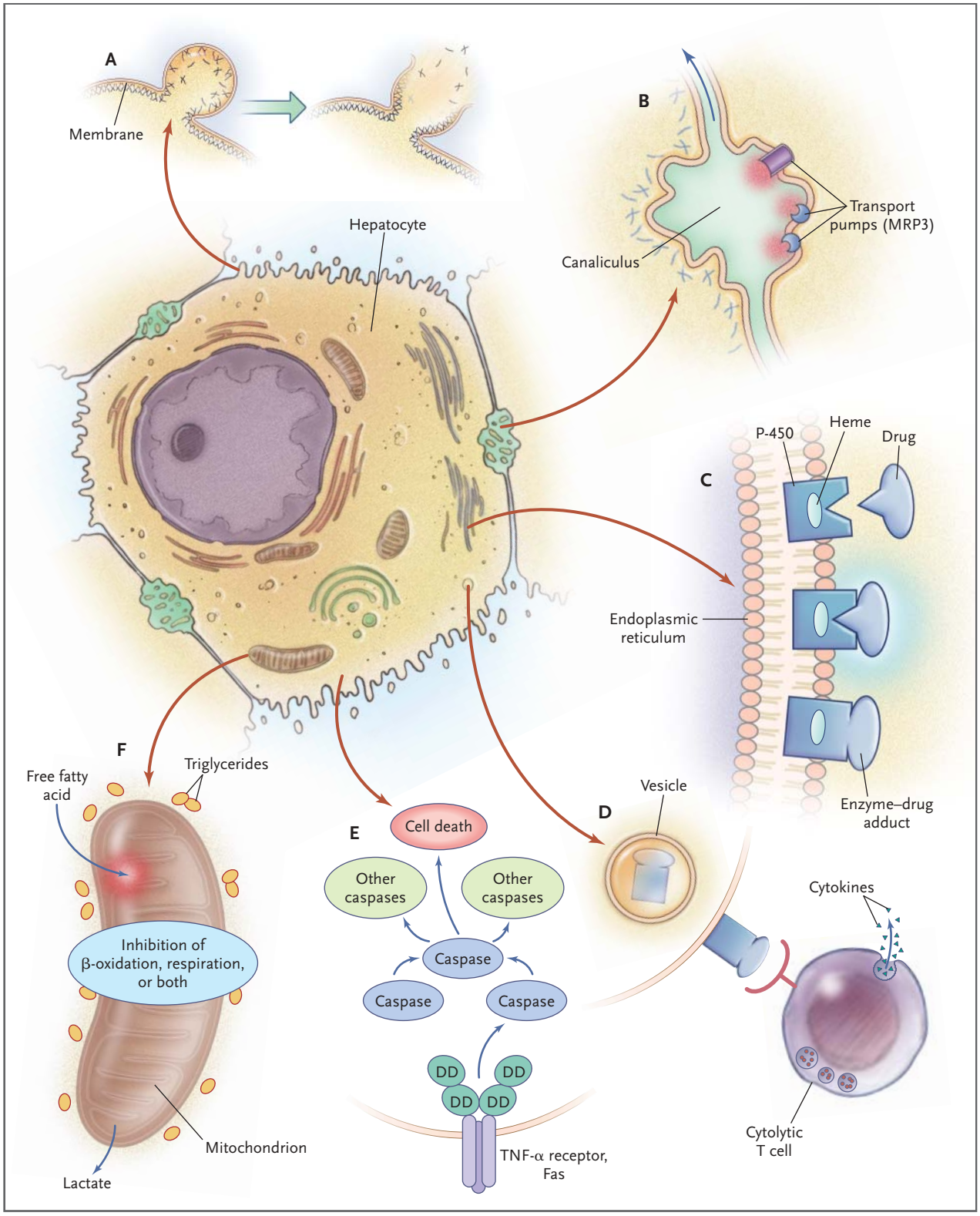
Drugs are relatively small molecules and, therefore, are unlikely to evoke an immune response. However, biotransformation involving high-energy reactions can result in the formation of adducts — that is, drugs covalently bound to enzymes. Adducts that are large enough to serve as immune targets may migrate to the surface of the hepatocyte, where they can induce the formation of antibodies (antibody-mediated cytotoxicity) or induce direct cytolytic T-cell responses (Fig. 2C and 2D).[12] The secondary cytokine response thus evoked may cause inflammation and additional neutrophil-mediated hepatotoxicity.[17] Programmed cell death (apoptosis) can occur in concert with immune-mediated injury, destroying hepatocytes by way of the tumor necrosis factor (TNF) and the Fas pathways, with cell shrinkage and fragmentation of nuclear chromatin (Fig. 2E).[13] Proapoptotic receptor enzymes, if activated by drugs, will compete with protective so-called survival pathways within the cell, and this dynamic interaction may shift the balance either in favor of or against further cell damage.

