CURRENT OPINION

Drug Safety 2001; 24 (7): 483-490
0114-5916/01/0007-0483/$22.00/0

Drug-Induced Liver Disorders
Implications for Drug Development and Regulation

Neil Kaplowitz

USC Research Center for Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Abstract

Drug-induced hepatotoxicity is a frequent cause of liver disease. Although often presenting as acute hepatitis and/or cholestasis, virtually any clinical-pathological pattern of acute or chronic liver disease can occur. Most reactions occur in a small proportion of the population using a particular drug. Each drug associated with hepatotoxicity tends to have a characteristic signature regarding latency and pattern of injury. The mechanism can be drug metabolism-dependent or related to the chemical properties of the parent drug. The former are immune mediated or due to metabolic idiosyncrasy. Monitoring serum ALT levels is of unproven effectiveness but should be considered when there is an increased risk of delayed onset serious hepatitis-like reactions. The key for the future is improved identification of toxic potential in preclinical studies, clinical trials and postmarketing experience. The elucidation of the genetic and environmental mechanisms contributing to delayed idiosyncratic reactions is a major barrier to overcome in this field.

Drug-induced liver disease represents a major problem for drug development and safety. Hundreds of drugs have been implicated in causing liver disease at least on rare occasions and in the US, drug-induced liver disease is the most common cause of acute liver failure, accounting for one-third to one-half of cases.[1,2] In addition to representing an important diagnostic/therapeutic challenge for physicians caring for patients presenting with liver disorders, the frequency and economic impact of this long standing problem is a major challenge for the pharmaceutical industry and regulatory bodies. Recent problems with bromfenac and troglitazone have once again put the spotlight on this problem.

The purpose of this review is to call attention to this important problem and the issues it raises for clinicians, pharmaceutical industry and regulatory bodies. The material which forms the basis of the facts and opinions in this review was obtained from the authors' files and a literature search on drug-induced liver disorders since 1994 to provide the most up to date information.

1. Clinical Overview

Drug-induced liver disease can mimic all forms of acute and chronic hepatobiliary diseases (table I).[3,4] However, the predominant clinical presentations resemble acute icteric hepatitis or cholestatic liver disease. The former is of grave significance as the mortality approximates 10% irrespective of the causative drug.[3] This type of reaction is accompanied by systemic symptoms, jaundice, markedly elevated serum transaminase levels and, in the more severe cases, coagulopathy and encephalopathy indicative of acute (fulminant) liver failure.

Table I. Spectrum of hepatic manifestations of drug-induced liver disorders

Acute hepatitis	Isoniazid, paracetamol (acetaminophen), troglitazone
Chronic hepatitis[a]	Nitofurantoin, methyldopa, diclofenac, minocyline
Acute cholestasis	Amoxicillin-clavulanic acid, erythromycin, sulindac, chlorpromazine
Mixed hepatitis/cholestasis or atypical hepatitis	Phenytoin, sulfonamides
Chronic cholestasis[a]	Chlorpromazine
Nonalcoholic steatohepatitis	Amiodarone
Fibrosis/cirrhosis	Methotrexate
Microvesicular fatty liver	Valproic acid (sodium valproate), nucleoside reverse transcriptase inhibitors
Veno-occlusive disease	Busulfan, cyclophosphamide

a Drugs which cause chronic disease more frequently cause acute disease.

Cholestatic disease, although not usually life threatening, presents with jaundice, disproportionate increased serum alkaline phosphatase levels and pruritus; cholestatic reactions tend to resolve very slowly (i.e. months versus weeks for hepatitis) and on rare occasion lead to vanishing bile duct disease and biliary cirrhosis.[5,6] Individual drugs tend to exhibit a consistent pattern or signature of the reaction with characteristic latency and clinical presentation. However, some drugs may show several patterns: e.g. nimesulide can cause a short latency hypersensitivity-mediated cholestatic injury and a delayed idiosyncratic acute hepatitis-like reaction.[7] Other types of reactions are listed in table I with some examples of causative drugs.

