Management of Drug-induced Liver Disease

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The treatment and prevention of drug-induced liver injury starts with the recognition of hepatotoxicity at the earliest possible time so that the suspected drug can be discontinued expeditiously. Both liver enzyme monitoring and vigilance for signs of hypersensitivity involving the liver are useful strategies for many agents known to cause hepatocellular necrosis leading to liver failure. Specific antidotes to prevent or limit hepatic damage exist for only a few drugs, the most important being *N*-acetylcysteine for the treatment of acetaminophen hepatotoxicity. Corticosteroids are of unproven benefit in the setting of fulminant failure. Ursodiol may be helpful in instances of cholestatic injury. For other agents, supportive measures and the increasing use of liver-assist devices as well as emergency liver transplantation are available when drug injury evolves into irreversible liver failure. It is hoped that a better understanding of hepatotoxicity mechanisms will lead to the development of more specific and effective forms of therapy in the near future.

Introduction

Hans Popper once remarked that drug-induced liver disease was "a penalty for progress" [1]. Unfortunately, a growing number of agents are found to be hepatotoxic, and each year several are withdrawn from the market or cut off from further development because of serious, sometimes fatal hepatic injury [2•]. For the majority of potentially hepatotoxic medications that are introduced or remain in use, strategies for the management of liver injury continue to evolve. This article reviews the general and specific measures employed to prevent and treat various forms of drug-induced liver disease (DILD). Because relatively few agents have specific antidotes, prevention is of paramount importance. Minimization of injury by withdrawal of the agent once its injurious effects have been detected, and supportive care for the liver disease that may have resulted, serve as the basis for initial treatment. Liver transplantation for patients with irreversible liver failure is increasingly available, and the development of liver-assist devices may provide a bridge between supportive care and transplantation. The relative importance of each of these management decisions depends on the nature of the hepatic injury, the clinical setting in which it has occurred, and the apparent mechanism of injury.

Prevention and Treatment of Hepatic Injury Caused by Predictable (Intrinsic) Hepatotoxins

Among drugs in use today, only acetaminophen, iron salts, and aspirin lead to acute injury from intentional or unintentional overdose caused by their intrinsic toxicity. Acetaminophen is the most important potential cause of acute liver failure in these settings [3,4••]. Iron poisoning remains a significant problem in the pediatric age group [5]. Aspirin overdose leads to systemic toxicity, but rarely to liver failure [6]. The prevention and treatment of hepatic injury from each of these agents are described in this review.

Acetaminophen hepatotoxicity

Acetaminophen (*N*-acetyl-*p*-aminophenol, or APAP) is the most frequent means of attempted suicide and of drug-induced fulminant hepatic failure (FHF) in Great Britain and the United States as well as in other parts of the Western world [4••]. In a prospective study involving 16 US centers that enrolled 206 patients undergoing liver transplantation for FHF between 1998 and 2000, acetaminophen was the most common cause of acute liver failure, accounting for 38% of all cases [7]. Other drugs leading to acute liver failure in this series accounted for 14% of the total. The majority of instances of APAP-related injury resulted from large single overdoses, usually above 10 to 15 g [8]. Previous retrospective reports indicate that, in most cases, the overdose had been taken in a suicide attempt or gesture, but an increasing number of reported cases in both adults [9,10] and children [11•,12,13,14•] concern patients who take the drug with therapeutic intent or experience an accidental overdose. In a series of 79 patients prospectively studied between 1998 and 2000 by the Acute Liver Failure Study Group [15], the overdose was taken accidentally in 46 patients (58%), with suicidal intent in 31 individuals (39%), and in an indeterminate manner in two other instances. This series also showed a high use of concomitant antidepressants (greater than 35%)

and chronic alcohol ingestion (in approximately half of the patients) in both groups.

The syndrome of APAP toxicity caused by intentional overdose is triphasic [4••]. The first phase, which begins within several hours of ingestion, includes anorexia, nausea, vomiting, and, rarely, shock. The duration is usually less than 12 hours. The second phase, in which the acute gastrointestinal features abate, continues for 24 to 48 hours. During this apparent subsidence of severity, biochemical evidence of hepatic injury appears, and oliguria is usual. The third phase, that of overt hepatic damage, becomes clinically apparent 3 to 5 days after ingestion, with the appearance of jaundice. The severity of the hepatic injury is variable and can be modified by proper treatment during the first 16 to 24 hours after intake of the drug. Progression to the syndrome of fulminant hepatic failure, evidenced by hemorrhagic phenomena and hepatic encephalopathy, has occurred in up to one third of patients who had presumably not been treated in time.