Still other pathways to injury may develop when drugs damage mitochondria, disrupting fatty-acid oxidation and energy production. When drugs bind to or otherwise disable respiratory-chain enzymes or mitochondrial DNA, oxidative stress results, with ensuing anaerobic metabolism, lactic acidosis, and triglyceride accumulation (microvesicular fat within cells) (Fig. 2F).[14] Steatohepatitis (fat that primarily accumulates in the large vesicles outside the liver cells, with associated inflammation) is commonly associated with alcohol abuse, but it may also result from drugs.

Other cells within the liver may be the target of drug injury or serve as modulators of an incipient reaction. For example, Kupffer's cells activate cytokines that may amplify injury,[18] and fat-storage cells (stellate cells) or macrophages may augment injury, produce fibrosis, or form granulomas. Chemotherapeutic agents can injure sinusoidal endothelial cells, a process that can lead to veno-occlusive disease.[19] Therapeutic hormone administration

Figure 2 (facing page). Six Mechanisms of Liver Injury.

Injury to liver cells occurs in patterns specific to the intracellular organelles affected. The normal hepatocyte shown in the center of the figure may be affected in at least six ways, labeled A through F. Disruption of intracellular calcium homeostasis leads to the disassembly of actin fibrils at the surface of the hepatocyte, resulting in blebbing of the cell membrane, rupture, and cell lysis. In cholestatic diseases, disruption of actin filaments (B) may occur next to the canaliculus, the specialized portion of the cell responsible for bile excretion.[11] Loss of villous processes and the interruption of transport pumps such as multidrug-resistance–associated protein 3 (MRP3) prevent the excretion of bilirubin and other organic compounds. Many hepatocellular reactions involve the heme-containing cytochrome P-450 system (C), generating high-energy reactions that can lead to the covalent binding of drug to enzyme, thus creating new, nonfunctioning adducts. These enzyme–drug adducts migrate to the cell surface (D) in vesicles to serve as target immunogens for cytolytic attack by T cells, stimulating a multifaceted immune response involving both cytolytic T cells and cytokines.[12] Activation of apoptotic pathways by tumor necrosis factor α (TNF-α) receptor or Fas may trigger the cascade of intercellular caspases (E), which results in programmed cell death with loss of nuclear chromatin.[13] Certain drugs inhibit mitochondrial function by a dual effect on both β-oxidation (affecting energy production by inhibition of the synthesis of nicotinamide adenine dinucleotide and flavin adenine dinucleotide, resulting in decreased ATP production) and the respiratory-chain enzymes (F). Free fatty acids cannot be metabolized, and the lack of aerobic respiration results in the accumulation of lactate and reactive oxygen species. The presence of reactive oxygen species may further disrupt mitochondrial DNA. This pattern of injury is characteristic of a variety of agents, including nucleoside reverse-transcriptase inhibitors, which bind directly to mitochondrial DNA, as well as valproic acid, tetracycline, and aspirin.[14] Toxic metabolites excreted in bile may damage bile-duct epithelium (not shown). DD denotes death domain.



may induce hepatocyte dedifferentiation, resulting in benign adenomas and, rarely, carcinomas.[20] Clearly, multiple cellular pathways to liver injury are possible.

