

DRUG & THERAPEUTICS LETTER



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- Drug induced hepatotoxicity
- H1N1 vaccine
- Drug Information Unit, TUTH

Drug induced hepatotoxicity

Introduction

Drugs are an important cause of liver injury and they account for 20-40% of all instances of fulminant hepatic failure. Drug-induced hepatic injury is the most common reason cited for withdrawal of an approved drug. The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure.

Mechanisms of Hepatotoxicity

Intrinsic or predictable drug reactions

The injury is dose related. The injury can be due to the drug itself or to a metabolite. eg. Acetaminophen (Paracetamol)

Idiosyncratic drug reactions

Hypersensitivity

The response is characterized by fever, rash, and eosinophilia and is an immune-related response with a typical short

latency period of 1-4 weeks. eg. Phenytoin

Metabolic-idiosyncratic

This type of reaction occurs through an indirect metabolite of the offending drug. Unlike intrinsic hepatotoxins, the response rate is variable and can occur within a week or up to one year later. eg. INH toxicity

Clinical manifestations

The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. Drug-induced liver injury is designated hepatocellular if the ALT levels are increased to more than twice the upper limit of the reference range, with alkaline phosphatase levels that are within the reference range or are minimally elevated. Elevation of aspartate aminotransferase (AST) greater than ALT, especially if more than 2 times greater, suggests alcoholic hepatitis. Elevation of AST less than ALT is usually observed in persons with viral hepatitis. In viral and drug-induced hepatitis, the AST and ALT levels steadily increase and peak within 7-14 days. With increasing hepatocellular injury, bilirubin levels are invariably increased, suggesting a worse prognosis.

Diagnosis

History

It must include dose, route of administration, duration, previous administration, and use of any concomitant drugs, including over-the-counter medications and herbs. Obtaining a history of every drug ingested in the past 3 months is essential.

- The onset is usually within 5-90 days of starting the drug.
- Exclusion of other causes of liver injury/cholestasis

Dechallenge

A positive dechallenge is a 50% fall in serum transaminase levels within 8 days of stopping the drug. A positive dechallenge is very helpful in cases of use of multiple medications.

Track record of the drug

Previously documented reactions to a drug aid in diagnosis.

Rechallenge

Deliberate rechallenge in clinical situations is unethical and should not be attempted; however, inadvertent rechallenge in the past has provided valuable evidence that the drug was indeed hepatotoxic.

Agents frequently causing hepatotoxicity

Drugs causing asymptomatic elevations in aminotransferase

Tacrine, HMG-CoA reductase inhibitors, sulfonamides, salicylates, sulfonyleureas, and quinidine.

Drugs causing elevated aminotransferase levels with acute hepatocellular injury

Acetaminophen, NSAIDs, ACE inhibitors, nicotinic acid, INH, sulfonamides, erythromycin, and antifungal agents such as griseofulvin and fluconazole. In acetaminophen overdose, transaminase levels greater than 10,000 IU/L are also noted.

Drugs causing subfulminant hepatic necrosis

Acetaminophen, halothane, methoxyflurane, enflurane, trovafloxacin, troglitazone, ketoconazole, dihydralazine, mushroom poisoning, ferrous sulfate poisoning, phosphorus poisoning, and cocaine toxicity.

Drugs causing massive hepatic necrosis

Propylthiouracil, INH, phenytoin, phenelzine, sertraline, naproxen, diclofenac, and ecstasy

Drugs causing elevated alkaline phosphatase (acute cholestatic injury) levels

Chlorpromazine, ciprofloxacin, ofloxacin, cimetidine, phenytoin, naproxen, captopril, erythromycin, azithromycin, dicloxacillin, amoxicillin-clavulanic, and octreotide.

