

Drug Induced Liver Diseases in the Elderly

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Introduction

The ever increasing exposure to drugs and an increase in longevity in the population has given rise to an increase in incidence of drug-induced liver diseases. Paralleling this, there has been an explosion in the basic science understanding in hepatic pharmacology, toxicology and immunology. Exciting new developments have provided better insights, which have then helped us plan newer strategies to prevent or deal with drug - induced liver disease. Information about apoptosis, cloning of numerous genes encoding for P450 isoenzymes and the understanding of drug induced impairment of bile acid transporters in intact hepatocytes resulting in cholestasis have helped us understand the phenomenon of drug induced liver toxicity better. Translating this knowledge into practical application— prevention and treatment is the exciting challenge ahead of us.

Age and drug toxicity in liver

About 20% of hepatitis in the elderly is drug induced as compared to 2-5% in all age groups.¹ There are several reasons for this:

1. Elderly tend to use more medications. The National Health and Nutrition Examination Survey (NHANES) III data obtained between 1988 and 1994 showed that 74% of people over 65 years of age used prescription drugs as against 39% of adults between the ages 19 and 64.² The elderly are more likely to be on multiple medications and this increases the risk of toxicity.^{3,4} 51 % of individuals between ages 65 and 74 used two or more medications while 12% were on five or more drugs. In contrast, only 19% of individuals studied between ages 19 and 64 were on two or more

drugs.²

2. The elderly are likely to have more serious illnesses and may have conditions like renal insufficiency which predispose to drug toxicity.
3. With increase in age, there is more likelihood of previous exposure to a drug and the possibility of immunoallergic reactions.
4. Age related impairment of drug metabolism and disposition can contribute to an increase in incidence of drug toxicity.
5. There is a gradual decline in renal function which can potentiate drug accumulation in liver.⁵
6. Age related decline in blood flow to the liver can result in drug accumulation. Age dependent decrease in hepatic blood flow has been estimated to be 20 to 50%.
7. Decrease in liver mass and serum albumin, increase in body fat and decrease in muscle mass alter the distribution of drugs in the tissue distribution.⁶
8. Capillarisation, which is the loss of fenestrae in sinusoidal endothelial cells with increased basement membrane formation in the space of Disse precedes fibrosis. Age-related capillarisation can result in reduced oxidative drug metabolism and hepatic drug clearance.⁷

Older patients on multidrug regimens with Isoniazid (INH), rifampicin or pyrazinamide have a high incidence of elevated liver enzymes and/or liver toxicity. Byrd et al, in a study of 1000 patients treated with INH found that liver enzymes more than five times the upper limit of normal were more frequent in older patients.⁸

Clinical presentation

The presentation is often as an asymptomatic patient with raised liver enzymes. A symptomatic patient with jaundice merits immediate attention and corrective action. Making a diagnosis in a patient on

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hepatotoxic drugs is not difficult when there are signs of liver cell failure.

In an asymptomatic patient with enzyme elevation, it is important to take a history of intake of drugs likely to be hepatotoxic. INH, used in the prevention of pulmonary tuberculosis, antiepileptics like phenytoin and statins are known to cause elevation of enzymes. Studies have shown that 10 – 20 % of patients on INH and 2–5 % of patients on statins develop abnormal liver enzymes.^{9,10} Loss of appetite, fatigue, lassitude and abdominal discomfort are some of the symptoms patient presents with. In case of hypersensitivity reactions due to drugs, patients tend to have fever, rash and/or eosinophilia. Liver dysfunction due to non-steroidal anti inflammatory drugs (NSAIDs) is fortunately rare. NSAIDs can cause a spectrum of liver manifestations— asymptomatic elevation of liver enzymes, acute hepatitis, cholestatic hepatitis, and very rarely, acute hepatic failure.^{10,11} Elderly women are found to be more prone to develop severe injury.

One of the criteria for diagnosis of drug – induced liver disease is the recurrence on re-exposure to the drug. This happens when the physician considers the risk-benefit and administers a drug known to have resulted in raised liver enzymes earlier.¹² The far more common situation is the inadvertent re-exposure of a patient to a drug that has previously resulted in hepatotoxicity, which went unnoticed or when the treating physician is unaware of the event.¹³ Another example of such a possibility is when a patient has been on a combination drug and the offending component is not identified.

The often quoted example of inadvertent re-exposure to a drug leading to hepatotoxicity is halothane. Repeated exposure may occur owing to contamination by halothane of the equipment used to administer the anesthetic for a previous surgery.¹⁴

Treatment of tuberculosis and epilepsy requires the use of drugs known to cause liver injury. Co-administration of drugs that potentiate liver cell damage is often the cause for the presentation.

Acute icteric hepatitis (hepatocellular jaundice) is of grave significance as the mortality can be up to 10 % irrespective of the drug. This is called Hy's Law after the late Hy Zimmerman, who noted that mortality from drug-induced hepatocellular jaundice ranged between 10 – 50%.¹⁵ Zimmerman also noted that in most cases at risk of fatal outcome, alanine

aminotranferase was between 8 and 100 times the upper limit of normal. Such a presentation is associated with systemic symptoms, jaundice, and in more severe cases, coagulopathy and encephalopathy indicative of acute or fulminant hepatic failure.