PATHOGENESIS

Most idiosyncratic drug reactions result from a succession of unlikely events, a "multihit" process. Genetic variants in isoenzymes that generate toxic byproducts are unlikely to cause severe toxicity alone, given that severe liver toxicity occurs so infrequently.[5,21] In addition, hepatotoxicity may wax and wane with continuing drug use, implying that suppressor or attenuator pathways are active.[17,22] Immune responses, once initiated, may be amplified or suppressed by means of the class I and class II major-histocompatibility-complex cell-surface receptors.[12,17] The efficacy of drug-adduct peptide binding for antigen presentation depends on HLA configurations that have been genetically defined. For example, a specific HLA haplotype believed to be associated with hepatitis induced by the administration of amoxicillin–clavulanate was found in 57 percent of patients with the illness but in only 12 percent of unaffected persons.[23]

Cell-surface neoantigens may be short-lived, but they reappear with continued exposure to the drug.[24] Late events in the immune sequence, such as expression of interleukin-10 or TNF-α, may augment or inhibit injury. For example, a specific interleukin-10 promoter phenotype that inhibits interleukin-10 secretion, which results in downregulation of type 2 helper T-cell immune reactions, is linked to diclofenac toxicity.[25] Variant TNF-α phenotypic expression has been implicated as a determining factor in the severity of drug reactions related to acetaminophen.[26] The xenobiotic constitutive androstane receptor has recently been shown to be another key modulator of acetaminophen toxicity in mice and potentially in humans, as well as a new target for hepatoprotective strategies that is not mediated by immune responses.[27]

A series of events that first involve intracellular disruption, cell necrosis, or apoptosis, followed by activation of the immune sequence, might explain the features of idiosyncratic drug reactions: their rarity, their severity, and their resolution despite continued use of the drugs by patients with phenotypes that appear to be adaptive.[22]

It is possible, but not yet proven, that the genetic background of each patient could be addressed by pharmacogenomic approaches. Eventually, drug-mediated injuries may be prevented by screening methods that can identify aberrant gene polymorphisms or RNA-expression profiles before a patient uses a drug.[21] Pharmacogenetic testing can identify unique cytochrome P-450 alleles that affect drug levels, but it is not clear whether specific markers of very rare idiosyncratic reactions can be identified, particularly if the reaction involves multiple steps.[28]

CLINICAL CONSEQUENCES

The most frequent hepatotoxic drug reactions evoke moderate-to-severe injury to hepatocytes with a clinical picture that resembles viral hepatitis, characterized by a rapid onset of malaise and jaundice in association with elevated aminotransferase levels. Each drug has its own pattern of injury. If hepatocyte injury predominates, aminotransferase levels may be at least five times as high as normal. Elevations of alkaline phosphatase and bilirubin levels predominate in cholestatic syndromes. Signs of allergic reaction are absent in most patients. Acute liver failure may develop after a week or more of illness, particularly if the patient has continued the drug after the onset of symptoms. Death is not uncommon; elderly persons seem to be at particular risk, but specific data supporting this pattern are sparse.[2]

IDIOSYNCRATIC REACTIONS

Idiosyncratic drug reactions made up 20 percent of cases of severe liver injury requiring hospitalization in a U.S. study involving 307 patients at six hospital centers (unpublished data). A variety of clinical patterns are observed (Table 1). The majority of idiosyncratic drug reactions involve damage to hepatocytes throughout the hepatic lobule, with various degrees of necrosis and apoptosis (Fig. 3A and 3B). Symptoms of hepatitis occur typically within days or weeks after the initial exposure and may continue to evolve even after the offending drug is withdrawn. Liver biopsy is seldom helpful for diagnosis.

ALLERGIC REACTIONS

Some drug reactions have a striking allergic component. Sulfa drugs may induce fever, rash, and eosinophilia. Phenytoin is associated with fever, lymphadenopathy, rash, and severe hepatocyte injury — a group of signs that has been termed the "reactive metabolite syndrome" and that is slow to resolve in most instances.[29] Halothane is also associated with this type of liver injury, though only after multiple

Table 1. Idiosyncratic Drug Reactions and the Cells That Are Affected.