2. Pathogenesis

Adverse hepatic events due to drugs can be considered simply as predictable (high incidence) or unpredictable (low incidence). The bulk are unpredictable and can be viewed as either immune-mediated hypersensitivity reactions or as idiosyncratic. Latency between the initiation of therapy and the onset of liver disease provides some clue as to the pathogenesis. Early onset within a few days (particularly if there has been no previous exposure) is strong evidence for direct toxicity of the drug or its metabolite which is characteristic of predictable reactions; paracetamol (acetaminophen) overdose is an example.[8] Unpredictable reactions manifested as overt or symptomatic disease can occur with intermediate (1 to 8 weeks) or long latency (up to 12 months). Intermediate latency is characteristic of hypersensitivity reactions. These tend to be associated with fever, rash and eosinophilia and a rapid positive rechallenge.[3,4] Hepatotoxicity of sulindac,[9] phenytoin[10] and amoxicillin-clavulanic acid[11] are typical examples. It is important to recognise that these reactions may occur up to 3 to 4 weeks after a 1 to 2 week course of medication (e.g. amoxicillin-clavulanic acid). The long latency type of reaction is characteristically not associated with features of hypersensitivity and the response to rechallenge is variable. Thus, one assumes that these events reflect some type of delayed change in the metabolism of the drug or the response to injury (repair or regeneration). Drugs associated with delayed reactions include isoniazid[12] and troglitazone.[13] However, in the case of isoniazid, the latency may be shortened when used in combination with rifampicin (rifampin).[14] Also, as noted above, some drugs can produce either a short latency hypersensitivity or long latency idiosyncratic reaction.[7]

An interesting feature of these low frequency unpredictable reactions, either hypersensitivity or idiosyncratic, is that they often occur on a background, higher rate of mild, asymptomatic, and usually transient liver injury which is detected as abnormal biochemical tests, particularly serum ALT. Generally, the biochemical abnormality defined as an ALT level >3 times the upper limit of normal (ULN) may occur 10 to 20 more frequently than overt disease. Thus, in the majority of patients with an increased ALT level some type of adapta-

tion or 'tolerance' occurs and in the minority there is a failure to do so. This issue is further complicated by the mysterious nature of the long latency in some of the idiosyncratic reactions.

Hepatotoxicity of drugs can be principally metabolism-dependent, parent drug-dependent or a combination of both. Metabolism takes place largely in the liver which accounts for its susceptibility to drug-induced injury.[4] The metabolites may be electrophilic chemicals or free radicals which deplete reduced glutathione, covalently bind to proteins, lipids or nucleic acids, or induce lipid peroxidation. The consequences include hepatocellular necrosis, apoptosis or sensitisation to cytokines or inflammatory mediators produced by nonparenchymal cells. Alternatively, the reactive metabolites may covalently bind to or alter liver proteins such as cytochrome P450 enzymes leading to sensitisation and immune mediated injury. The immune phenomena nevertheless are metabolism-dependent. Thus, the rare occurrence of immune-mediated liver disease is often superimposed on a higher frequency of mild injury (abnormal ALT level) suggesting that the drug has a mild toxic potential (e.g. phenytoin or halothane) but in rare individuals this toxic potential leads to metabolism-dependent hypersensitivity. Genetic polymorphisms of enzymes involved drug activation or detoxification have been implicated in the susceptibility to hypersensitivity reactions to sulfonamides[15,16] and anticonvulsants.[10,17] Presumably genetic polymorphisms of either major histocompatibility complex (MHC)–I-dependent antigen presentation in hepatocytes or MHC–II-dependent antigen presentation in macrophages, which have scavenged necrotic or apoptotic hepatocytes directly killed by the drug, may further contribute to determining the rare occurrence of these hypersensitivity reactions[18] which most often have an incidence of 1 **:** 1000 or less.

Parent drug–dependent toxicity occurs as a result of the properties of the parent drug (or metabolite) to: (i) accumulate in organelles (e.g. weak bases such as amiodarone accumulate in mitochondria);[19] (ii) undergo nonspecific redox cycling [e.g. quinones cycle electrons from nicotinamide adenine dinucleotide phospate (NADPH) to O_2 generating reactive oxygen species]; or (iii) specifically inhibit enzymes or transporters (e.g. nucleoside reverse transcriptase inhibitors block mitochondrial DNA polymerase[20] and cyclosporin inhibits canalicular transporters).[21] In these cases, if the parent drug's chemical properties account for direct toxicity, factors which enhance its availability, such as decreased metabolism or export, may increase susceptibility.

With the advent of new technologies in genomics and proteomics, one can anticipate that new insights into the mechanisms of susceptibility and liver injury from drugs will be forthcoming.

3. Risk Factors

Regardless of whether hepatotoxicity is predictable (frequent) or unpredictable (rare), hypersensitivity-mediated or idiosyncratic, metabolism-dependent or chemical structure-dependent, the interplay of genetic and environmental risk factors influences susceptibility.[22] Table II lists examples of drugs and associated risk factors.

