Antituberculosis drug-induced hepatitis: Risk factors, prevention and management

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Viral hepatitis is a systemic infection affecting primarily the liver. At least 8 different types of viruses directly associated with viral hepatitis have been identified. The causes of hepatitis can be broadly classified into infectious and non-infectious. The infectious causes include bacteria and more commonly viruses. The non-infectious causes are alcohol (alcoholic hepatitis), cholestatic, drugs and toxic materials.

Apart from infectious or viral hepatitis, other common non-infectious causes that lead to liver injuries are antituberculosis drug-induced hepatitis. Tuberculosis continues to be a major health problem in both developing and developed countries because of its resurgence in immunosuppressed patients. Epidemiological data suggest that antituberculosis drug-induced hepatitis is due to its metabolic idiosyncrasy rather than direct toxicity. Some host factors that increase the hepatotoxicity of ATT are old age, pregnancy, malnutrition, and concurrent administration of other drugs such as rifampicin, alcohol, etc. The great susceptibility of liver damage to chemical agents (such as ATT drugs) is a consequence of its primary role in the metabolism of foreign substances. Liver injury is present when abnormalities of liver tests include an increase to more than twice the upper limit of serum alanine aminotransferase (ALT), serum alkaline-phosphatase (ALP), or bilirubin. The severity of drug-induced liver injury varies from minor non-specific changes in hepatic structure to fulminant hepatic failure, cirrhosis and liver cancer. The term drug-induced liver disease should be confined to cases in which the nature of liver injury has been confirmed histologically. Short course chemotherapy containing isoniazid and rifampicin in combination has proved to be highly effective in the treatment of tuberculosis, but one of its adverse effects is hepatotoxicity. Several reports suggest that hepatitis is more frequent and severe with chemotherapeutic regimens containing both isoniazid and rifampicin than those

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isoniazid alone with other antitubercular drugs. Lesbre et al. also described 12 cases (24%) of jaundice with 4 deaths among 50 patients receiving isoniazid and rifampicin, although many of these patients had pre-existing liver disease with high doses of isoniazid and rifampicin.

Lees et al. observed 4 cases (8%) of hepatitis among 50 patients without known liver disease. The hepatotoxicity of isoniazid plus rifampicin is synergistic rather than additive. This is due to the remarkably potent inducing effect of rifampicin on the hepatic P-450 mixed oxidase enzyme pathways leading to the increased formation of toxic intermediate from monoacetylhydrazine. The time required for the toxic metabolites (hepatotoxicity) to reach is much earlier on isoniazid plus rifampicin treatment than isoniazid alone. In addition, rifampicin can induce isoniazid hydrolase resulting in an increase in the formation of hydrazine from isoniazid through the direct pathway, with consequent manifestation of hepatic injury. Today, we are speaking much more of an “INH hepatotoxicity” which is aggravated by the microsomal enzyme-inducing effect of rifampicin. Many questions in the pathogenesis of liver cell necrosis caused by noxae still remain open, it seems to be certain that the damage to the membrane is the decisive incident triggering the pathology. The preparation of Essentielle Forte besides vitamins mainly contains “essential” phospholipids can positively influence this damage, because phospholipids are an integral component of the cellular membrane systems and sub-cellular particles. Their importance in the liver therapy becomes obvious by their role as structural elements, mediators between the intracellular and intercellular space, activators of different enzyme systems and in immunological processes.

**Hepatic drug metabolism and toxic mechanisms of liver injury**

Biotransformation reactions in liver have traditionally been considered protective as detoxifiers of potentially toxic foreign compounds. Such reactions can also convert nontoxic agents to potentially toxic products. It has become clear that the formation of reactive, and therefore toxic, metabolic intermediates within the hepatocyte accounts for injury that the liver sustains from many of the known toxic chemicals and drugs. Most drugs and other xenobiotics that react with body tissues are nonpolar, lipid-soluble compounds, since absorption from the intestine requires lipid solubility. Accordingly, biotransformation of lipid solubility to water solubility is necessary to prevent intolerable accumulation of foreign and endogenous molecules. The enzyme systems responsible for the biotransformation are integral parts of smooth endoplasmic reticulum. The pathway of drug metabolism divides into phases I and II. Phase I reactions are largely oxidative, yielding active transient metabolites. Their reactivity serves to permit to produce hepatic injury. Phase II reactions may be regarded as detoxification reactions. The enzyme system responsible for phase I reaction is called mixed function oxidase or monoxygenase. Cytochrome P-450 is a key enzyme of phase I metabolism, a haemoprotein located in SER. The haem-moiety binds O2 which is then reduced by accepting an electron from flavoprotein reductase, the resultant activated O2 is incorporated into lipophilic substances. Such activation results in the formation of chemically reactive intermediates such as N-acetyl-P-benzoquinonemine (NAPQI) as shown in Fig. 1. It causes cell damage by per-oxidative damage of lipid moiety of biological membrane, forms direct covalent binding with protein or DNA. Co-valent binding of reactive metabolite with macromolecule may produce injury by inactivating key enzymes or forming protein drug adducts that are potential target for immune-mediated injury. Phase II reactions may be regarded as detoxification reactions. Conjugation with glutathione (GSH) serves to detoxify an active intermediate as shown in Fig. 2.

