SUPPLEMENT ARTICLE

Drug-Induced Liver Injury

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Drug-induced hepatotoxicity is a frequent cause of liver injury. The predominant clinical presentation is acute hepatitis and/or cholestasis, although almost any clinical pathological pattern of acute or chronic liver disease can occur. The pathogenesis of drug-induced liver disease usually involves the participation of the parent drug or metabolites that either directly affect the cell biochemistry or elicit an immune response. Each hepatotoxin is associated with a characteristic signature regarding the pattern of injury and latency. However, some drugs may exhibit >1 signature. Susceptibility to drug-induced hepatotoxicity is also influenced by genetic and environmental risk factors. Unpredictable, low-frequency, idiosyncratic reactions often occur on a background of a higher rate of mild asymptomatic liver injury and, although difficult to predict, they may be detected by monitoring serum alanine aminotransferase levels. Recent and future advances in toxicogenomics and proteomics should improve the identification of risk factors and the understanding of idiosyncratic hepatotoxicity.

Drug-induced liver toxicity is a common cause of liver injury. It accounts for approximately one-half of the cases of acute liver failure and mimics all forms of acute and chronic liver disease [1]. An estimated 1000 drugs have been implicated in causing liver disease on >1 occasion [2]. Although, with the exception of rare cases, drug-induced liver injury subsides after cessation of treatment with the drug, this represents an important diagnostic and therapeutic challenge for physicians. The present article provides an overview of the mechanisms involved in drug-induced liver disease, together with the risk factors and disease characteristics associated with drug-induced hepatotoxicity.

PATHOGENESIS

Adverse hepatic events caused by drugs can be considered to be either predictable (high incidence) or unpredictable (low incidence). Drugs that produce predictable liver injury, such as paracetamol, usually do so within a few days and are generally a result of direct liver toxicity of the parent drug or its metabolites [3]. Unpredictable events manifest as overt or symptomatic disease and can occur with intermediate (1–8 weeks) or long (1 year) periods of latency. A typical example of the former is phenytoin [4], and an example of the latter is isoniazid [5]. The majority of adverse drug-induced hepatic events are unpredictable and are either immune-mediated hypersensitivity reactions or are idiosyncratic.

The pathogenesis of drug-induced liver injury usually involves the participation of a toxic drug or metabolite that either elicits an immune response or directly affects the biochemistry of the cell. In either case, the resultant cell death is the event that leads to the clinical manifestation of hepatitis [2, 6]. Metabolism of chemicals takes place largely in the liver, which accounts for the organ's susceptibility to metabolism-dependent, drug-induced injury [7]. The drug metabolites can be electrophilic chemicals or free radicals that undergo or promote a variety of chemical reactions, such as the depletion of reduced glutathione; covalently binding to proteins, lipids, or nucleic acids; or inducing lipid peroxidation (figure 1). All of these have consequent direct effects on organelles such as mitochondria, the endoplasmic reticulum, the cytoskeleton, microtubules, or the nucleus. They may also indirectly influence cellular or-

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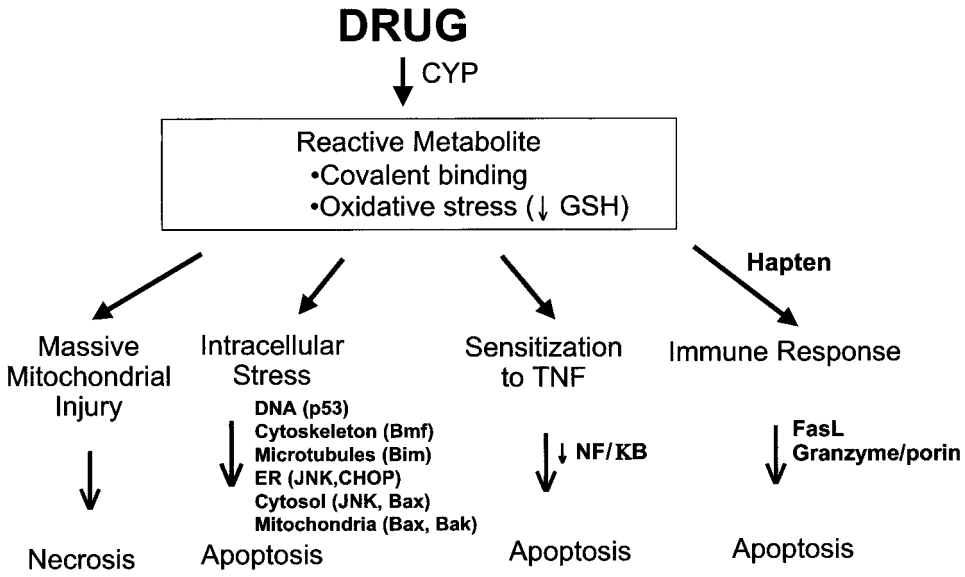

