

LIVER TOXICITY CAUSED BY SYNTHETIC DRUGS

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ABSTRACT

Liver disease can result from dosage-dependent hepatotoxicity or from adverse reactions to drugs used in therapeutic dosage. The latter idiosyncratic hepatotoxins can cause clinical syndromes that mimic all known liver diseases, so that drugs must be considered as the possible causal agent for all unexplained cases of liver disease. The only specific antidote for dosage-dependent hepatotoxicity is N-acetylcysteine (and some other sulfhydryl donors), which is highly effective for the prevention of significant hepatotoxicity after acetaminophen overdose. Early diagnosis and prompt withdrawal of the offending drug is the key to successful management of most drug-induced liver diseases. The mainstay of treatment is supportive care, with careful monitoring for signs of acute liver failure or progression to chronic liver disease. In cases of liver failure, close liaison with a liver transplant center is crucial; referral for liver transplantation should be considered if standard transplant criteria are fulfilled. Pruritus is a major symptom of drug-induced cholestasis; protracted cases may respond to ursodeoxycholic acid. Corticosteroids can be considered for cases of drug-induced hepatitis, especially those with evidence of immune hypersensitivity, if no improvement is seen in 8 to 12 weeks.

Key words: Drug-induced liver disease (DILD), N-acetylcysteine (NAC), Hepatotoxicity, Pharmacologic treatment.

1. INTRODUCTION

Drug-induced liver disease (DILD) is a potential complication of any prescribed medication, because of the central role of the liver in drug metabolism and elimination (Lee, 1995). Early recognition of hepatotoxicity is crucial because continued ingestion of the drug is often associated with a poor prognosis (Farrell, 1997). Prescribers should be aware of compendiums of reported hepatic reactions to drugs (Zimmerman, 1999; Biour, 1999; Farrell, 1994; Stricker, 1992). Recent additions to the burgeoning list of DILD are included in Table 1.

The main focus of this article is on acetaminophen (paracetamol) hepatotoxicity. This remains the leading cause of acute liver failure in the United States and the only form of DILD for which a specific antidote is available (Scioldt, 1999). The preferred treatment for acetaminophen hepatotoxicity is N-acetylcysteine (NAC) (Vale, Proudfoot, 1995). It can be administered orally (United States) or intravenously (Australia, Canada, and Europe). The treatment plan is based on well-established monograms showing serum acetaminophen levels plotted against

time postingestion (Vale, Proudfoot, 1995; Smilkstein, 1988).

Severe liver injury can also result from therapeutic doses of acetaminophen (eg 2 to 6 g daily over several days), especially in chronic alcohol abusers or in those taking other medications (Johnston, Pelletier, 1997; Murphy, 1990). The latter include antiepileptics, azovudine and isoniazid. A lower "treatment line" is used in some countries for such at-risk patients (Routledge, 1998). It is important to note that the 4-hour serum acetaminophen level can be misleading if a person has taken an overdose of an extended-release acetaminophen preparation (Zed, Krenzelok, 1999). In this situation, the serum acetaminophen level should be repeated after 4 to 6 hours (Zed, Krenzelok, 1999). The benefit of NAC also extends to late presenters (10 to 24 hours post overdose) and to those who have developed fulminant hepatic failure (Vale, Proudfoot, 1995; Zed, Krenzelok, 1999).

Oral methionine is also an effective antidote against acetaminophen poisoning (Vale, Proudfoot, 1995). However, it has to be administered early (within 10 hours), causes vomiting and may precipitate hepatic encephalopathy in patients with cirrhosis (Vale, Proudfoot, 1995; Jones, 1997). The role of

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methionine, therefore, is limited to the occasional patient with known hypersensitivity to NAC.

There is debate about the optimal route and regime for administration of NAC. When administered orally, it can cause troublesome vomiting. On the other hand, the higher dosage (1300 mg/kg) that can be given, together with a prolonged regimen and the use of antiemetics, prevent treatment failure. Intravenous NAC remains investigational in the United States, despite statements as to its apparent safety (Yip, 1998; Falk, 1998; Smilkstein, 1991). NAC is easy to administer intravenously, is rapidly effective and is particularly useful in those who cannot tolerate the oral regimen. Anaphylactic reactions are relatively common (6% to 15%) with intravenous NAC, but are usually mild and rarely lead to treatment discontinuation (Yip, 1998). Among high-risk patients, it has been claimed that hepatotoxicity is less likely to develop with the oral or 48-hour intravenous protocol compared with the 20-hour intravenous regimen (Zed, Krenzelok, 1999). Patient selection may explain these discrepant results (Vale, Proudfoot, 1995).