**Metabolism of isoniazid**

Isoniazid is the major drug incriminated in antituberculosis drug-induced hepatitis. The frequency that causes 6-12% mortality if the drugs are continued after the onset of symptoms is typically between 1 and 36%. Isoniazid (INH) gets acetylated to acetylisoniazid (AcINH) by N-acetyltransferase (NAT) enzyme which is nonhepatotoxic. Acetylisoniazid in turn gets hydrolyzed to monoacetylhdyrazine (MAH) and isonicotinic acid (INA). P-450-dependent hepatic microsomal enzymes hydrolyze to a potent acylating agent that binds covalently to apparently vital hepatic

![Acetaminophen](O2) → N-acetyl-P-benzoquinonemine (NAPQI)

Fig. 1 — Formation of chemically reactive intermediate, N-acetyl-P-benzoquinonemine (NAPQI)
macromolecules and causes hepatic necrosis can convert MAH. Alternatively MAH can be acetylated to diacetylhydrazine (non-hepatotoxic) as shown in Fig. 2. INA on the other hand is conjugated with glycine to form isonicotinylglycine (INAG). It has been directly hydrolyzed by isoniazid hydrolase to INA and hydrazine that is hepatotoxic.

Role of rifampicin
When rifampicin is used in combination with isoniazid the interval between the commencement of therapy and onset of hepatitis is much shorter. This is due to the fact that rifampicin is a known microsomal enzyme (P-450E1) inducer and increases the concentration of toxic metabolites of isoniazid. Rao et al. reported that the average interval for the onset of jaundice was 15.5 days in patients treated with isoniazid and rifampicin combination. While it was 71 days in the patients treated with isoniazid and other companion drugs. In the study conducted by Lees et al. it was found that jaundice occurred within 7 weeks with a mode and 3 weeks in-patients receiving isoniazid and rifampicin. Gupta et al. also reported similar results with nearly all of their patients (26 out of 29) developing hepatitis within 2 weeks of starting therapy.

Relationship of acetylator status to hepatotoxicity of isoniazid and rifampicin combination
In the study of isoniazid-induced hepatitis observed that out of 21 patients with probable isoniazid liver injury 18(86%) was rapid acetylator, although the expected frequency was 45%. Hence, they suggested that isoniazid may be more hepatotoxic for rapid acetylator than for slow acetylators. The rapid acetylators might be expected to form monoacetylhydrazine (MAH) from isoniazid more rapidly than slow acetylator and MAH can be converted by hepatic microsomal enzymes to a potent hepatotoxic agent. This hypothesis was questioned on the ground that rapid acetylator acetylates MAH more rapidly than slow acetylator to the non-toxic diacetylhydrazine DAH. Therefore slow acetylators instead of rapid acetylator have been determined to cause antituberculosis drug-induced hepatitis. Evidence abounds from clinical studies that the risk of hepatic reactions during treatment with isoniazid with or without rifampicin is no greater for rapid acetylator than slow acetylator. A subsequent study has shown that hepatitis in patients receiving isoniazid and rifampicin occurred more often in slow than in rapid acetylators. The proportions among those whose acetylator phenotype was determined were 11% of 317 slow and 1% of 244 rapid acetylators. Recent study shows that polymorphism of the N-acetyltransferase 2 (NAT2) genes are the major susceptibility risk factors. N-acetyltransferase (NAT) is one of the major liver enzymes involved in biotransformation of drugs and other exogenous substances. NAT catalyzes the transfer of acetyl group from acetyl coenzyme A to the primary amino group of the acceptor molecule, which results in the formation of N-acetyl derivatives. The hepatic (NAT) is involved in the metabolism of several carcinogenic amines and drugs. This enzyme has a genetic polymorphism in human. N-acetyltransferase 2 genes (NAT2) have been located on chromosome 8p22. Identified to be responsible for genetic polymorphism of slow and rapid acetylation. NAT is composed of one intronless open reading frame.
(ORF) of -870-bp fragments containing the protein coding region of the gene\(^{39}\). Polymorphisms in NAT2 are also associated with higher incidence of cancer and drug toxicity\(^{39,52,53}\). Classification of humans as rapid and slow acetylators is based on hereditary differences in rates of N-acetylation of therapeutic and carcinogenic agents\(^{57}\).