Figure 1. Cellular mechanisms of drug hepatotoxicity. Bmf, Bim, Bax, and Bak are proapoptotic members of the B cell lymphoma–2 protein family; CHOP, c/EBP homologous protein-10; GSH, glutathione; JNK, c-jun-N-terminal kinase; ↓, inhibition.

ganelles through the activation and inhibition of signaling kinases, transcription factors, and gene-expression profiles. The resultant intracellular stress leads to cell death caused by either cell shrinkage and nuclear disassembly (apoptosis) or swelling and lysis (necrosis) [6, 8–10]. Hepatocyte death is the main event that leads to liver injury, although sinusoidal endothelial cells [11] or bile duct epithelium [12] may also be targets.

Sensitization to liver-specific cytokines can also occur, thereby causing cytokine-induced hepatotoxicity [6, 9]. Alternatively, the reactive metabolite may covalently bind to or alter liver proteins, such as cytochrome P450 enzymes, leading to an immune response and to immune-mediated injury [13, 14]. This immune-mediated, drug-induced hepatitis is usually characterized by fever, eosinophilia, or other allergic reactions that distinguish it from non–immune-mediated drug-induced hepatitis [15]. The mechanism for the induction of the immune-mediated drug reaction is not clear, but it may involve a hapten-like action [16]. Generally, low-molecular-weight organic chemicals or drugs are not immunogenic, but they may become so when they are bound to a macromolecule, such as a protein. If a drug metabolite produced by cytochrome P450 is able to act as a hapten, it would covalently bind to a liver protein and, subsequently, alter that protein [17]. This altered protein would then be perceived as foreign by the immune system, resulting in an autoimmune attack on normal hepatocellular constituents.

This hypothesis, however, does not explain many aspects of immune-mediated drug-induced hepatitis. For instance, covalent binding (haptenation) is a regular occurrence with drugs, such as halothane, that rarely cause immune-mediated toxicity [18]. It is possible that a reactive metabolite may also have to injure or stress liver cells, in addition to modifying a protein, to induce an immune response [19].

Certain drugs exclusively or predominantly induce cholestasis. Several of these, such as sulindac [20] and chlorpromazine [21], are associated with hypersensitivity-type reactions. The specific immunological targets of these hypersensitivity-type adverse reactions are poorly understood. However, given that the predominant histological features are portal inflammation and biliary injury, they are likely to be related to the bile duct. It is possible that toxic metabolites undergoing canalicular excretion react with macromolecules in the duct cells or undergo further metabolism within these cells, resulting in ductal injury [15]. Drug-induced immune-mediated injury, therefore, is an adverse immune response against the liver and/or bile duct that results in a disease with clinical features that are hepatic, cholestatic, or a mixture, the mechanisms of which are not clearly understood.

CLINICAL AND PATHOLOGICAL SYMPTOMS OF DRUG-INDUCED LIVER DISEASES

Individual drugs that induce liver disease tend to have a characteristic signature, which is composed of a clinical and pathological pattern and a latency period (table 1). As was previously stated, the majority of adverse reactions are similar to the symptoms of acute hepatitis, cholestasis, or mixed presentations. The accepted definitions for these reactions are given in figure 2. Not all drugs exhibit a single specific signature reaction; some, such as augmentin, show more than one. The latency period can be short (hours to days), intermediate (1–8 weeks), or long (1–12 months). In some cases (e.g., augmentin or erythro-

mycins), a delayed reaction can occur after the medication is withdrawn. This may occur up to 3–4 weeks after the completion of a course of antibiotic treatment. The mechanism is not understood, but the effect may be caused by the slow development of an immune response to the drug, combined with its prolonged retention in the body. Cholestatic reactions tend to be prolonged after the discontinuation of the causative drug; presumably, cholangiocytes repair and regenerate more slowly than hepatocytes. Also, a self-propagating immune response may persist (although probably very rarely).