4. Monitoring

The background incidence of drug-induced mild, reversible liver injury provides the rationale for monitoring or surveillance. From this background of mild injury a minority of individuals will emerge with overt disease. Thus, by stopping the medications at the first sign of mild injury one should prevent serious consequences. Although this seems a logical approach, a number of problems must be considered. First, the approach only applies to delayed reactions. Secondly, one is sacrificing potentially important therapy to a much larger number of patients than would actually develop overt disease. Thirdly, compliance with such approaches is known to be poor and fourthly, the rate of development of overt disease from the first appearance of elevated ALT levels needs to be gradual for monthly monitoring to be effective in preventing life-threatening disease.

Table II. Risk factors for drug-induced hepatotoxicity

Drug	Factors
Methotrexate	Chronic alcohol abuse, obesity, diabetes mellitus, chronic hepatitis, psoriasis
Isoniazid	Hepatitis B infection, hepatitis C infection, HIV infection, alcohol abuse, older age, female gender, slow acetylator phenotype, concurrent use of rifampicin (rifampin) or pyrazinamide
Paracetamol (acetaminophen)	Chronic alcohol abuse,[a] fasting, concurrent use of isoniazid
Valproic acid (sodium valproate)	Young age, concurrent use of other anticonvulsants, genetic defects of mitochondrial β-oxidation and respiratory chain enzymes
Diclofenac	Female gender, osteoarthritis
Anticonvulsants	Genetic defect in detoxification
Sulfonamides	HIV infection, slow acetylator phenotype, genetic defect in detoxification

a Controversial.[23,24]

Testing more frequently than monthly is not practical, although the future development of a fingerstick ALT test, that could be applied in a fashion similar to monitoring glucose, might change this by improving compliance and allowing more frequent monitoring. In any case, monthly monitoring for delayed idiosyncratic reactions is the best approach available, but the effectiveness of the approach is assumed and not proven. Furthermore, this should not substitute for the need to educate patients about symptoms of hepatotoxicity such as fever, malaise, fatigue, gastrointestinal complaints, abdominal pain, dark urine, jaundice, pruritus, etc, and the need to report them to their physicians to insure expeditious cessation of offending agents. Despite monthly monitoring, some adverse events may appear rapidly in a few weeks following a normal test. This was the experience with troglitazone; the incidence of adverse events reported to the US Food and Drug Administration (FDA) appeared to decrease after monthly monitoring was recommended but rare cases of severe disease rapidly occurred ('rapid risers') within a few weeks after a normal ALT or mild ALT elevation [<3 times the upper limit of normal (ULN)] at the previous check-up.

Ultimately, the most difficult challenge to the application of monitoring is cost effectiveness – monthly monitoring is expensive and one needs to weigh this quantitatively against the morbidity and mortality of adverse liver events. If hospitalisation occurs in 1 in 10 000 patients taking a medication and acute liver failure in 1 in 100 000, is monitoring with its attendant issues of compliance and efficacy, really justified? What rate of adverse events justifies monitoring? At present there are no definitive answers to these questions. Regulatory agencies and the pharmaceutical industry must decide if any risk to life from drug-induced liver toxicity, irrespective how rare, is justifiable with a specific drug.

This extremely difficult question was faced by industry and the FDA recently with bromfenac and troglitazone. In the case of the nonsteroidal anti-inflammatory drug, bromfenac, continued use of the drug in the face of infrequent, delayed idiosyncratic severe hepatotoxicity,[25] could not be justified since many alternative treatments were available. In the case of troglitazone, the decision to withdraw was delayed and more complicated due to the important and unique therapeutic properties of the drug in managing a serious medical condition, albeit with benefits which would not be evident for many years (i.e. the effect long term control of blood sugar on complications of diabetes mellitus), whereas the life-threatening complication of acute liver failure occurred in the first year and with an incidence of about 1 : 20 000. It was decided that the implementation of monthly monitoring would likely protect the users and the drug was continued. Although this strategy may have worked to some extent, the issue of compliance with monitoring and the possibility of occasional 'rapid risers' meant that the population could not be completely protected. At the same time, several new drugs in this

class were approved and after a number of months of postmarketing experience with the alternative new agents, it was concluded that these agents were probably less likely to induce severe hepatotoxicity, leading to the withdrawal of troglitazone.