Type of Reaction	Effect on Cells	Examples of Drugs
Hepatocellular	Direct effect or production by enzyme–drug adduct leads to cell dysfunction, membrane dysfunction, cytotoxic T-cell response	Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin
Cholestasis	Injury to canalicular membrane and transporters	Chlorpromazine, estrogen, erythromycin and its derivatives
Immunoallergic	Enzyme–drug adducts on cell surface induce IgE response	Halothane, phenytoin, sulfamethoxazole
Granulomatous	Macrophages, lymphocytes infiltrate hepatic lobule	Diltiazem, sulfa drugs, quinidine
Microvesicular fat	Altered mitochondrial respiration, β-oxidation leads to lactic acidosis and triglyceride accumulation	Didanosine, tetracycline, acetylsalicylic acid, valproic acid
Steatohepatitis	Multifactorial	Amiodarone, tamoxifen
Autoimmune	Cytotoxic lymphocyte response directed at hepatocyte membrane components	Nitrofurantoin, methyldopa, lovastatin, minocycline
Fibrosis	Activation of stellate cells	Methotrexate, excess vitamin A
Vascular collapse	Causes ischemic or hypoxic injury	Nicotinic acid, cocaine, methylenedioxymethamphetamine
Oncogenesis	Encourages tumor formation	Oral contraceptives, androgens
Mixed	Cytoplasmic and canalicular injury, direct damage to bile ducts	Amoxicillin–clavulanate, carbamazepine, herbs, cyclosporine, methimazole, troglitazone

exposures.[30] The slow resolution of immunoallergic reactions suggests that allergens remain on the hepatocyte surface for weeks or months. Rapid recognition of toxic effects and immediate discontinuation of the offending agent are the keys to limiting hepatic and cutaneous damage. Even in the absence of systemic signs of allergy or peripheral-blood eosinophilia, eosinophilic infiltrates or granulomas may be present in a liver-biopsy specimen.

BILE-DUCT INJURY

When cholestasis predominates, injury to bile secretory components is present, either at the canalicular membrane or beyond (Fig. 3C). Associated jaundice and pruritus may be severe, with permanent loss of bile ducts (Fig. 3D).[31]

DOSE-RELATED ACETAMINOPHEN TOXICITY

Acetaminophen, as an example of a drug with dose-related toxic effects, rapidly causes hepatocyte injury, predominantly in the centrilobular region (Fig. 3E). Acetaminophen toxicity produces the most common form of acute liver failure in the United States, accounting for 39 percent of cases in a recent survey of tertiary care centers.[2] This type of liver injury occurs both after attempted suicide by acetaminophen overdose and after unintentional "therapeutic misadventures," in which use of the drug for pain relief in excess of the dose specified in the package labeling typically occurs over a period of several days.[32] A careful medical history taking will clarify the quantity ingested; blood levels can be confirmatory but may not be elevated in cases of unintentional overdose. Extremely high aminotransferase values (typically exceeding 3500 IU per liter) help clinicians distinguish the toxic effects of acetaminophen from viral hepatitis or other drug injuries. N-acetylcysteine given for 36 to 72 hours reliably repletes glutathione and prevents injury if begun within 12 to 24 hours after ingestion. Cases of unintentional poisoning have a poorer outcome than suicide attempts. Chronic alcohol abuse, concomitant treatment with phenytoin and isoniazid, and starvation worsen liver injury related to acetaminophen.[33,34] The incidence of acetaminophen poisoning and the severity of the outcomes vary widely throughout the world[35]; children are also occasionally susceptible to this form of acute liver failure.[36] Changes in packaging that limit the number of doses and the accessibility of the drug may