A recent emerging aspect of the signature reaction is the gene-expression profile. The use of toxicogenomics to identify a signature pattern of gene expression for hepatotoxins will lead to a better understanding of the mechanism of unpredictable reactions [22]. The combination of toxicogenomics and proteomics may also provide the technology to identify individuals at risk and predict toxic potential when overt liver damage does not occur in a small study population.

- **Hepatitis (cytotoxic) – parenchymal cell**
  - **Necrosis/apoptosis**
  - **↑ ALT (ALT/ULN ÷ alk ptase/ULN ≥5)**
  - **Jaundice and ↑INR: prognostic**
- **Cholestasis (canalicular or ductular)**
  - **↑ Alk ptase (ALT/ULN ÷ alk ptase/ULN ≤2)**
  - **Jaundice: prolonged**
- **Mixed hepatitis/cholestasis**
  - **ALT/alk ptase >2 to <5**

Figure 2. Definitions of drug-induced liver disease, indicating affected laboratory values. Alk ptase, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio; ULN, upper limit of normal;↑, increase in level.

RISK FACTORS

The risk of developing hepatotoxicity involves a complex interplay between the chemical properties of the drug, environmental factors (e.g., the use of concomitant drugs or alcohol), age, sex, underlying diseases (e.g., HIV or diabetes), and genetic factors [23, 24] (figure 3). The most extensively documented risk factors are concomitant drug use and diseases. There is recent evidence for an increase in drug-induced liver disease among patients with HIV, hepatitis B virus, and hepatitis C virus infections, which suggests a role for cytokine imbalance in these patients. Genetic factors include genes that control the handling of the drug (metabolism, detoxification, and transport), as well as those that influence cell injury and repair. Additionally, genetic polymorphisms with functional effects occur with many of the genes that encode drug-metabolizing enzymes and drug transporters [25]. However, whether a genetic polymorphism of a drug-metabolizing enzyme has clinical relevance depends on its functional role in the metabolism of a drug. Familial sensitivity to the toxic effects of metabolites has also been shown, which indicates that these may be inherited defects in the defense against specific drug-related injuries [26].

ASSESSMENT OF CLINICAL DRUG-INDUCED LIVER DISEASE

Drug-induced liver diseases mimic all forms of acute and chronic hepatobiliary diseases. However, the predominant clinical presentation resembles acute icteric hepatitis or cholestatic liver disease. The former is the more serious and often has a 10% mortality rate, regardless of the causative drug [1, 2, 27]. Acute icteric hepatitis is accompanied by markedly elevated serum transaminase levels and a minimal increase in the level

Table 1. Clinical and pathological features of drug-induced liver disease.

Signature disease	Drug(s) causing the feature
Acute hepatitis	Acetaminophen, bromfenac, isoniazid, nevirapine, ritonavir, troglitazone
Chronic hepatitis	Dantrolene, diclofenac, methyldopa, minocycline, nitrofurantoin
Acute cholestasis	ACE inhibitors, amoxicillin/clavulanic acid, chlorpromazine, erythromycins, sulindac
Mixed pattern or atypical hepatitis	Phenytoin, sulfonamides
Nonalcoholic steatohepatitis	Amiodarone, tamoxifen
Fibrosis/cirrhosis	Methotrexate
Microvesicular steatosis	NRTIs, valproic acid
Veno-occlusive disease	Busulfan, cyclophosphamide

NOTE. ACE, angiotensin-converting enzyme; NRTI, nucleoside reverse-transcriptase inhibitor.