5. Issues for Drug Development

Nonclinical assessment using animal models undoubtedly screens out most potent toxins. However, liver injury at extremely high doses in animal models does not necessarily predict problems in humans. Obviously, drugs that pass through animal testing and reach clinical trials have been considered of no or negligible risk to humans. Compounds which are not hepatotoxic in animals usually do not induce serious hepatotoxicity in humans. The occurrence of rare hypersensitivity or idiosyncratic reactions in humans cannot be reliably predicted at present from preclinical studies. Thus, whether or not animal testing shows some toxic propensity at extreme doses, vigilance during clinical trials and postmarketing needs to be universally practised.

The key arena for identification of drugs with significant hepatotoxic potential is phase I to III clinical trials. At this stage it is critical to determine the incidence of abnormalities in treated versus control patients. The value of >3 times ULN for ALT is commonly used as a signal for concern. The background incidence of this signal depends on the nature of the control population (obesity, diabetes mellitus, heart failure, chronic hepatitis C infection) and ranges between 0.1 to 1.0%. Thus, if the incidence of ALT in drug recipients is 2 to 3%, this is cause for some concern. However, even more concerning would be the occurrence of ALT >8 to 10 times ULN, in conjunction with hyperbilirubinaemia and/or symptomatic hepatitis. The rule of threes applies to this situation: in order to be >95% sure of not missing an adverse event (e.g. overt icteric symptomatic disease) one needs to study nearly 3-fold more patients than the true incidence.

Most phase I to III trials involve of a total of 2000 to 3000 patients and volunteers who receive a drug for variable time; a subgroup may undergo long term exposure (e.g. 6 months or more). If the drug in question turns out to cause overt liver disease in 1 in 100 patients, 300 patients would need to be treated to ensure that the adverse event is not missed. However, if overt liver disease occurs in approximately 1 in 1000 patients, the number of patients needed would be 3000. This is exactly what was seen with troglitazone: a 2- to 3-fold increased incidence ALT > 3 times ULN and 2 patients with jaundice in the cohort of 2500 patients treated with the drug.[26] Thus, the clinical trials provided the signals for concern.

On the other hand, if the true incidence of overt drug-induced liver disease is 1 in 10 000, there would be a high likelihood of missing overt disease in the clinical trials due to insufficient numbers of patients involved. Thus, the absence of hyperbilirubinaemia and markedly elevated ALT levels in 3000 study patients predicts that the incidence of overt disease should be somewhere between zero and less than 1 per 1000 and fatal disease between zero and less than 1 per 10 000 (remembering that we are concerned with this issue because overt drug-induced cytotoxic disease carries about a 1 in 10 chance of death or liver transplantation).

A major dilemma is whether to not approve a drug with a signal of increased incidence of ALT > 3 times ULN and more than 1 case of hyperbilirubinaemia with elevated ALT level versus approval with a recommendation for monitoring. In general, it would seem prudent to require more extensive premarketing assessment of safety when time-tested, well-tolerated alternatives are already available. The decision depends on the uniqueness or importance of the new drug and the prediction (unproved) for the effectiveness of monitoring. The latter approach should include careful postmarketing surveillance or expanded phase IV studies including an assessment of the impact of monitoring. There are situations in which a statistically significant increase in mild liver injury (ALT level >3 times ULN) has been observed without overt disease. Under such circumstances, predictions about risk of serious liver injury cannot be made and decisions concerning the need for monitoring are

very difficult to support. The cholesterol-lowering HMG-CoA reductase inhibitors ('statins') exemplify this problem. Some have been associated with an increase in incidence of ALT level increases versus controls in clinical trials but extensive postmarketing experience has shown little cause for concern.

Although most drugs with a propensity for hepatotoxicity will be identified in preclinical testing and clinical trials, occasional drugs slip through because the reactions are rare and either hypersensitivity or delayed idiosyncratic in nature. Postmarketing surveillance of newly approved drugs is very important but is associated with limitations due to lack of compliance with reporting adverse events and lack of controls. Occasional unexplained liver failure in a patient receiving a drug must be weighed against the background incidence of liver failure in the general population or associated with the disease being treated. For example, it is estimated that about 2000 cases of acute liver failure occur in the US population of 300 000 000 (incidence <1 **:** 100 000). At least 10 to 20% of these cases have no identifiable cause, resulting in a background incidence of 1 to 2 cases per million. Thus, the reporting of 1 or 2 cases of acute liver failure in the first million recipients of a new drug must be viewed differently than 10 to 100 times that number.