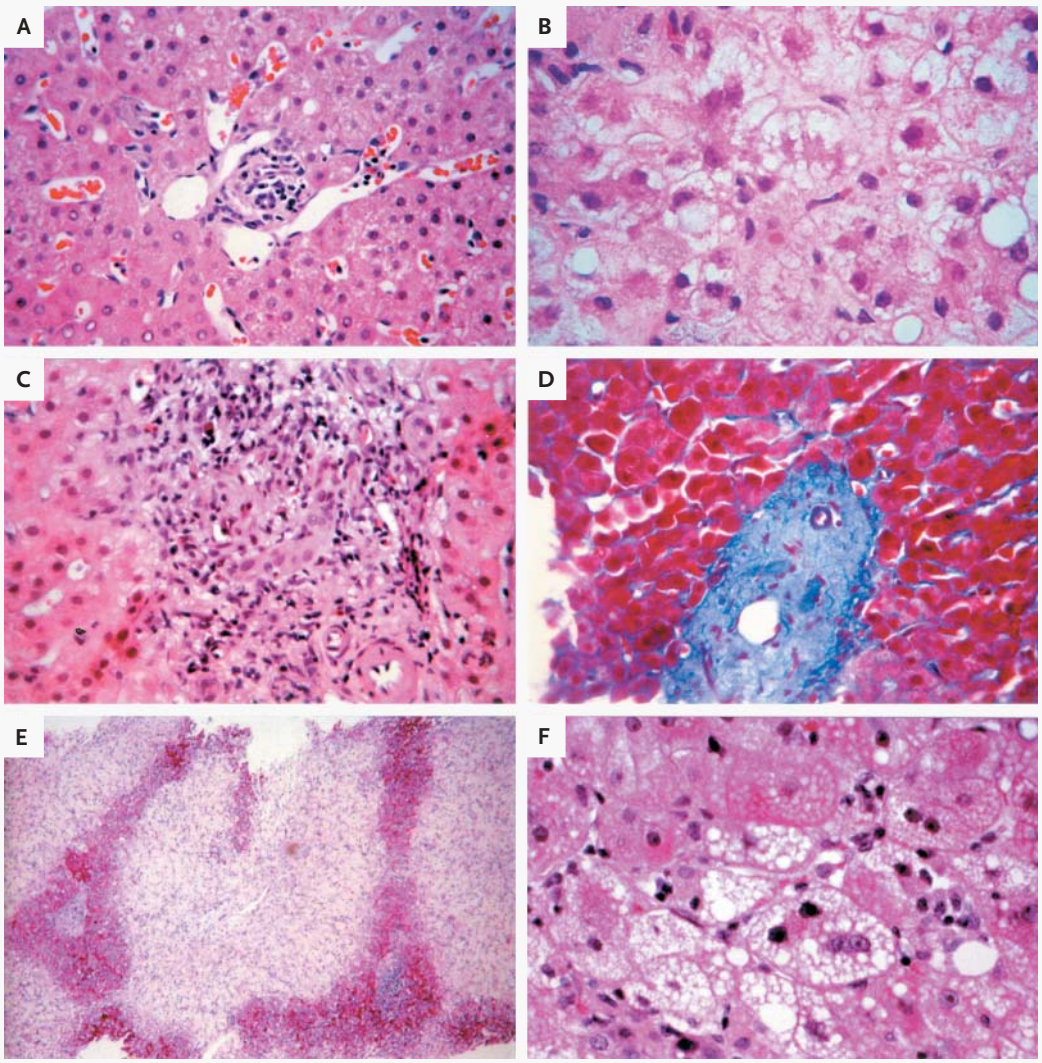


Figure 3. Histologic Characteristics of Drug-Induced Liver Injury.

Panel A shows a high-power view of a normal liver that includes a portal tract and surrounding hepatic sinusoids. Cells and their nuclei are relatively uniform in size and staining characteristics. No hepatic venule is shown (hematoxylin and eosin, ×240). Panel B shows the hepatotoxic effects of troglitazone in a 54-year-old woman with diabetes. This midzonal view shows ballooning degeneration of hepatocytes with lobular disarray (hematoxylin and eosin, ×320). Panel C shows cholestatic injury due to trimethoprim–sulfamethoxazole in a 42-year-old woman. This portal tract shows a severely damaged bile duct surrounded by lymphocytes and eosinophils. The percentage of eosinophils in the peripheral blood reached 42 percent (hematoxylin and eosin, ×320). In Panel D, a follow-up biopsy specimen from the same patient eight months later demonstrates the loss of bile ducts (vanishing bile duct syndrome). This portal tract shows a normal artery and vein with no evident bile duct remaining (Masson trichrome, ×360). Panel E shows the results of unintentional acetaminophen overdose in a 34-year-old woman, which includes severe centrilobular and midzonal necrosis with sparing of portal tracts and periportal hepatocytes (periodic acid–Schiff with diastase, ×60). Panel F shows toxic effects in a 34-year-old man with human immunodeficiency virus infection who was admitted with severe lactic acidosis and shock three weeks after beginning didanosine. There is a striking accumulation of small fat vesicles within cells, as well as a moderate inflammatory infiltrate, primarily lymphocytes and plasma cells (hematoxylin and eosin, ×360).