It is important to be aware of the 'signals' of hepatotoxicity. These signals have been classified by Maddrey WC as major, intermediate and minor as shown in Table 1.¹⁶

Table 1: Signals of hepatotoxicity.

Major:	development of acute liver failure development of symptoms onset of clinically apparent jaundice onset of ascites, encephalopathy, coagulopathy
Intermediate:	ALT > 8 x ULN ALT > 5 x ULN ALT > 3 x ULN
Minor:	any elevation of ALT (<3xULN) in an asymptomatic patient

(ALT – Alanine aminotransferase, ULN – Upper limit of normal)

General observations

Some general observations can help the clinician in dealing with drug induced liver disease. Diagnosis of drug induced liver disease is one of exclusion of other etiologies. Hepatocellular injury is more likely to lead to a fatal outcome than cholestatic injury. Patients presenting with drug induced hepatocellular injury don't fare as well as those who suffer from acute viral hepatitis of similar severity. Histological evidence of injury is often more severe than is suggested by clinical signs and biochemical parameters. In patients in whom there is granulomatous inflammation, liver disease is less severe than in those in whom hepatocellular injury is seen without granulomatous inflammation.

Several drugs cause chronic hepatitis which cannot be distinguished from autoimmune hepatitis.¹⁷ If the correct diagnosis is not made, the offending drug will not be withdrawn and corticosteroids may be instituted. Such a course can lead to further damage while corticosteroids may temporarily reduce the manifestation of the injury. Nitrofurantoin and methyldopa are drugs that can cause liver injury which mimics autoimmune hepatitis type 1.¹⁸ Most of the reported

cases were in women.

Management

The most important aspect of management is timely identification of toxic changes in the liver as evidenced by a rise in liver enzymes. The offending drug should be withdrawn immediately. If the patient needs immediate or continued treatment for the condition, the physician should introduce another drug that is not hepatotoxic with caution. In elderly patients with tuberculosis, rifampicin and INH should be stopped and a combination of drugs like cycloserine and ethambutol can be introduced. Some physicians favour a challenge with either rifampicin or INH. In our opinion, this is a risky option.

In the case of statins causing elevated liver enzymes, we would advocate continuing the drug while monitoring the patient closely. The incidence of raised liver enzymes in patients on statins is 2–5 % and probably dose related. With lovastatin, the incidence of severe hepatitis is 1/1.4 million.¹⁹ Besides, the presence of liver disease does not increase the risk of an adverse reaction with statins.²⁰

The continued use of a drug like amiodarone may be indicated even in the presence of raised liver enzymes, if it is the only drug available to prevent a lethal event like ventricular tachycardia.²¹ The risk-benefit to the patient will have to be assessed in such a situation. In the treatment of patients with epilepsy, phenytoin can be replaced with valproic Acid.

Among the antidotes that prevent significant damage to the liver, the best known is N-acetylcysteine (NAC) which limits the injury by the toxic metabolic products of acetaminophen by generating glutathione. Most other adverse drug reactions do not have specific therapy. Physicians often use steroids or ursodeoxycholic acid (UDCA) in the hope of hastening recovery but there is inadequate data in literature to support such a course of action. Though there are anecdotal reports of the successful use of steroids or UDCA, there has been no randomised control trial done so far. The only exception is in treating drug induced autoimmune hepatitis caused by alpha-methyl dopa or nitrofurantoin.^{22,23}

Acute liver cell failure

Acute liver cell failure is most dreaded complication of drug hepatotoxicity. Liver injury may occur due to

a known hepatotoxin like acetaminophen or from an idiosyncratic reaction seen with drugs like halothane, isoniazid or phenytoin. In a patient with drug-induced liver disease, jaundice as a presentation associated with raised liver enzymes is predictive of an increased risk of death. Bjornsson et al showed that age is a risk factor in the prognosis. Elderly patients have a poorer outcome.²⁴ The important step in the management of these patients is the early identification of the association and stopping the drug. Once jaundice appears, prognosis is much worse. If bilirubin exceeds twice the upper limit of normal, the mortality rate is 9.2%. Patients with predominantly cholestatic pattern have a lower risk for death (7.8%) while those with hepatocellular type injury have a higher risk (9.2%) once they become jaundiced.²⁴

Liver transplantation

Liver transplantation is often the only solution when faced with acute liver cell failure in the context of drug hepatotoxicity. The authors saw an elderly gentleman who was on cloxacillin for a skin infection and presented with jaundice as well as raised liver enzymes. He had developed liver cell failure. The only treatment option was liver transplantation. In view of his age and the overall prognosis, we were unable to consider that option. Overall outcome following liver transplantation at advanced centers is not very encouraging.²⁵ An early diagnosis followed by corrective measures is the best option.

Summary

Drug induced hepatotoxicity in the elderly calls for an early, effective response from the clinician. Identifying the problem and offending drug expeditiously is of paramount importance. In the case of drugs like isoniazid, a quick withdrawal of the drug before bilirubin levels rise is critical for success. With drugs like statins which cause elevated liver enzymes, but rarely cause serious liver injury, the decision should be to continue treatment with close monitoring. In situations where the benefit far outweighs the risk of significant liver injury, the clinician will have to make a decision based on a careful risk-benefit analysis.

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