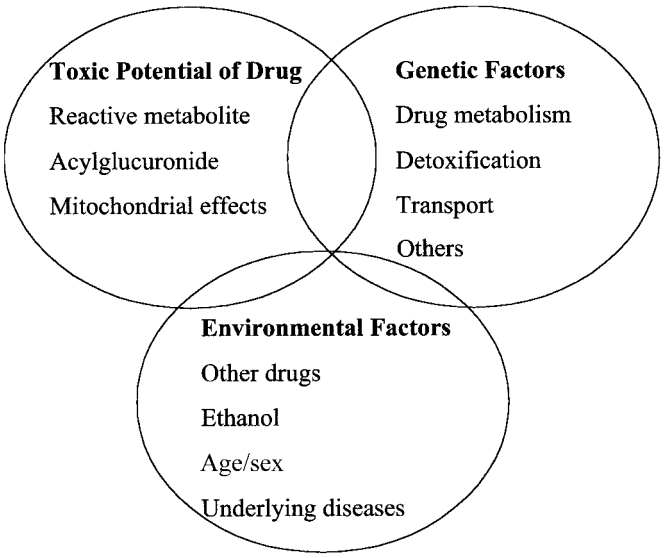

Figure 3. Risk factors for susceptibility to drug-induced hepatotoxicity

of alkaline phosphatase. Coagulopathy and encephalopathy are present in more severe cases. Cholestatic disease (which is also referred to as cholestatic hepatitis) is not usually life threatening; it presents with jaundice, pruritus, and marked increases in alkaline phosphatase levels, as well as mild increases in alanine aminotransferase (ALT) levels. Mixed injury patterns with intermediate to marked increases in ALT and alkaline phosphatase levels can resemble atypical hepatitis or granulomatus hepatitis [27].

Very few drugs currently in clinical use are associated with predictable dose-related liver toxicity; an example is acetaminophen [3]. Most instances of drug-induced liver disease are unpredictable, and symptoms occur either with intermediate or long periods of latency before onset. Low-frequency, unpredictable reactions, either immune-mediated hypersensitivity or idiosyncratic, often occur on a background of a higher incidence of mild, asymptomatic, and usually transient liver injury [27]. The physician is therefore able to assess the risk of the drug-induced liver disease by taking into account the signature of the disease, the latency period, the patient's risk factors, and the exclusion of concomitant drugs and other possible causes. In unpredictable and idiosyncratic cases, the routine monitoring of ALT levels may be helpful in identifying a population with toxic potential, although issues of cost-effectiveness and compliance with therapy render this approach problematic. This is not the case, however, with predictable or immune-mediated reactions that have a short latency period and a rapid onset of symptoms. Management should include the cessation of treatment with the drug, where appropriate; possibly, a short course of high-dose corticosteroids, if the systemic features of hypersensitivity are severe; and the withdrawal of cross-reacting drugs (e.g., anticonvulsants and halogenated anesthetics). In all cases of drug-induced liver disease, it is pertinent to assess whether the adverse reaction has been noted previously, is alleviated by the discontinuation of the drug, or recurs if the drug is reintroduced. Also, it is necessary to ensure that other potential causes of the adverse reaction have been excluded. The early identification of an adverse event, together with effective assessment and monitoring, can prevent the occurrence of irreversible liver damage.

SUMMARY

Drug-induced liver disorders occur frequently, can be life threatening, and mimic all forms of liver disease. However, except in rare cases of drug-induced chronic hepatitis and vanishing bile duct disease, the liver injury subsides and the adverse event disappears after the cessation of treatment with the drug. The liver is a particular target for drug toxicity because of its role in clearing and metabolizing chemicals. The parent drug, or metabolite, may affect critical biochemical functions, sensitize the liver to the effects of cytokines, or elicit an immune response. This induced reaction is often unpredictable, which implies that other factors—such as environment, age, sex, and genetic factors—are able to alter the susceptibility to the adverse event.

Most drugs with predictable liver toxicity are screened out during preclinical drug development, but unpredictable and rare hypersensitivity or idiosyncratic reactions are often not noted until a drug is used in the clinical situation. A wide range of liver diseases can occur, but individual hepatotoxic drugs generally have a characteristic clinical and pathological signature and latency period. Most are similar to acute hepatitis, cholestasis, or mixed presentation. Drug-induced, immune-mediated hepatic injury is an adverse immune response against

the liver that also exhibits hepatic, cholestatic, or mixed clinical features. However, it should be noted that some drugs exhibit more than one signature reaction.

Hepatotoxicity caused by drugs, in particular idiosyncratic reactions, is a major challenge to the pharmaceutical industry and physicians. The application of new technologies, such as pharmacogenomics, toxicogenomics, proteomics, and metabonomics, offers the potential to identify risk factors and clarify the pathogenesis of idiosyncratic hepatotoxicity. Pharmacogenomics holds promise in identifying the genetic polymorphisms associated with drug metabolism, toxicogenomics characterizes patterns of altered gene expression, proteomics characterizes patterns of altered protein expression, and metabonomics characterizes patterns of altered metabolites in urine or blood. These altered patterns can provide clues as to pathogenesis and define the molecular signature of the toxicity of a specific drug or groups of drugs by its mechanism of action or clinical manifestations. These technologies may be useful during drug development in predicting trouble during animal-model studies and in the postmarketing assessment of idiosyncratic reactions.

