

REVIEW ARTICLE

ANTITUBERCULOUS DRUGS IN CHILDREN AND LIVER

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ABSTRACT

This review article deals with the incidence of hepatotoxicity of various anti-tuberculous drugs (anti-TB drugs) in children, the mechanism of hepatotoxicity and various risk factors responsible for it. The management of tuberculosis if hepatotoxicity occurs as well as in known liver disorders is also being discussed. As the data from studies done in children is scanty, so the help is taken from those of adults for the review.

KEY WORDS:

Childhood tuberculosis; drug induced hepatotoxicity; hepatitis B; hepatitis C; monitoring; management; latent tuberculous infection

ABBREVIATIONS USED:

ALT: alanine aminotransferase;

ALP: alkaline phosphatase;

AST: aspartate aminotransferase;

ULN: upper limit of normal;

LFT: liver function test; anti-TB drugs: anti tuberculous drugs;

DILI: drug induced liver injury;

HIV: Human immune deficiency virus;

LTBI: latent tuberculous infection;

INTRODUCTION:

There are a number of ways by which the child liver is affected by tuberculosis:

- 1 Direct liver involvement; in childhood tuberculosis this is quite high ^{1,2} but rarely causes marked impairment of hepatic function ^{3,4,5}.
- 2 A child having pre-existent liver disease may also develop tuberculosis.
- 3 A child undergoing treatment for tuberculosis may develop hepatic dysfunction as a adverse reaction to drugs or may develop some other liver disease like acute viral hepatitis during treatment
- 4 Hepatic dysfunction can alter absorption or distribution of anti-TB drugs which are metabolized or excreted through the liver ⁶. There is very little data available about the management of childhood tuberculosis in liver diseases as well as management of hepatotoxicity induced by anti TB drugs. The purpose of review of this article is to discuss the management of tuberculosis in relation with liver disorders as well as hepatotoxicity induced by antiTB drugs. It was attempted to collect data from studies done in children for the review. If such data was not available for children, then the help was taken from the articles written for adults especially "state of art/ national guidelines" one. The opinions expressed below are those of the authors; the reader should keep in mind that there is scanty data, and lack of consensus among experts in many of these areas.

CLINICAL ENTITIES:

The clinical entities of liver injury vary from "asymptomatic enzyme elevation" to "asymptomatic bilirubin elevation" to symptomatic (malaise, poor appetite, vomiting weight loss, pruritus, dark coloured urine, scleral icterus, and pain in right upper quadrant) elevation in liver enzymes and or bilirubin called "hepatitis". Acute hepatic failure is the most dangerous form which may result in death. Typically, three patterns of liver test abnormalities due to anti-tuberculous drugs (anti-TB drugs) are recognized in adults: hepatitis or hepatocellular, cholestatic, and mixed. The accepted definitions for these reactions are ⁷.

Hepatitis: ALT/ULN ~ ALP/ULN ≥ 5

Cholestasis: ALT/ULN ~ ALP/ULN ≥ 2

Mixed: ALT/ULN ~ ALP/ULN > 2 to < 5

Isoniazid and pyrazinamide usually cause hepatitis while rifampicin usually causes cholestasis.

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INCIDENCE OF HEPATOTOXICITY:

It is very difficult to estimate the exact incidence of hepatotoxicity due to the possible effects of a number of anti-tuberculosis drugs given together with varying dosage as well as varying duration, any other drugs used, severity of the disease, nutritional status and the diagnostic criteria for hepatotoxicity.

Most of the studies showed that asymptomatic transient rise in transaminase due to isoniazid (with or without concomitant use of rifampicin, pyrazinamide and ethionamide) are common which usually resolves without stopping the drug or adjusting the dose (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19). The dose of isoniazid used in most of the studies was more than 10mg/kg/day (19). The reported frequency of isoniazid hepatotoxicity in children varies from 0% to 13.6% (9) but fulminant liver failure is rare (9, 20). Wu et al 2007 et al (21) estimated the incidence of liver failure as 3.2/100,000. Rapp et al 1978 (22) did not find any child with abnormal transaminase. The hepatitis associated with isoniazid therapy is much less common in children as compared to in adults (20, 23). In the largest prospective series 13,838 patients receiving isoniazid for latent TB, found clinically significant hepatitis in 0.1% of children versus 1.3% of adults (20). Children treated with isoniazid-rifampicin showed an increase in aminotransferase levels in 3.3%-83% cases (10, 11, 12, 14). 7.84% - 44% children with tuberculous meningitis showed a rise in transaminase (13, 24) while 11.7%- developed severe hepatitis which resolved with or without stopping rifampicin (13). et al (12) demonstrated that 41.67% patients with severe tuberculosis developed clinical hepatitis but the level normalized with or without pause in the treatment in all cases except one (14). In a meta-analysis done by Steele et al, the presence of rifampin in a multidrug treatment regimen increased the incidence of significant hepatotoxicity from 1.0 to 6.9% in children and from 1.6 to 2.55% in adults (25). Among children being treated with triple therapy, using pyrazinamide, rifampicin, and isoniazid in standard recommended doses, 4.63% developed abnormal LFTs (15, 17, 18, 26) while only 4.65% children developed symptoms (one jaundice, one pruritus) needing treatment being stopped temporarily.