improve outcomes in all age groups.[37] In addition to acetaminophen, other drugs also display a degree of dose-dependency in their capacity to cause liver injury (Table 2).

LESS COMMON DRUG REACTIONS

Several less frequent types of drug reactions involving the liver are included in Table 1. The rarer reactions typically involve nonparenchymal cells of the liver, such as sinusoidal endothelial cells.

DIAGNOSIS AND TREATMENT OF DRUG REACTIONS

It is difficult to identify a drug reaction with certainty. However, the possibility of a drug reaction must be considered in any patient with liver dysfunction. A careful drug history should be taken, which includes the patient's use of prescription, over-the-counter, herbal, or alternative medications. Injury induced by complementary and alternative medications has become more common as the use of these medications has increased.[38,39] Various compounds — including germander, chaparral leaf, weight-loss preparations containing usnic acid,[40] and many others — have been reported to be hepatotoxic. Other causes of liver dysfunction, such as viral hepatitis, hypotension, and biliary tract or liver disease related to alcohol abuse, must be excluded by a thorough medical history taking, ultrasonography, and appropriate serologic tests.

Assessment of causality can be difficult; often, many agents are used simultaneously, and questions about other potential causes may be inadvertently omitted. Causality-assessment methods provide a uniform approach to determine the likelihood of drug involvement in a suspected episode of hepatitis.[41-44] Included among the standard factors that should be considered are the temporal relation (whether the onset of the symptoms was between 5 and 90 days after the initial exposure); the course after the patient stopped taking the drug (improvement within weeks); risk factors such as alcohol use, pregnancy, or old age; the concomitant use of drugs; the exclusion of causes other than drugs (e.g., viral hepatitis); patient's history with regard to previous toxic effects of the particular agent; and the response to rechallenge, if performed. In many instances, data are incomplete. Cautious rechallenge should be considered only if the diagnosis of drug-induced toxicity was highly questionable and only if no other drug is available to treat a serious problem.

Table 2. Effects of Increased or Cumulative Doses of Drugs.*

Drug	Dose Effect
Acetaminophen	Increased dose: hepatocyte necrosis, apoptosis
Amiodarone	Cumulative dose: steatohepatitis
Bromfenac	Cumulative dose: hepatocyte necrosis
Cocaine, phencyclidine	Increased dose: ischemic necrosis
Cyclophosphamide	Increased dose: hepatocyte necrosis (worse with increased aminotransferase levels)
Cyclosporine	Increased dose: cholestatic injury
Methotrexate	Increased or cumulative dose: hepatocyte necrosis, fibrogenesis
Niacin	Increased dose: ischemic necrosis
Oral contraceptives	Cumulative dose: associated with hepatic adenomas

* Though many of these reactions may be considered idiosyncratic, the individual or total dose has a role with these agents.

Therapy for hepatotoxic effects of drugs consists of the immediate withdrawal of any and all suspected drugs. If a severe allergic reaction is observed, corticosteroids may be used, but no controlled trials have been performed to ascertain their efficacy. Similarly, ursodiol is frequently given for cholestatic liver injury, but it has not been subjected to careful study in this setting. Except for N-acetylcysteine for acetaminophen poisoning, there are no specific antidotes. The patient should be transferred to a liver-transplantation center if coagulopathy (as measured by an international normalized ratio of 1.5 or greater) or encephalopathy is present.