References

1. Kaplowitz N. Drug-induced liver disorders: implications for drug development and regulation. Drug Saf **2001**; 24:483–90.
2. Zimmerman H. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, **1999**.
3. Pham T-V, Lu S, Kaplowitz N. Acetaminophen hepatotoxicity. In: Taylor MB, ed. Gastrointestinal emergencies. 2nd ed. Baltimore: Williams & Wilkins, **1997**:371–88.
4. Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. J Clin Invest **1988**; 82:1826–32.
5. Thompson N, Caplin M, Hamilton M, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J **1995**; 8:1384–8.
6. Kaplowitz N. Biochemical and cellular mechanisms of toxic liver injury. Semin Liver Dis **2002**; 22:137–44.
7. Kaplowitz N. Drug metabolism and hepatotoxicity. In: Kaplowitz N, ed. Liver and biliary diseases. 2nd ed. Baltimore: Williams & Wilkins, **1996**:103–20.
8. Kaplowitz N. Mechanisms of liver cell injury. J Hepatol **2000**; 32:39–47.
9. Kaplowitz N. Mechanisms of cell death and relevance to drug hepatotoxicity. In: Drug-induced liver disease. Kaplowitz N, DeLeve LD, eds. New York: Marcel Dekker, **2002**:85–95.
10. Kaplowitz N. Cell death at the millennium: implications for liver distress. Clin Liver Dis **2000**; 4:1–23.
11. DeLeve L, Wang X, Kuhlenkamp J, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. Hepatology **1996**; 23:589–99.
12. Odin JA, Huebert RC, Casciola-Rosen L, et al. Bcl-2–dependant oxidation. J Clin Invest **2001**; 108:223–32.
13. Beune PH, Lecoeur J. Immunotoxicity of the liver: adverse reactions to drugs. J Hepatol **1997**; 26(Suppl 2):37–42.
14. Robin MA, Le Roy M, Descatoire V, et al. Plasma membrane cytochrome P450 as neoantigens and autoimmune targets in drug-induced hepatitis. J Hepatol **1997**; 26(Suppl 1):23–30.
15. Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. Clin Liver Dis **2002**; 6:467–86.
16. Kitteringham NR. Drug-protein conjugation and its immunological consequences. Drug Metab Rev **1990**; 22:87–144.
17. Knowles S, Uetrecht J, Shear N. Idiosyncratic drug reactions: the reactive metabolite syndrome. Lancet **2000**; 356:1587–91.
18. Uetrecht J. New concepts in immunology relevant to idiosyncratic drug reactions: the "danger" hypothesis and innate immune system. Chem Res Toxicol **1999**; 12:387–95.
19. Matzinger P. Tolerance, danger and the extended family. Annu Rev Immunol **1994**; 12:991–1045.
20. Tarazi EM, Harter JG, Zimmerman H, et al. Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. Gastroenterology **1993**; 104:569–74.
21. Moradpour D, Altorfer J, Flury R, et al. Chlorpromazine-inducing vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology **1994**; 20:1437–41.
22. Ulrich R, Friend SH. Toxicogeneomics and drug discovery: will new technology produce better drugs? Nat Rev Drug Discov **2002**; 1(1): 84–8.
23. DeLeve L, Kaplowitz N. Prevention and therapy of drug-induced hepatic injury. In: Wolfe M, ed. Therapy of digestive disorders. Philadelphia: WB Saunders, Harcourt, Brace, **2000**:334–48.
24. Zimmerman H. Drug-induced liver disease. In: Schiff E, Sorell M, Madding W, eds. Schiff's diseases of the liver. 8th ed. Philadelphia: Lippencourt Raven, **1999**:973–1064.
25. Loeper J, Descatoire V, Maurice M, et al. Presence of functional cytochrome P450 on isolated rat hepatocyte plasma membrane. Hepatology **1990**; 11:850–8.
26. Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. J Clin Invest **1988**; 82:1826–32.
27. Kaplowitz N. Drug-induced liver disorders: introduction and overview. In: Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. New York: Marcel Dekker, **2002**:1–13.