Predicting APAP liver injury

Treatment may be pursued without specific knowledge of the APAP level; however, whenever possible, blood should be drawn to measure the serum concentration of APAP during the most predictive post-ingestion period (*ie*, 4 to 16 hours after ingestion). Nomograms based on blood levels of APAP in the first 24 hours of ingestion can accurately predict outcome and are widely employed (Fig. 1) [4••,16,17]. Treatment, however, should be initiated prior to knowledge of the blood level in patients where an APAP overdose is clinically suspected. If the level is found to be clearly predictive of no injury, treatment can be stopped at that point. If the level is borderline or predictive of liver injury, treatment should, of course, be continued.

Treatment of intentional APAP overdose

The treatment of acute APAP poisoning consists of prevention of hepatic injury by early removal of residual acetaminophen from the stomach by gastric lavage and by administration of substances that enhance production of glutathione, which serves to bind and detoxify the toxic quinone metabolite. Gastric lavage, while most likely to be effective in the first 2 or 3 hours after ingestion, may still be performed even after this period because there may be residual drug in the stomach. Efforts to prevent absorption by oral administration of activated charcoal are most effective within 1 to 2 hours after the drug has been taken. Later administration may interfere with absorption of oral *N*-acetylcysteine [17,18]. However, decreased incidence of toxic APAP concentrations was found in patients who had been given charcoal up to 24 hours after APAP ingestion [19•].

The currently available treatment of APAP overdose is highly successful and a gratifying example of the clinical application of elegant experimental studies that defined the mechanism of injury [4••,20,21]. Demonstration of the critical role that glutathione (GSH) depletion plays in the necrogenic effects of APAP overdose led to the therapeutic employment of *N*-acetylcysteine (NAC), which leads to its re-synthesis [21,22]. The length of time between ingestion of APAP and initiation of treatment is the critical determinant of treatment effectiveness (Fig. 1). Treatment with *N*-acetylcysteine during the first 16 hours after the overdose of APAP can minimize hepatic injury and prevent fatal hepatic disease in nearly all patients [10,22]. Earlier reluctance to treat patients after 16 hours has been replaced by an apparent consensus that *N*-acetylcysteine may still be of benefit and, indeed, that initiating treatment with NAC is appropriate during the first 24 hours after intake. There is also a growing view that treatment may be of some benefit even after that time point [23,24]. The standard oral regimen of NAC is a 140 mg/kg loading dose, followed by 70 mg/kg every 4 hours for 16 additional doses. Shorter-duration therapy may be considered in patients in whom no evidence of hepatotoxicity develops within 36 hours of an APAP overdose, as demonstrated by Woo *et al.* [25••]. These authors suspended treatment with NAC when APAP serum levels were no longer detectable in 75 patients with an acute APAP overdose and initial concentrations in the toxic range. One third of this group was treated for less than 24 hours, and another third was treated for 24 to 36 hours, with the remaining patients treated for up to 64 hours rather than the standard 72-hour regimen. The mean duration of treatment was 31 hours. A total of six patients (8%) developed hepatotoxicity using this shorter regimen, but no deaths or need for liver transplantation occurred.

NAC is usually given orally in the United States, but it is available as an approved intravenous (IV) preparation in Great Britain and Canada. The efficacy of a 48-hour intravenous regimen also has been demonstrated among patients in US centers. Smilkstein *et al*. [24] treated 179 patients with acute APAP overdoses with a NAC regimen of 140 mg/kg, IV, for loading dose, followed by 12 doses of 70 mg/kg, IV, every 4 hours. They reported hepatotoxicity developing in 10% of patients at "probable risk" when IV NAC was started within 10 hours of APAP ingestion; the risk of hepatotoxicity rose to 58% among "high-risk" patients treated between 16 and 24 hours after overdose, with two deaths. When started within 10 hours, a 24-hour IV regimen appears to be of equal efficacy to a longer treatment protocol [24]. Adverse reactions occurred in 14% of treated patients, with most reactions being transient erythema of the skin or mild urticaria during the loading dose. In a meta-analysis of the combined experience comparing oral NAC in 1462 patients with intravenous NAC in 341 patients, no statistically significant differences in the rates of hepatotoxicity were found. The authors concluded that the claimed differences in efficacy between these two forms of administration of NAC were artifactual [26]. The IV preparation has led to anaphylactic reactions in 0.2% to 21% of patients [27–32]; most