### Host factors: Genetic polymorphism of human cytochrome P-450E1

Antituberculosis drug (ATT)-inducible cytochrome P-450E1 (CYP2E1) is constitutively expressed in the liver\(^{27,30,55,57}\). The substrate specificity is broad and includes at least 80 different characterized substrates\(^{59}\). The enzyme is induced by a variety of chemicals, mainly substrates, and induction in these cases is to a major extent mediated at the posttranslational level\(^{58}\). It is evident that CYP2E1 plays an important toxicological role\(^{16,25}\). It activates precancers, and drugs to cytotoxic or carcinogenic products that might be harmful and of importance for the synergistic effect of ATT on many types of liver diseases\(^{39,43,47,55,57}\). This reaction is implicated as being of importance in the etiology of ATT-induced liver disease. Because of the important toxicological role of CYP2E1, a lot of research has been conducted aimed at elucidating a genetic polymorphism of the human CYP2E1 gene and the linkage of various allele forms to different types of ATT-induced liver diseases\(^{09}\). Restriction fragment length polymorphism (RFLP) analysis of the human CYP2E1 gene revealed polymorphism detectable with the restriction endonuclease \(\text{HindIII}\)\(^{56}\). The polymorphic sites are all present in the non-coding regions of the gene\(^{09}\). The open reading frame (ORF) of the human CYP2E1 gene has been found to be well conserved, and functional mutations are very rare\(^{09}\). Two major polymorphic sites have been studied in relation to this disease. The first is located in the 5'-flanking region at about 1020 bp upstream\(^{49}\) and in intron 6\(^{09}\). This allele has been sequenced and found to carry mutations near the promoter and in the 3'-flanking region, but not in the open reading frame (ORF)\(^{41}\).

### Host factors: Glutathione-S-transferase

Drug hepatotoxicity in general, is the outcome of dynamic processes involving toxic metabolite generation and its detoxification in the liver\(^{6,16}\). Glutathione (GSH) plays an important protective role as an intracellular free radical scavenger by conjugating with toxic reactive metabolites that are generated from biotransformation of drugs and xenobiotics\(^{62}\). Sulphydryl (SH) conjugation of the metabolites facilitates their elimination from the body, and so reduces the potential for toxicity\(^{62,63,65}\). Thus, it plays an important role in preventing acetaminophen and ATT-induced hepatotoxicity. Glutathione-S-transferase (GST) catalyze these conjugation reactions and they exist in several isoforms with varying tissue-specific expression\(^{63}\). Deficiency in GST activity, because of homozygous null mutations at GSTM1 and GSTT1 loci, may modulate susceptibility to drug and xenobiotic-induced hepatotoxicity\(^{60}\). Some genetic loci of these isoenzymes, notably GSTM1 and GSTT1 are polymorphic\(^{66-69}\). Polymorphisms at GSTM1, GSTT1 and NAT2 loci had been linked to various forms of liver injury, including hepatocellular carcinoma\(^{65,66}\).

### Individual risk factors

Many factors influence the risk of drug-induced liver disease: dose\(^{6,66}\), blood level\(^{16}\), and duration of intake for dose dependent hepatotoxins\(^{5}\) and occasionally some idiosyncratic reactions. For these drugs, however, other host determinants are more relevant, examples: age\(^{8,26}\), sex\(^{8,26}\), genetic factors\(^{10,28}\). Most hepatic drug reactions are more common in adults than in children\(^{16,19}\). Women are particularly predisposed to drug-induced hepatitis\(^{12}\).