HEPATOTOXICITY IN PATIENTS WITH CHRONIC LIVER DISEASE

Is the patient with liver disease more susceptible than others to liver injury? If liver function is impaired, one might expect a diminished likelihood of toxic reactions as a result of decreased enzyme activity. However, many enzyme systems are preserved, even in advanced liver disease, particularly those involved in conjugation reactions. In severe liver disease, the activity of the cytochrome P-450 2C19 isoenzyme is greatly decreased, whereas that of the 2D6 isoenzyme is intact.[45,46] Increased lev-

els of cytochrome P-450 2E1, as observed in nonalcoholic steatohepatitis, might enhance the toxicity of acetaminophen, but this effect has not been reported.[47,48] Rates of drug metabolism in patients with cirrhosis may be reduced as much as 50 percent. Changes resulting from the increased fibrosis along the hepatic sinusoids in patients with cirrhosis further separate the bloodstream and hepatocyte.[49]

In general, patients with liver diseases are not uniformly at increased risk for hepatic injury, but there are some exceptions. Patients with hepatitis C do appear to be at increased risk for veno-occlusive disease after myeloablative therapy in preparation for bone marrow transplantation.[50] Patients infected with the human immunodeficiency virus (HIV) who are being treated with highly active antiretroviral therapy may be at increased risk for hepatotoxic effects when they are coinfected with underlying liver diseases such as hepatitis B and C.[51,52] The use of toxic drugs in the patient with established cirrhosis increases the risk of hepatic decompensation.[53] Nonetheless, physicians cannot withhold vital medications from such patients. Thus, extra caution should be used in treating patients with underlying liver disease, because of potential for serious consequences. Frequent monitoring may be valuable but has not been shown to be cost effective and is often not performed. Since patients with cirrhosis are also prone to renal injury, aminoglycosides, radiocontrast agents, and prostaglandin inhibitors must be used with extreme caution in this group.

THE PROCESS OF DRUG APPROVAL

Why is severe drug-induced liver injury often identified only after the drug is approved by the FDA? Each phase of clinical testing before approval includes close monitoring of serum liver-enzyme levels. Occasional increases in aminotransferase levels during clinical trials will not by themselves lead to the discontinuation of testing of a new drug, but the finding of frequent or more severe increases in aminotransferase levels (greater than eight times the upper limit of normal) or accompanying increases in bilirubin may do so. To detect a single case of clinically significant liver injury due to a drug with 95 percent confidence, the number of patients studied must be about three times the incidence of the reaction. A phase 3 study typically involves approximately 3000 patients. Idiosyncratic reactions can be expected to occur in less than 1 in 10,000 patients exposed; detecting a single reaction when its frequency is 1 in 10,000 would therefore require testing 30,000 patients. As a result, many drugs complete phase 3 testing and are approved before a case of idiosyncratic drug reaction is identified, since there is little chance of such a reaction in a small study cohort. Drugs that cause hepatotoxic effects will lead to acute liver failure in approximately 10 percent of those in whom drug-related jaundice develops.[54] Thus, any drug that causes jaundice in preapproval trials will probably lead to acute liver failure when larger numbers of patients are exposed. Such drugs now require additional scrutiny before approval by the FDA.[4]

After approval, a much larger and more diverse group of patients is often exposed than was the case in the carefully controlled prelicensing trial. This wider range of patients, with doses, durations of treatment, and concomitant conditions beyond those encountered in the preapproval trials, will include several categories of patients at elevated risk for adverse effects: patients with renal failure or heart failure, patients with HIV infection or the acquired immunodeficiency syndrome, pregnant women, elderly persons, and children. After FDA approval, pharmaceutical companies are required to report serious adverse events (any incident resulting in death, a threat to life, hospitalization, or permanent disability) to the agency within 24 hours.[55] Surveillance becomes a passive process once a drug is on the market, with most cases reported through the FDA's MedWatch program, through which physicians and pharmacists may voluntarily file written reports. It is estimated that MedWatch receives reports of fewer than 10 percent of adverse drug reactions.[56] A recent study from France suggests that, at least in that country, fewer than 6 percent of hepatic adverse drug reactions are ever reported.[57]