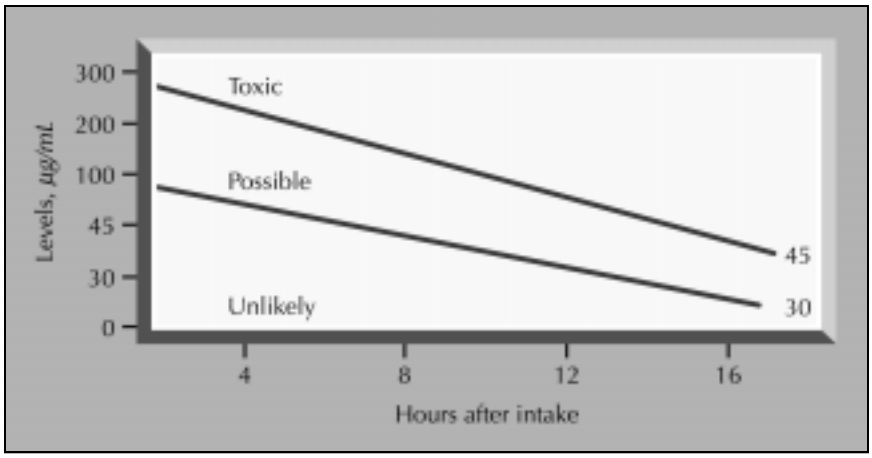

Figure 1. This simplified nomogram illustrates the manner in which blood levels of acetaminophen (APAP) at specific periods after a single toxic dose can help predict the outcome of poisoning and direct need for treatment. Levels of APAP in blood were drawn between 4 and 16 hours after ingestion. Values that fall in the lowest zone indicate that the liver damage will probably not occur and that specific therapeutic measures are not needed. Blood levels in the uppermost zone are predictive of serious liver damage and mandate treatment with acetylcysteine. Values in the intermediate zone offer less conclusive prediction but warrant similar treatment. *Data from* Zimmerman [4••].

of these incidents occurred within the first hour of NAC infusion. These adverse effects have resolved with diphenhydramine treatment, which did not interfere with subsequent intravenous *N*-acetylcysteine treatment, as reported by Yip *et al*. [33]. Nevertheless, the IV formulation is not currently approved by the US Food and Drug Administration, although it remains an important alternative for those individuals with persistent vomiting, encephalopathy, or gastrointestinal bleeding, or in neonates or non-compliant patients who cannot readily take the oral formulation.

A number of other therapies have been considered as alternatives to NAC in the treatment of acute APAP overdose, although none has been shown as effective. Methionine, which acts as a glutathione precursor [34], has been used in Great Britain as an oral antidote against APAP, and has protected against hepatic and renal toxicity when given within 8 to 10 hours of ingestion [35]. However, in some cases it may exacerbate hepatic encephalopathy when administered after the first hour of APAP ingestion [36]. Cimetidine, a histamine-2 receptor antagonist, inhibits cytochrome P-450 and in animal models has been found to decrease APAP toxicity [37,38]. However, available human studies to date have not shown significant benefit [12]. Anecdotally, IV cimetidine is sometimes given adjunctively with oral NAC, although its role is uncertain [39,40]. In mice, hypothyroidism induced by methimazole, propylthiouracil, or thyroidectomy protected against acetaminophen hepatotoxicity by apparently shifting the activation of acetaminophen from the centrilobullar area to the periportal region, where cytochrome 2E1 is not found and where GSH is more abundant [41]. To our knowledge, this strategy has not been attempted in the treatment of human APAP poisoning.

Supportive treatment includes hydration, particularly for those with vomiting, and monitoring of arterial blood gases to rule out acidosis, which occurs commonly 24 hours after the overdose in severe cases. Treatment of hepatic failure (in patients who are seen too late to prevent hepatic injury) is similar to that of other forms of fulminant hepatic failure. Once acute liver failure occurs, similar outcomes are found in accidental, compared with suicidal, overdose [15]. Bacterial and fungal infections have been documented in 82% and 34% of patients, respectively, with grade 3/4 encephalopathy [42]. Two sentinel markers of fungal infection are leukocytes greater than 20,000/mm^3 and an arrest in the recovery of coagulation activity. Aggressive IV antibiotic treatment (*eg*, ceftazidime, 1 g every 8 hours, or flucloxacillin, 500 mg, IV, every 6 hours) reduced bacterial infections to 26% in one series but was associated with bacterial multi-resistance in 9% of encephalopathic patients [43].

Prognostic criteria have been developed by investigators at King's College Hospital in England to identify patients in whom survival without liver transplantation is unlikely [44,45,46•]. The accuracy of the application of these criteria (Table 1) has been confirmed by a UK study of 548 patients admitted for acetaminophen-induced hepatotoxicity, in which sensitivity was 72%, specificity was 98%, and positive predictive value was 89% in identifying those patients with a poor prognosis who needed urgent transplantation [46•]. Patients with severe hepatotoxicity are often critically ill and have a short "window of opportunity" to be successfully transplanted before undergoing irreversible deterioration [47]. Indeed, in this UK series, 45% of patients who fulfilled transplant criteria were not listed, mainly because of multiple organ failure and cerebral edema. Nineteen percent of these patients were listed, but orthotopic liver transplantation (OLT) was not possible due to rapid clinical deterioration, and only 35% (44 of 124) of those who fulfilled criteria ultimately underwent OLT. Among these patients, 66% who underwent transplantation were alive at a median follow-up of 37 months, ranging up to 72 months [46•].