Criteria have been defined to identify those patients with acetaminophen poisoning who should be referred for liver transplantation (Bernal, 1998). The Acute Physiology and Chronic Health Evaluation III score, which reflects the severity of the multisystem illness, may help in treatment decisions (Bernal, 1998). The results of liver transplantation for acetaminophen-induced liver failure are comparable with other liver diseases (Bernal, 1998). Other forms of artificial liver support remain investigational (Rahman, Hodgson, 1999).

There is no specific treatment for drug-induced hepatitis or cholestasis. The use of adjunct therapy (corticosteroids, ursodeoxycholic acid) is based on anecdotal evidence. Corticosteroids can be considered in cases of drug-induced hepatitis that fail to resolve after 6 to 8 weeks and particularly in reactions with a presumed immune basis, such as allopurinol (Farrell, 1994; Teitelbaum, 1998; Sterling, 1996).

The management of pruritus due to cholestasis has been reviewed elsewhere (Franco J Pruritus, 1999). In patients with drug-induced cholestatic liver injury, ursodeoxycholic acid has been used in cases that are prolonged (3 to 6 months). It appears to improve symptoms in a majority of instances; reports include its

use with cyclosporin, amoxicillin-clavulanic acid, flucloxacillin, and flutamide reactions (Kallinowski, 1991; Piotrowicz, 1995; Cicognani, 1996). In severe and intractable cases, fat-soluble vitamin deficiency arises from prolonged cholestasis and should be corrected. In such cases, which are characterized by ductopenia (the vanishing bile duct syndrome), the liver injury may be irreversible and progressive and referral for transplant assessment should be considered in a timely fashion (Richardet, 1999).

Drugs are occasionally the cause of chronic liver disease or tumors. Methotrexate can be implicated in progressive hepatic fibrosis, but only in the presence of risk factors such as regular alcohol ingestion (more than 15 g daily), obesity, diabetes, impaired renal function and older age. These are also the risk factors for non-alcoholic steatohepatitis, which may interact with methotrexate. At-risk patients should undergo biopsy before treatment and a repeated liver test abnormality in someone taking methotrexate requires histologic assessment (Farrell, 1994). Estrogen use is associated with development of liver tumors, particularly liver adenomas. Early recognition may be beneficial as these tumors may regress with steroid withdrawal (Farrell, 1994). Regular abdominal examination is important in those taking such preparations (mainly contraceptive steroids) for over 6 months.

TREATMENT

Diet and lifestyle

- Diet does not influence the outcome of most forms of DILD, but malnutrition has a negative impact on liver transplantation outcomes.
- Fasting increases susceptibility to acetaminophen hepatotoxicity. Obese patients are at risk of halothane and methotrexate hepatotoxicity (Farrell, 1997). Concomitant use of alcohol influences the severity of drug-induced liver injury (increased fibrosis with isoniazid and methotrexate, acetaminophen toxicity) (Farrell, 1997).

Pharmacologic treatment

- The aim of treatment is to prevent progression to acute liver failure. Early intervention (antidote in the case of acetaminophen poisoning, stopping incriminated agents with idiosyncratic hepatotoxins such as isoniazid) is critical.

- Symptomatic measures, such as replenishment of fat-soluble vitamins and control of pruritus (with drug-induced cholestasis) improve quality of life.
- The pharmacotherapy of end-stage liver disease (diuretics, beta-blockers, octreotide, somatostatin) is the same as for other forms of liver disease.

N-acetylcysteine

Standard dosage: *Intravenous:* N-acetylcysteine (Parvolex; David Bull Laboratories, Victoria, Australia) 150 ml/kg in 200 mL 5% dextrose solution over 15 minutes, followed by 50 ml/kg in 500 ml 5% dextrose over 4 hours and 100 ml/kg in 1 L 5% dextrose over 16 hours (MIMS Australia, 1999). Alternate regimen: 140 mg/kg in 5% dextrose over 1 hour, followed by 12 maintenance doses (70 mg/kg) given over 1 hour in 5% dextrose, given 4 hours apart (calculated from time of initiation of the previous dose) (Smilkstein, 1991).

Oral: 140 mg/kg, followed 4 hours later by 70 mg/kg every 4 hours for 17 doses (Smilkstein, 1988).

Contraindications: Known sensitivity to acetylcysteine.

Main side effects: Vomiting (oral route), Flushing, urticaria, wheezing, respiratory distress, hypotension, hypertension (intravenous route). Usually occur early in the treatment. Minor reactions can be managed with antihistamines without interruption of the infusion. When severe reactions develop, the infusion should be stopped and antihistamines administered. The infusion can be usually resumed an hour after this (Bailey, McGuigan, 1998).

Special points: The unpleasant odor and flavor of the oral preparation can be masked by dissolving it in fruit juice and by dilution of NAC (made up to a 5% solution) (United states of pharmacopoeia dispensing information, 1996).