6. Diagnosis

Establishing a diagnosis of drug-induced liver disease in an individual case is mainly based upon circumstantial evidence aided by the signature type of reaction (if known) with respect to latency and clinical characteristics as well as exclusion of other more plausible alternative causes. Additional information can be gained from the response to the removal of the drug, i.e. rapid improvement in cytotoxic reactions and slow improvement in cholestatic reactions. A rechallenge with recrudescence of liver abnormalities is the most definitive evidence, i.e. highly probable, but hardly ever justified and not always positive in idiosyncratic cases. A practical approach is to consider the diagnosis probable/possible if the signature latency and pattern of disease fit and other causes are excluded (e.g. viral hepatitis, ischaemic hepatitis, biliary disease). The remainder of cases are unlikely or unrelated depending on the completeness of the workup and the strength of the evidence in favour of an alternative diagnosis. This *ad hoc* approach is equivalent to diagnosing as yes, no, or maybe.

The presence of autoantibodies to specific forms of cytochrome P450 enzymes have been associated with hypersensitivity reactions to certain drugs.[18,27,28] Although of uncertain but intriguing significance with respect to pathophysiology, their presence may be helpful in the diagnosis of drug-induced liver disease in these special cases (table III). However, testing for these autoantibodies is mainly a research tool at present.

Several groups have attempted to generate quantitative systems designed to generate a numerical score which reflects the probability of a drug as the cause for liver disease.[29-32] The Council for International Organisation of Medical Sciences (CIOMS) scoring system appears to be the most accurate[33,34] and puts numerical weight on the factors discussed at the beginning of this section to generate a composite score which reflects the probability that liver injury is drug-induced. The advantage is that this system is less subjective than the *ad hoc* approach. This type of scoring system performs well when validated against well documented cases of drug-induced liver disease. Specialists, pharmaceutical industry and regulatory bodies should be encouraged to use this scale. It also would be reasonable to apply the scoring system to individual case reports submitted to medical jour-

Table III. Autoantibodies in drug-induced liver disorders

Autoantibody target	Drug
CYP 2C9[a]	Tienilic acid
CYP 1A2[b]	Dihydralazine
CYP 3A[b]	Anticonvulsants
CYP 2E1	Halothane
mEH	Germander

a Also referred to as anti-LKM2 autoantibody.

b Also referred to as anti-LM autoantibody.

CYP = cytochrome P450; **mEH** = microsomal epoxide hydrolase.

nals. Although it is not perfect and may not discriminate between multiple concurrently used candidate toxins, it does provide consistency and focuses the attention of the evaluator on most of the critical parameters which need to be considered in estimating the probability of causality.

7. Conclusions

Drug-induced liver disorders occur frequently, may be life-threatening and can mimic all forms of liver disease. Preclinical drug development screens out potent toxins but is imperfect in identifying the potential for unpredictable rare hypersensitivity and idiosyncratic reactions. Although knowledge of the metabolism of drugs and the identification of toxic metabolites may be helpful in improving the value of preclinical studies, advancement will require the elucidation of the mechanism of toxicity in humans so as to employ animal models which express the determinants of risk. This will allow deployment of transgenic and knockout models and other pretreatments which unmask the toxic potential. In the clinical development phase, greater attention to the identification of signals, such as increased frequency of ALT level elevations, and more precise definition of true versus false positive signals is needed. In the postmarketing phase, along with improving compliance in reporting adverse events and causality assessment, studies of the value of monitoring are of critical importance. The employment of new technologies such as genomics and proteomics should lead to better understanding of the mechanisms of unpredictable reactions, identification of individuals at risk, and development of relevant animal model systems to screen new drugs. These new technologies will be useful at multiple levels. In animal and *in vitro* systems, the identification of signature patterns of gene expression (toxicogenomics) may predict toxic potential even when overt organ damage does not occur. In the patients with ALT level abnormalities or overt disease, the new technologies offer the hope of identifying the genetic predisposition to rare immunological or idiosyncratic hepatotoxicity (pharmacogenomics).