In patients recovering from emergency OLT due to acetaminophen overdose, a background of psychiatric illness or alcohol or drug dependency is frequently found. Close psychiatric follow-up is recommended in these patients to keep the rate of further suicide attempts low, as 4 of 33 transplanted patients (12%) who survived to leave the hospital in the King's College series died as a result of another overdose or other "deliberate self-harm" [46•].

Table 1. King's College criteria for transplantation in acetaminophen-induced fulminant hepatic failure

Acidosis (arterial pH <7.3) regardless of grade of encephalopathy
Or all of the following
Prothrombin time >100 seconds
Grade 3 or 4 encephalopathy
Creatinine >3.4 mg/dL

Data from O'Grady *et al.* [44].

Among patients in whom liver transplantation is not feasible, treatment with artificial liver support devices has been attempted with variable success [48]. Hemodiabsorption systems appear to shorten the clinical course of hepatotoxicity [49]. The use of charcoal hemoperfusion to remove acetaminophen from the blood in cases of overdose may reduce the severity and mortality of APAP-induced liver failure in patients admitted within the first 42 hours after overdose [50].

Several other therapies for APAP hepatic injury have been studied [39], including various phytonutrients and other hepatoprotective extracts, but efficacy in humans awaits further examination [51–53].

Preventing APAP overdose

Because APAP can traditionally be purchased in large quantities, in order to help prevent APAP overdose, legislation introduced in the United Kingdom beginning in September 1998 limited the sale of APAP to 8 g at a time, using blister-packs containing sixteen 500-mg tablets [54]. This practice led to a 21% reduction in all APAP overdose cases and a 64% reduction in severe overdoses at the Royal Free Hospital [55••], as well as reductions at other British hospitals. [56••]. These studies suggest that limiting the availability of multiple doses may be a reasonable measure to control the rate of acetaminophen overdose in areas with a high incidence of this problem [57••]. Improved labeling would be expected to reduce the number of accidental APAP poisonings in children given adult doses inadvertently [11•,58]. The combined use of methionine simultaneously with acetaminophen as a preventive measure has been advocated but not fully evaluated [59].

Treatment of APAP toxicity as a therapeutic misadventure

An estimated 30% of the cases of APAP toxicity in the United States result from the drug having been taken with therapeutic intent by patients who are abnormally susceptible [9,10,60]. The increased susceptibility is thought to result from either enhanced conversion of APAP to its toxic metabolite (*N*-acetyl-*p*-benzoquinone imine, or NAPQI) in the absence of an intentional overdose, or from insufficient stores of GSH to detoxify the active metabolite. One of the most frequently cited risk factors among adults is the regular use of alcohol, in excess of three drinks per day [9], which induces cytochromes p450 2E1 and 3A4, thereby increasing the conversion of APAP to NAPQI, while at the same time leading to decreased synthesis of GSH. Alcoholism also leads to impaired nutrition, which contributes to depleted GSH stores [4••,9]. Although numerous reports have cited alcohol as a risk factor for "therapeutic misadventure" [9], others point out that many questions remain regarding this interaction [61]. Indeed, the Acute Liver Failure Study Group has noted that the consumption of alcohol was similar between patients with intentional versus unintentional APAP overdose [15], and additional study of this relationship is warranted. Patients with an APAP overdose in the setting of alcohol use or abuse are sometimes misdiagnosed as having alcoholic hepatitis, an error that should not occur, as the aminotransferase values are usually at towering levels (1000 to 50,000 IU/L), which are dramatically different from levels seen with alcoholic hepatitis (aspartate aminotransferase [AST] less than 300 IU/L; alanine aminotransferase [ALT] less than 100 IU/L).

Other factors that may enhance the susceptibility to APAP taken in therapeutic doses include a period of fasting [62] and the concomitant use of other drugs (*eg*, isoniazid, anticonvulsants, and zidovudine) [60]. Hepatotoxicity after multiple supratherapeutic doses of acetaminophen in children is another frequent form of therapeutic misadventure [11•,12,13,14•]. Heubi *et al*. [11•] analyzed 47 reports of children who had received 60 to 420 mg/kg/d for 1 to 42 days. Half of these children had received adult preparations of acetaminophen, often as a result of difficulties following label instructions. Twenty-four of 43 (55%) children in this series died, and three others survived after liver transplantation. In a US series from Salt Lake City in which single unintentional ingestion of APAP-containing products was evaluated in children, those ingesting between 140 and 200 mg/kg of APAP could be managed at home with ipecac-induced emesis, whereas those ingesting greater than 200 mg/kg or an unknown amount were referred to a healthcare facility [14•].