Cost-effectiveness: Intravenous 20-hour regime (for a 70-kg adult) costs \$171.79 (Australian). The 48-hour intravenous regimen (for a 70-kg adult) would cost approximately \$561.18 (Australian) (MIMS Australia, 1999). These costs exclude hospital expenses. Failure to administer antidote could result in the costs of intensive care admission, liver transplantation, or death.

Methionine

Standard dosage: Methionine (Methnine; Medical Research Pty Ltd, New South Wales, Australia), 2.5 g (36 mg/kg) every 4 hours for four doses (MIMS Australia, 1999).

Contraindications: Metabolic acidosis (may be exacerbated), chronic liver disease (can precipitate hepatic encephalopathy) (Martindale, 1996).

Main drug interactions: May decrease the therapeutic effects of levodopa.

Main side effects: Vomiting; May worsen hepatic encephalopathy if used beyond 12 hours following acetaminophen overdose.

Special points: To be used within 12 hours of overdose.

Cost-effectiveness: Inexpensive: \$4.46 (Australian) for the whole 10-g course (MIMS Australia, 1999).

Prednisolone

Standard dosage: Dose and duration are not clearly defined. The usual dose ranges from 30 to 60 mg/d.

Contraindications: Uncontrolled sepsis, active tuberculosis.

Main side effects: Weight gain, acne, mood swings, psychosis, development of candidiasis. May worsen diabetic control. Long-term use associated with osteoporosis, cushingoid features, cataract formation. Abrupt withdrawal may precipitate acute adrenal insufficiency.

Special points: Risk-to-benefit ratio has to be considered. Only limited evidence of efficacy for reactions with features such as rash, vasculitis, auto antibodies and prolonged course.

Cost-effectiveness: Inexpensive when used for a short duration. Long-term use can lead to serious complications that may require prolonged medical therapy or hospitalization.

Ursodeoxycholic acid

Standard dosage: Ursodeoxycholic acid (Ursofalk; Orphan Australia Pty Ltd, Victoria, Australia), 10 to 20 mg/kg/d in two divided doses (MIMS Australia, 1999).

Contraindications: Acute cholecystitis or biliary tract obstruction, pregnancy (first trimester) (MIMS Australia, 1999).

Main drug interactions: Ciprofloxacin, cyclosporin, cholestyramine (theoretical), charcoal, colestipol, some antacids (United states pharmacopoeia dispensing information, 1996).

Main side effects: Diarrhea, pruritus, sensitivity phenomena, increased cholestasis, nausea, vomiting, and sleep disturbance (United states pharmacopoeia dispensing information, 1996).

Special points: Evidence of efficacy is limited. Confine use to prolonged and severe cases.

Cost-effectiveness: Inexpensive, compared with transplant costs.

Surgery

- To prevent death from complications of acute liver failure or decompensated chronic liver disease.
- To improve the quality of life in patients with intractable complications (pruritus, ascites, recurrent variceal bleeding, encephalopathy) of chronic liver disease.

Liver transplantation

Standard procedure: Total hepatectomy and implantation of donor graft.

Contraindications: Multiorgan failure, advanced age, severe psychosocial or psychiatric factors (especially in drug overdose patients), extrahepatic malignancy, systemic sepsis.

Complications: Adverse effects of immunosuppressive therapy, surgical complications including vascular and biliary problems, neurologic complications, metabolic problems including obesity, diabetes mellitus, hyperlipidemia and osteoporosis.

Special points: Referral for transplantation should not be delayed as the clinical circumstances may change rapidly and may render the patient inoperable (Bernal, 1998). Early liaison with the transplant centre is imperative. Indications may include deepening jaundice, impaired coagulation, early changes in consciousness, repeated vomiting and failure to improve 2 to 3 weeks after stopping incriminated agent.

Cost-effectiveness: Both the operation and follow-up therapy are very expensive.

Table 1. Hepatotoxicity of recently introduced drugs

Drug	Indication	Clinical syndrome
Atorvastatin		Hypercholesterolemia Cholestatic hepatitis [7]
Bromfenac		NSAID ALF [8]
Ecarazine		Hypertension ALF [9]
Nefazodone		Depression ALF [10]
Nimesulide		Arthritis ALF [11]
Pemoline		ADHD ALF [12]
Riluzole		Amyotrophic lateral sclerosis Acute hepatitis [13]
Terbinafine		Antifungal agent ALF [14]
Tolcapone		Parkinson's disease ALF [15]
Troglitazone		Diabetes mellitus ALF [16]
Trovofloxacin		Antibiotic ALF [17]

ADHD—attention deficit hyperactivity disorder;

ALF—acute liver failure; NSAID—nonsteroidal anti-inflammatory drug.

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