References

1. Ostapowicz G, Fontana RB, Larson AM, et al. Etiology and outcome of acute liver failure in the USA: preliminary results of a prospective multi-center study [abstract]. Hepatology 1999; 30 (4): 221A
2. Shakil A, Kramer D, Mazariegos G, et al. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 2000; 16: 163-9
3. Zimmerman H. Drug-induced liver disease, In: Schiff E, Sorrell M and Maddrey W, editors. Schiff's diseases of the liver. 8th ed. Philadelphia (PA): Lippincott-Raven Publishers, 1999: 973-1064
4. Kaplowitz N. Drug metabolism and hepatotoxicity. In: Kaplowitz N, editor. Liver and biliary diseases. 2nd ed. Baltimore (MD): Williams and Wilkins, 1996: 103-20
5. Desmet VJ. Vanishing bile duct syndrome in drug-induced liver disease. J Hepatology 1997; 26 Suppl. 1: 31-5
6. Degott C, Feldmann G, Larrey D, et al. Drug-induced prolonged cholestasis in adults: a histological semiquantitative study demonstrating progressive ductopenia. Hepatology 1992; 15: 244-51
7. Van Steenberen W, Peeters P, DeBondt J, et al. Nimesulide-induced acute hepatitis: evidence from six cases. J Hepatology 1998; 29: 135-41
8. Pham T-V, Lu S, Kaplowitz N. Acetaminophen hepatotoxicity. In: Taylor, editor. Gastrointestinal emergencies. 2nd ed. Baltimore (MD): Williams & Wilkins, 1997: 371-88
9. Tarazi E, Harter JG, Zimmerman HJ, et al. Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. Gastroenterology 1993; 104: 569-74
10. Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. J Clin Invest 1988; 82: 1826-32
11. Larrey D, Vial T, Micaleff A, et al. Hepatitis associated with amoxycillin-clavulanic acid combination. Report of 15 cases. Gut 1992; 33: 368-71
12. 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
13. Murphy E, Davern T, Shakil O, et al. Troglitazone-induced fulminant hepatic failure. Dig Dis Sci 2000; 45: 549-3
14. Durand F, Bernuau J, Pessayre D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculosis treatment including isoniazid. Hepatology 1995; 21: 929-32
15. Rieder M, Uetrecht J, Shear N, et al. Diagnosis of sulfonamide hypersensitivity reactions by in vitro 'rechallenge' with hydroxylamine metabolites. Ann Int Med 1989; 110: 286-9
16. Rieder M, Shear N, Kanee A, et al. Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. Clin Pharmacol Ther 1991; 49: 13-7
17. Gennis M, Vemusi R, Burns E, et al. Familial occurrence of hypersensitivity to phenytoin. Am J Med 1991; 91: 631-4
18. Robin M, LeRoy M, Descatoire V, et al. Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. J Hepatol 1997; 26 (1): 23-30
19. Berson A, DeBeco V, Letteron P, et al. Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes. Gastroenterology 1998; 114: 764-4
20. Brinkman K, Hofstede H, Burger D, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS 1998; 12: 1735-44

21. Kowdley K, Keeffe E. Hepatotoxicity of transplant immunosuppressive agents. Gastroenterol Clin North Am 1995; 24: 991-1001
22. DeLeve L, Kaplowitz N. Prevention and therapy of drug-induced hepatic injury. In: Wolfe MM, editor. Therapy of digestive disorders. Philadelphia (PA): W.B. Saunders, Harcourt Brace & Company, 2000: 334-48
23. Zimmerman H, Maddrey W. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995; 22: 767-3
24. Makin A, Williams R. Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. Q J Med 2000; 93: 341-9
25. Moses P, Schroeder B, Alkhatib O, et al. Severe hepatotoxicity associated with bromfenac sodium. Am J Gastroenterol 1999; 94: 1393-6
26. Watkins P, Whitcomb R. Hepatic dysfunction associated with troglitazone. N Engl J Med 1998; 338: 916-7
27. Beaune P, Lecoeur S. Immunotoxicology of the liver: adverse reactions to drugs. J Hepatol 1997; 26 Suppl. 2: 37-42
28. Neuberger J. Immune mechanisms in drug hepatotoxicity. Cli Liver Dis 1998; 2: 471-82
29. Maria V, Victorino R. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997; 26: 664-9
30. Benichou C. Criteria of drug induced liver disorders: Report of an international consensus meeting. J Hepatol 1990; 11: 272-6
31. Danan G, Benichou C. Causality assessment of adverse reactions to drugs – I: a novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993; 46: 1323-30
32. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs – II: an original model or validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol 1993; 46: 1331-6
33. Lucena M, Camargo R, Andrade R, et al. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology 2001; 33: 123-30
34. Kaplowitz N. Causality assessment versus guilt by association in drug hepatotoxicity. Hepatology 2001; 33: 308-10

Correspondence and offprints: Dr *Neil Kaplowitz*, GI/Liver Division, Keck School of Medicine, University of Southern California, 2011 Zonal Avenue, HMR 101, Los Angeles, CA 90033, USA.
E-mail: kaplowit@hsc.usc.edu