Treatment of acetaminophen toxicity that develops as a result of therapeutic misadventure in adults poses problems that seem to be entirely different from the toxicity of a single intentional overdose. Instead of presenting in a timely fashion to prevent serious injury, these patients often present late with fully developed injury [10]. Whereas treatment with NAC would be expected to be of no help at this stage of injury, it may still be beneficial in some instances, even after APAP-induced hepatic failure has evolved [23]. Clearly, however, the usual role of NAC in preventing injury does not apply. Although the mechanism for the benefit that the late administration of NAC appears to confer is not clear, it may be improved delivery of oxygen [23,63]. Alcoholic or other patients who present with very high AST levels (1000 to 50,000 IU) with a history of having taken APAP, even in modest doses, should be treated with NAC for at least 48 hours or until clinical improvement becomes apparent [10]. As with adults, NAC

should also be considered in children who have received multiple supratherapeutic doses of APAP, even when evidence of liver injury is present [11•,63]. In patients with irreversible liver failure, emergency liver transplantation offers the only hope of survival in those who are otherwise suitable candidates [7,15].

Iron poisoning

Acute ferrous salt intoxication is a well-recognized entity occurring mainly in children aged under 5 years who gain access to bottles containing medicinal preparations, including chewable vitamins, that may be mistaken for candy [64–66]. This dramatically serious condition is characterized by vomiting, gastrointestinal bleeding, shock, and acidosis, and, in about 50% of hospitalized patients with hepatic failure, a fatal outcome [4••,65]. However, only a small minority of children who take an overdose require hospital treatment. Hepatic necrosis, usually in zone 1 of the lobule, associated with hepatic iron overload is expected, although some fatal cases show little or no iron staining [67]. Treatment consists of administration of the chelating agent deferoxamine as soon as possible (by continuous-infusion IV, 15 to 25 mg/kg/hr for 12 hours a day over 3 consecutive days [68,69], as well as supportive care depending on the dose of iron taken and the clinical manifestations of injury [64,69]. Reliable information that less than 20 mg/kg has been taken permits discharge of the patient without further treatment. Patients having taken doses of 20 to 40 mg/kg also may be dismissed without further treatment. Doses above that amount or of unknown quantity are treated according to the plasma iron level, with doses greater than 60 mg/kg associated with the potential for serious hepatic injury, and those greater than 200 to 250 mg/kg being potentially fatal [4••,70]. Patients with levels above 500 μg/dL should be treated with deferoxamine, as should those with levels between 350 and 500 μg who are symptomatic. However, deferoxamine treatment should not wait for blood levels in symptomatic patients with mental status changes, bleeding, or hypotension. Other aspects of treatment include reestablishing or maintaining hydration and performing gastric lavage, especially if doses above 20 mg/kg are suspected or the kidney and upper bladder radiography shows radiopaque densities [71]. Oral magnesium preparations may reduce the absorption of iron, but activated charcoal is considered ineffective [69]. Vitamin C should be avoided because it may increase iron-induced end-organ damage by redistributing iron from nonparenchymal cells to parenchymal cells, enhancing lipid peroxidation by iron, and leading to DNA damage [72].

Aspirin toxicity

Aspirin is rapidly converted to salicylic acid after absorption. The major metabolites of aspirin are salicyluric and salicylphenolic glucuronide. It has been suggested that these metabolic pathways are readily saturated in children as well as adults, leading to the accumulation of an otherwise minor non-toxic metabolite that may cause hepatic injury [73]. The exact mechanism of the cellular injury is unclear, although several possible modes of action have been postulated. These include lipid peroxidation, mitochondrial damage, hydroxyl radical scavenging, and injury to hepatocyte membranes [74,75].

Levels exceeding 40 to 50 mg/dL are associated with signs of intoxication, including tinnitus, nausea, vomiting, and diarrhea, and, in more severe cases, altered mental status, noncardiac pulmonary edema, acid-base disturbances, and death. Salicylates cause a dose-related focal hepatic injury in some patients [76–79], particularly those with active juvenile rheumatoid arthritis (JRA) and systemic lupus erythematosus (SLE) [80]. Hepatic injury is usually seen when blood salicylate levels are above 25 mg/dL, with only 7% of reported instances of hepatic injury occurring in patients whose blood levels of salycilates are below 15 mg/dL [81]. Aspirin injury is primarily hepatocellular, with aminotransferase levels five to 40 times the upper limit of normal (ULN). In general, it is clinically mild and reversible, with ALT/AST levels elevated less than tenfold. Bilirubin levels usually remain normal or are minimally elevated, with jaundice seen in less than 5% of patients [6]. Liver biopsy characteristically shows areas of focal necrosis with a mild inflammatory response in the portal areas. In addition, cellular unrest, ballooning, and eosinophilic degeneration have been described [6]. Withdrawal of the drug leads to rapid resolution of hepatic damage [82].

Susceptibility to aspirin injury is reported to be greater in patients with JRA, SLE, and rheumatic fever, perhaps because of the relatively higher doses taken for these disorders [83,84]. The incidence of abnormal hepatic-associated enzymes detected in these patients ranges from 20% to 70%, with children aged under 12 years having a higher incidence, compared with adults. Hypoalbuminemia has been reported to increase the risk from decreased protein binding [85].