Treatment

Early recognition of drug-induced liver reactions is essential to minimizing hepatic injury. ALT values are more specific than

AST values. ALT values 4-5 times higher than the reference range should lead to prompt discontinuation of the drug. No specific treatment is indicated for drug-induced hepatic disease. Treatment is largely supportive and based on symptomatology. The first step is to discontinue the suspected drug. Specific therapy against drug-induced liver injury is limited to the use of N -acetylcysteine in the early phases of acetaminophen toxicity. L-carnitine is potentially valuable in cases of valproate toxicity. In general, corticosteroids have no definitive role in treatment. Cholestyramine may be used for alleviation of pruritus. Ursodeoxycholic acid may be used.

No specific antidote is available for the vast majority of hepatotoxic agents. Emergency liver transplantation has increasing utility in the setting of drug-induced fulminant hepatic injury. The prognosis is highly variable depending on the patient's presentation and stage of liver damage.

Conclusion

Drug induced hepatotoxicity may be due to intrinsic or idiosyncratic reactions. Monitoring aminotransferase levels monthly for the first 6 months of treatment has been suggested for patients taking hepatotoxic medications, but, in cases of rare adverse reactions, this is unlikely to be effective. A serious event may be prevented if the offending drug is discontinued at the first sign of an adverse reaction.

Reference:

Mehta N, Ozick L, Gbadehan E, Drug-Induced Hepatotoxicity. Online article available from <http://emedicine.medscape.com/critical-care>. Updated: June 4, 2009. (Accessed on October 24, 2009)

Brief Information

H1N1 vaccine

Following the rapid spread of a new influenza A H1N1 virus, also called swine flu, the World Health Organization (WHO) declared influenza pandemic on 11 June 2009. This prompted the development of a 2009 H1N1 vaccine.

Single dose vials containing 15 microgram of haemagglutinin in 0.5 mL and multidose vials containing 5 mL or 10 mL vaccine have been approved for the prevention of 2009 H1N1 influenza.

Using the same methods employed to make the seasonal influenza vaccine, a monovalent split-virus inactivated vaccine that does not have adjuvant has been developed. The virus, which was grown in embryonated chicken eggs, was prepared from the reassortant vaccine virus NYMC X-179A derived from the influenza A/California/7/2009 H1N1 virus (recommended by the WHO).

Two doses of the vaccine would be needed as most people would not have had previous exposure to the H1N1 virus.

The vaccine is indicated for adults, adolescents and children over 10 years of age and should be given by intramuscular or deep subcutaneous injection. However, it should not be given to people who have had a life-threatening reaction to influenza vaccination, or who have had Guillain-Barré syndrome within six weeks of a previous influenza vaccination. Likewise, it is contraindicated in people who have anaphylactic hypersensitivity to eggs, chicken protein or other constituents of the vaccine.

Responses to the vaccine may be lower in immunocompromised patients. Immunisation should be postponed in people who have a febrile illness of acute infection.

The most commonly reported adverse events are tenderness, pain and induration at the injection site. Other common events included headache, malaise and myalgia, influenza-like illness.

Drug Information Unit (DIU), TUTH

The DIU has provided following services during the period July 2008 to September

2009:

Publication of Drug and Therapeutics Letter

Five issues were published.

Adverse Drug Reaction (ADR) monitoring

Twenty seven cases of ADRs have been reported from the OPD and wards of TUTH.

Question-answering service

Question-answering service included answers to questions regarding:

- Rationale of combination and clinical uses of bisoprolol and hydrochlorothiazide; cefixime and clavulanic acid; and cefotaxime and sulbactam
- Rationale and clinical uses of teimonium methylsulphate
- Adverse effects of repaglinide
- Maximum oral dose of prednisolone in myasthenia gravis
- Route of administration of methotrexate in rheumatoid arthritis
- Loss of potency of ganciclovir solution after opening the vial

"Drug and Therapeutics Letter" is also available in the following website:
<http://www.teachinghospital.org.np/diu.html>, <http://www.iom.edu.np/diu.html>

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