### Concomitant exposure to other agents

One drug can increase the hepatotoxicity of another drug when administered concurrently, by inducing the cytochrome P-450 (CYP) mediated metabolism to toxic intermediates e.g. acetaminophen\(^1\), alcohol\(^{27,28,67}\), isoniazid\(^{4,41}\), valproic acid\(^4\) anticancer drugs\(^4\) and nutritional status\(^{26}\). Chronic excessive alcohol ingestion decreases the dose threshold and enhances the severity of acetaminophen induced hepatotoxicity\(^{61}\), increases the risk and severity of isoniazid hepatitis. Many extrahepatic manifestations may be seen in conjugation with certain medicinal agents as part of clinical spectrum\(^{64}\). Hallmarks of hypersensitivity reactions such as fever, rash, arthralgia and eosinophilia, point to an immunologic basis of injury\(^{1,64}\).

### Diagnosis of drug-induced liver disease

Drug-induced liver disease is discovered by finding abnormalities in hepatic associated enzymes\(^{48}\) or, in some cases, by the development of hepatitis-like symptoms of jaundice\(^{39,41,42}\). The diagnosis are often
based on a high index of clinical suspicion and whether the implicated drugs fit the known
description has similarly reported cases. A temporal
relationship is usually evident with an implicated
drug, with most cases of acute drug-induced liver
disease occurring within 1 week to 3 months of
exposure. A positive response to discontinuing
the agent (de-challenge) enhances the suspicion
especially when the biochemical and clinical
manifestations of the injury subside rapidly. The
general rule is a 50% reduction in hepatic associated
enzymes after 2 weeks, with a return to normal by 4
weeks in cases of acute hepatocellular injury. Drugs
causing cholestatic injury may have a more prolonged
recovery time. A positive re-challenge to a
suspected drug may be a definitive means of
confirming drug-induced liver disease but this is
generally not done, especially when dealing with
agents causing hepatocellular necrosis, because a
more severe reaction may precipitate hepatic failure.

Early detection
It is a critical point to warn patients to report any
untoward symptoms, particularly unexplained nausea,
malaise, right upper quadrant abdominal pain,
lethargy or fever. These non-specific features may
represent the prodrome of drug-induced hepatitis.
They are the indications to perform liver tests and if
the results suggest liver injury, to stop treatment. A
more difficult issue is protocol screening with liver
tests. Although often recommended by authors and
drug manufacturers, its efficacy and cost effectiveness
are unknown. It has been shown that the onset of liver
injury is often rapid, rendering monthly or even
second screening futile. If liver tests are monitored,
the level of abnormality at which drugs should be
discontinued is often uncertain. A classical example is
isoniazid, which causes some liver test abnormality in
30% of exposed subjects. Generally, it is
recommended that the drug be stopped if alanine
transferase (ALT) values exceed 250 IU/L or more
than 5 times the upper limit of the normal, but the
presence of abnormalities in serum bilirubin or:
albumin concentrations or prothrombin time provides
a clearer indication to stop therapy. Conversely, a
rise in GPT or minor elevation of SAP does not
usually indicate liver injury. Protocol screening is not
routinely recommended, but could be useful for
agents such as isoniazid (INH) because the onset of
liver injury may be delayed and gradual in some cases
to underscore the hepatotoxic potential of particular
drugs in the minds of patients and physicians. Active
management might include removal of the drug and
the administration of antidotes and anti-inflammatory
and cytoprotective agents.

Prevention and management
With the exception of acetaminophen hepatotoxicity there is little effective treatment for drug
induced liver disease. This puts a special onus on
prevention and early detection of liver injury as well
as on prompt withdrawal of the offending agent. The
majority of drugs associated with drug-induced liver
disease are idiosyncratic hepatotoxins. Thus, liver
injury occurs rarely. The overall incidence of adverse
hepatic reactions can be minimized only through
avoidance of overuse of these drugs. Similarly,
polypharmacy should be avoided where possible. The
rarity of adverse drug reactions also means that
the hepatotoxic potential of new agents may not be
recognized until after their induction. Thus, all
physicians share the responsibility to report suspected
adverse effects to monitoring agencies during post-
marketing surveillance of new drugs. For those
dependent hepatotoxins, prevention is dependent on
adherence to dosage guidelines or use of blood levels.
This approach has virtually abolished some forms of
drug-induced liver injury. In cases with specific risk
factors, strategies to avoid toxicity are essential.

References
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