Aspirin-associated injury in general has not been serious and resolves promptly on stopping the drug. Severe injury occurs in less than 3% of patients. No convincing cases of fatal necrosis have been reported [6], although a few instances of fatal illness associated with encephalopathy and coagulopathy in patients with JRA and SLE receiving high doses were reported prior to 1980 [6], and may have represented early examples of Reye's syndrome (RS), discussed in the following section.

Aspirin and Reye's syndrome

Epidemiologic studies in the 1980s demonstrated a strong association between aspirin and Reye's syndrome in children with influenza or varicella (chicken pox) [86]. Adults were also affected, as evidenced by several reports of older individuals developing RS after taking aspirin for a presumed viral infection [87]. Convincing evidence for the association also comes from the striking decline in

the incidence of Reye's syndrome in the United States, which paralleled the decreased use of aspirin [88]. The use of aspirin continues to be strongly discouraged in acute febrile illnesses, especially in children. The mechanism by which aspirin acts with the viral illness to produce RS is unclear, although the association between aspirin and RS in children recently has been challenged as more likely being the result of one of several inborn errors in ammonia metabolism that were first diagnosed in the 1980s [89•]. The management of acute Reye's syndrome is beyond the scope of this discussion but involves supportive care and prevention of intracranial hypertension and cerebral edema associated with a high mortality rate, as with other forms of fulminant hepatic failure [90].

Prevention and Treatment of Acute Hepatic Injury Caused by Unpredictable (Idiosyncratic) Hepatotoxins

Because no specific antidotal treatments exist for the forms of injury that are caused by drug allergy or metabolic idiosyncrasy, prevention is paramount. Severe immunologically mediated or allergic hepatitis is generally considered an indication for steroid therapy, but only anecdotal reports support its use, and there is scarce evidence of its benefits [91]. Management of acute non-immunologic hepatic injury consists of supportive and symptomatic treatment, the nature of which depends on the form of injury. Corticosteroids, ursodiol, and a few other agents have been used in isolated instances with variable success. The development of any clinical manifestations of liver disease in a patient taking a drug that is known to produce liver damage (or even a drug of unknown toxic potential) should prompt immediate withdrawal of the suspected agent and withholding of it until its role in the current symptoms and the need for further use have been assessed.

Early detection of idiosyncratic liver injury: the role of enzyme monitoring

Prevention of drug-induced liver disease due to idiosyncrasy begins with its detection as early in its evolution as possible. Of importance in this regard is knowing the potential of a drug for producing hepatic injury, the nature of the injury that it produces, and the manner in which it presents. For drugs that produce injury signaled by prominent systemic/allergic manifestations (*eg*, rash, fever, and eosinophilia), as is true of injury caused by hypersensitivity, there is little need for monitoring of aminotransferase levels in order to detect early toxicity because the systemic manifestations announce the injury. For drugs that lead to acute injury not heralded by such hallmarks of hypersensitivity and in which jaundice may be the first manifestation of disease, regular biochemical monitoring becomes far more important. Indeed, for drugs that lead to severe hepatocellular injury and fulminant hepatic failure (Table 2), a syndrome with an appreciable case-fatality rate or need for OLT (10% to 50%), the risk of its development should be anticipated and, if possible, prevented by regular monitoring for biochemical evidence of injury before jaundice has occurred. Isoniazid, diclofenac, valproate, and ketoconazole are examples of drugs for which biochemical monitoring is recommended (Tables 3 and 4) [92].

Minor asymptomatic elevations (less than threefold) of serum aminotransferase levels during the first weeks to months of therapy that do not rise progressively (or that may even subside despite continued administration of the drug) are commonly seen with many agents. This phenomenon, referred to as "drug tolerance" or "adaptation," occurs by unknown mechanisms, possibly by immunosuppressive cytokines and T cells that inhibit progression of immune reactions caused by various drugs [93]. It has been generally recommended that medications be discontinued in patients with ALT elevations exceeding three times the upper limit of normal. However, this level is somewhat arbitrary, and in well-selected cases, medications can still be continued with careful and frequent monitoring.

Re-challenge of hepatotoxic drugs

In cases where no alternative treatment exists, a cautious graded re-challenge can be considered in patients who have not had a life-threatening reaction. However, this practice is contraindicated in patients with severe or life-threatening events. In patients with presumed allergic or IgE-mediated reactions, desensitization monitored by an experienced allergist can be done [94]. For example, desensitization protocols have been successfully utilized to reduce the risk of sulfamethoxazole-trimethoprim allergic reactions in patients with AIDS [95].