DRUGS RECENTLY WITHDRAWN FROM THE MARKET

Two drugs that were withdrawn because of hepatotoxicity — bromfenac and troglitazone — provide examples of problems encountered in the postapproval period. Bromfenac, a nonsteroidal anti-inflammatory drug marketed as Duract, was introduced in 1997 as a short-term analgesic for orthopedic pain.[58] Nonsteroidal drugs, as a class, including the newer cyclooxygenase-2 inhibitors, have been associated with considerable hepatotox-

icity.[59-61] The FDA approved bromfenac for use for periods of 10 days or less, but longer periods of treatment were clearly possible after approval. Once released, bromfenac was associated with more than 50 cases of severe liver injury, and the drug was withdrawn in June 1998. All patients in whom toxicity was observed had been taking the drug for more than 30 days.[62]

Troglitazone (Rezulin) was the first of a new class of compounds, the thiazolidinediones, approved by the FDA in January 1997. A nuclear regulatory factor peroxisome proliferator-activated receptor gamma agonist, troglitazone reduces insulin resistance and increases insulin-stimulated glucose disposal, improving glucose control for patients with type 2 diabetes. In clinical trials, reversible elevations of serum aminotransferase levels were observed, occasionally exceeding eight times the upper limit of normal, but no examples of liver failure were identified. Once the drug was approved, however, reports of severe and fatal liver injury began to appear.[63-66]

The pathogenesis of troglitazone toxicity is not understood.[67] Unlike bromfenac, troglitazone was not immediately removed from the market, because its benefits were initially thought to outweigh the risks. Over time, despite the addition of a black-box warning to the package insert that suggested monitoring of aminotransferase levels monthly, the number and severity of cases of hepatotoxic effects (a total of more than 90, of which at least 68 were fatal and 10 necessitated transplantation) prompted the FDA to withdraw troglitazone from the open market three years after its approval. A factor in the decision to withdraw the drug was the approval in May 1999 and July 1999 of two new thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos). These newer agents do not have the same degree of toxicity, although severe liver injury has been reported.[68-70] Although there may be intrinsic differences in these newer drugs, more careful screening of patients by alert physicians, monitoring of aminotransferase levels, and early discontinuation of therapy in the event of moderately severe cases (as a result of the increased awareness) may contribute to the apparent greater safety of the newer drugs. Depending on the therapeutic importance of a drug, it may continue to be used despite its risks. Isoniazid[71] remains a first-line agent against tuberculosis, even though increased levels of aminotransferase are observed in 15 to 20 percent of patients who take the medication and 1 in 1000 patients will have severe hepatic necrosis.[72]

These examples highlight the difficulties encountered by the FDA in providing oversight of the drug-testing process. It is impossible to predict every possible eventuality accurately from clinical trials. In reviewing new agents for approval, the FDA is charged with protecting the public from harm while recognizing each drug's predicted health benefits. However, it is only after a drug is approved and tested on the open market that its ultimate benefit and risk can truly be determined.

APPROACH TO NEW DRUGS

Case reports of toxic effects that appear in the first years after a drug is approved may help the FDA determine which new agents require closer scrutiny, as exemplified by some recent case reports of hepatotoxic effects of newer agents.[73-100] Patients may not initially report taking complementary and alternative medications, which do not require prescriptions or FDA oversight. A careful inquiry by the physician may be necessary to identify the use of complementary medications and determine their role in liver injury.[38-40,101-103] Monitoring aminotransferase levels on a monthly basis for the first six months of treatment has been suggested for patients taking medications that are known hepatotoxins, such as isoniazid or diclofenac. However, monitoring is unlikely to be effective in the case of a rare adverse reaction, such as that seen with terbinafine (incidence, 1 in 50,000). Monitoring is seldom performed consistently, and even if it were, it provides no guarantee of safeguarding the patient, since many drug reactions develop abruptly.[104] Many deaths could be prevented if the offending drug were discontinued at the first sign of an adverse reaction.

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