Treatment of idiosyncratic acute hepatocellular injury

Drug-induced hepatocellular jaundice has a potential case-fatality rate of 10% or more. Accordingly, it warrants careful observation for evidence of impending hepatic failure. In the patient whose jaundice is not deep, whose prothrombin time is normal or negligibly prolonged, and who has no clinical evidence of impending encephalopathy or coagulopathy, medical management can be simply supportive, and the individual can be followed on an outpatient basis. Unless there is evidence of impending hepatic failure, a standard diet is appropriate, with no need to modify the protein or other components. Persistent anorexia may be managed by multiple small feedings and by providing fruits, vegetables, and dairy foods rather than meat. Carbonated drinks, fruit juice, and hard candy are usually well tolerated even when nausea is marked. There is no need to restrict physical activity, although patients should be urged to stay within limits of fatigability.

The patient with measurable prolongation of prothrombin time and elevated bilirubin levels should be hospitalized (or observed very closely as an outpatient), particularly if there is persistent nausea and anorexia after the drug has been withdrawn. If these features are accompanied by evidence of

Table 2. Drugs that have caused acute fulminant hepatic failure

Anesthetics	NSAIDs and analgesics
Enflurane	Acetaminophen
Halothane	Bromfenac
Isoflurane	Diclofenac
Antimicrobials	Etodolac
Dapsone	Indomethacin
Isoniazid	Oxaprozin
Ketoconazole	Piroxicam
Pyrazinamide	Sulindac
Rifampin	Miscellaneous agents
Sulfonamides	Disulfiram
Trovafloxacin	Flutamide
Anticonvulsants	Labetalol
Carbamazepine	Nefazodone
Felbamate	Nicotinic acid
Phenytoin	Pemoline
Valproic acid	Propylthiouracil
Halothane	Tolcapone
Isoflurane	Troglitazone

Table 3. Partial list of drugs for which liver enzyme monitoring is recommended*

Amiodarone
Carbamazepine
Diclofenac
Disulfiram
Felbamate
Fluconazole
Flutamide
Isoniazid
Itraconazole
Ketoconazole
Labetalol
Methotrexate
Nicotinic acid (extended release)
Pemoline
Pioglitazone
Pyrazinamide
Rosiglitazone
Tacrine
Tolcapone
Valproic acid

*Reflects monitoring intervals and other recommendations in the current prescribing information from the PDR [92].

encephalopathy, the patient should be hospitalized for close observation and treatment.

Management is the same as for other causes of fulminant hepatic failure requiring intensive care. The usual measures to minimize formation of ammonia and other enterogenous cerebrotoxic substances should be pursued. These include lactulose or neomycin administered orally, or by enema when the patient can no longer take it orally. Needless to say, protein should be withdrawn from the diet when the development of asterixis or confusion heralds impending liver failure. Nutrition can be maintained through enteric feeding. Electrolytes should be monitored, and hypokalemia should be treated. There should be a central venous pressure line to maintain plasma volume and to deal with the likelihood of renal failure from oligemia. Cerebral perfusion should be monitored to prevent herniation.

There is no evidence of benefit from corticosteroids in the treatment of fulminant hepatic failure. Nevertheless, it is still a widespread practice to include steroids in the treatment of drug-induced FHF, especially when the hepatic failure has accompanied a syndrome with features of hypersensitivity. The key decision in these patients is the recognition that recovery is unlikely and that orthotopic transplantation is warranted.

Treatment of acute cholestatic injury

Acute drug-induced cholestatic jaundice is rarely fatal. Over 99% of patients with cholestatic jaundice caused by erythromycin, chlorpromazine, amoxicillin-clavulanate, or anabolic steroids have survived the episode. There is no firm evidence that any therapeutic measures affect the rate of disappearance of drug-induced cholestasis. However, several anecdotal observations suggest that treatment with ursodeoxycholic acid increases the rate of return to normal status [96–98], and in our view the effort is warranted. The most important aspects of treatment of cholestatic jaundice relate to the treatment of pruritus. Cholestyramine, which can offer relief, presumably traps elements involved in the itching. Other potentially useful agents include hydroxyzine, rifampin, and narcotic antagonists. There is no evidence that glucocorticoids provide symptomatic or other benefit in drug-induced cholestasis. Perhaps most important is an awareness that certain drug-induced cholestatic reactions can be mistaken for syndromes of anatomic biliary obstruction calling for surgical intervention, as has been seen with erythromycin and amoxicillin-clavulanate [99].

Management of chronic drug-induced hepatic disease

Treatment of the various syndromes of chronic hepatic disease that may be drug-induced mainly involves recognition of symptoms and withdrawal of the responsible agent. The lesion and syndrome of chronic hepatitis may be caused by a number of agents and by different mechanisms.

Chronic autoimmune hepatitis

Drug-induced chronic autoimmune hepatitis may resemble, to a striking degree, the form of chronic necroinflammatory disease dubbed "autoimmune" in origin. This type of injury has been reported following use of several agents, including nitrofurantoin, minocycline, methyldopa, diclofenac, and pemoline, among others [100]. There may be antinuclear or smooth muscle antibodies or even the LE plasma factor, and renal or pulmonary lesions may develop. It is essential that this form of DILD be recognized because treatment consists of withdrawal of the agent. Indeed, in any form of nonviral chronic hepatitis,

Table 4. Partial list of drugs for which clinical signs of hepatitis and/or allergy should be monitored*

Dapsone
Ketoprofen
Phenytoin
Rifampin
Sulfamethoxazole-trimethoprim
Sulindac
Tolmetin

*Reflects monitoring intervals and other recommendations in the current prescribing information from the PDR [92].

especially with autoimmune features, a drug should be suspected as the cause. Following withdrawal, improvement should become noticeable within 1 to 4 weeks. In some instances where injury fails to abate despite withdrawal of the drug, glucocorticoid therapy may be included.

Chronic cholestasis

Drug-induced chronic cholestasis is usually a sequel to acute cholestatic injury with loss of portal area bile ducts ("vanishing bile duct syndrome," or VBDS). Currently, there is no accepted therapy for the cholestatic process in patients with VBDS; however, ursodiol has been used successfully in a few reported patients who had received amoxicillin-clavulanate, chlorpromazine, prochlorperazine (improving pruritus and liver function tests), androgens, anabolic steroids, and tetracycline [96–98,101]. Long-term treatment with ursodiol, 300 to 600 mg, has been required in some patients with VBDS to control the manifestations of cholestasis [97]. This syndrome usually resolves spontaneously, although it may take several months to years, and only a minority of these patients develop secondary biliary cirrhosis [102].

Drug-induced sclerosing cholangitis

Drug-induced sclerosing cholangitis as a consequence of arterial infusion of FUDR for the treatment of hepatic metastases of colonic carcinoma has no identified effective treatment other than ceasing administration of FUDR. Endoscopic dilatation and/or stenting of the involved ducts may be necessary [103].

Fatty liver, fibrosis, and cirrhosis

Drug-induced macrovesicular fatty liver is a lesion that, *per se*, offers little threat. The steatosis may, as with methotrexate (MTX), be the forerunner of a more severe form of liver disease, namely cirrhosis. Serious hepatic disease, however, appears to occur only in patients who are alcoholics or obese diabetics [4••]. Aminotransferase testing is considered to be adequate for monitoring of patients with rheumatoid arthritis [104,105] and juvenile rheumatoid arthritis [106] taking MTX. Patients with psoriatic arthritis who are taking MTX continue to have disease progression monitored by liver biopsy, usually at 2-year intervals or after every 1.5-g cumulative dose [107,108]. Earlier or more frequent biopsies may be preferable in high-risk groups such as alcoholics; patients with renal dysfunction, diabetes, and obesity; and those with advanced age, in whom damage may occur earlier in the course of therapy. The use of folic or folinic acid supplementation in patients receiving MTX therapy has been found to reduce ALT elevations by up to 60%, suggesting a role for folate depletion in MTX hepatotoxicity [111]. A dose of 0.25 to 0.5 mg of folinic acid per mg of MTX given 4 to 24 hours after MTX is recommended [111]. A recent retrospective analysis has also shown a reduction of MTX hepatotoxicity with administration of folinic acid in children with juvenile idiopathic arthritis [112].

Measurement of the amino-terminal propeptide of type III procollagen (PIIINP) has been proposed as a noninvasive marker of liver fibrogenesis in patients receiving MTX [113,114]. This test seems to be helpful in patients who maintain normal PIIINP levels, as no substantial fibrosis or cirrhosis was found to develop in patients with normal PIIINP levels who were followed for more than 10 years [115]. It has been proposed that the number of liver biopsies in patients with normal PIIINP levels can be reduced if PIIINP remains normal. However, patients with quiescent cirrhosis without active fibrogenesis may go undetected using this marker.

Another promising technique to detect MTX hepatotoxicity is dynamic hepatic scintigraphy. This test measures the portal venous contribution to the total hepatic blood flow. A portal contribution of more than 52% was found to be associated with a 95% chance of having grade 1 (normal or mild fatty infiltration, nuclear variability, and portal inflammation) liver biopsy changes in patients with psoriasis receiving MTX [116]. In another study, this test was associated with a 98.5% predictive value for the absence of or only mild fibrosis [117].

Conclusions

Several potential therapeutic approaches to prevent drug hepatotoxicity are now under investigation, including the use of agents to inhibit tumor necrosis factor (TNF)-α [118] and apoptosis (cell death) [119], the use of interleukins and other cytokines to downregulate inflammation [120], and agents that replenish glutathione stores [121] (such as *N*-acetylcysteine). It is hoped that, through a better understanding of hepatotoxicity mechanisms, including drug metabolism, immunogenicity, and allergic reactions, drug-induced liver disease will be a less frequent and less severe problem in the future, both in the development of new agents and in the use of currently available medications.

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