There is controversy over the increased risk of severe hepatotoxicity due to anti-TB drugs in tuberculous meningitis or other severe form of tuberculosis (27, 28, 29). This increased risk of hepatotoxicity may be due to high doses used for the treatment (16) but the abnormal serum ALT tends to normalize even in such cases (16). Gusmão Filho et al (30) showed in their study that hepatotoxicity due to anti-TB drugs occurred in 61.5% cases of TBM, but in only 9.4% cases drug substitution was necessary.

No data is available about hepatotoxicity of fluoroquinolones, ethionamide, para-aminosalicylic acid or cycloserine in children. The studies done in adults showed reversible transaminase elevation due to fluoroquinolones in up to 2 to 3% of cases while severe hepatotoxicity was very rare (31). Regarding hepatotoxicity among contacts of MDR-TB cases treated with a fluoroquinolone and pyrazinamide, the latter was presumed to be the cause of hepatotoxicity (31). The hepatotoxicity was recognized in about 2% of patients treated with ethionomide or prothionamide and in 0.3% of patients treated with para-aminosalicylic acid while cycloserine does not appear to be associated with hepatotoxicity (31)

RISK FACTORS:

The following factors are associated with increased risk of hepatotoxicity in children:

- 1 Moderate to severe malnutrition (10, 32), but not mild one (33).
- 2 Serious form of the disease (11)
- 3 Extra pulmonary tuberculosis (27).
- 4 Higher dosage of isoniazid (10, 11, 13, 28) or of rifampicin (11) or rifampicin given daily than twice-weekly (28, 34) and continuation of therapy once the hepatic damage was started (32).

The role of age is controversial. Ohkawa K et al (27) found that children younger than 5 years of age were at more risk while (12) did not find any association with age. The role of pyrazinamide as a risk factor is controversial but is said to be the most hepatotoxic drug (26, 27, 31).

The role of acetylator status with isoniazid induced hepatotoxicity is controversial (31). No correlation was found between clinical or biochemical indicator of liver dysfunction and hydrazine production, a metabolite of isoniazid (35, 36).

MECHANISM OF LIVER DAMAGE:

The pathogenesis of drug induced liver injury (DILI) is not well understood but hypersensitivity seems less likely. Altered profile of antioxidant enzymes with increased lipid peroxidation indicate that the isoniazid and rifampicin induced hepatotoxicity appears to be mediated through oxidative stress (37). The role of association of HLA in the development of DILI is controversial (38, 39). DILI occurs with greater frequency, earlier and with more severity when isoniazid and rifampicin are co-administered as compared to that when either of these is given alone. The exact mechanism is unknown but the increased risk has been attributed to the interaction between the metabolism of isoniazid and rifampicin. Acetyl-isoniazid, the principal metabolite of isoniazid, is converted to monoacetyl hydrazine. The microsomal p450 enzymes convert monoacetyl hydrazine to other compounds resulting in hepatotoxicity. Rifampicin is thought to enhance this effect by enzyme induction (40). Rifampicin also inhibits the secretion of bilirubin-glucuronides into the bile. It causes a build-up of conjugated bilirubin in hepatocytes and, consequently, a spillover into the plasma. It also impairs uptake mechanism resulting in elevation of unconjugated bilirubin (41). The DILI rate with the rifampicin and pyrazinamide regimen is higher among HIV-uninfected than HIV-infected persons treated for LTBI (42) probably due to the impaired host immunity which renders the HIV-infected persons incapable of manifesting the same degree of inflammation in the liver that occurs in immunocompetent persons (43). Further, the DILI rate observed with this 2-drug regimen was higher than that observed when three hepatotoxic drugs such as rifampicin, isoniazid and pyrazinamide were used to treat "active TB" during the initial 8 weeks of intensive phase. These issues and their molecular basis require further clarification. The mechanism of fluoroquinolone hepatotoxicity is believed to be a hypersensitivity reaction, often manifested by eosinophilia (31).

CLINICAL COURSE:

Half of the hepatotoxic reactions occurred during the first month of therapy, and all of the well-documented reactions were noted during the first 15 weeks. (11, 12, 15, 16) but Linna et al (14) mentioned that it can occur at any time during treatment.

In patients receiving a combination of isoniazid, rifampicin and pyrazinamide, two patterns of fulminant liver injury can be observed. The first one is characterized by an increase in serum transaminase activity that occurs soon (usually within the first 15 days) after initiation of treatment. This pattern is likely to be caused by rifampicin or isoniazid induced hepatotoxicity. The prognosis is good in most cases. The second pattern is characterized by an increase in serum transaminase activity that occurs late (usually after than 1 month) after the initiation of treatment. It has been suggested that this pattern may be related to pyrazinamide hepatotoxicity. The prognosis of this type of hepatitis is generally poor (44).

HEPATITIS B, C and HIV:

HIV-infected individuals appear to experience isoniazid-related hepatotoxicity in the same range as HIV-uninfected individuals, although no direct comparisons through clinical trials have been done. The overall influence of HIV infection alone on DILI during treatment of TB disease is difficult to assess, but appears to be slight (31).

Although additional data are needed, studies suggest that active, but not quiescent, hepatitis B may be a risk factor for increased incidence of isoniazid hepatotoxicity while the limited data leave sufficient concern that hepatitis B may be a risk factor for more frequent or severe hepatotoxicity during treatment of TB disease (31).

The studies showed no independent isoniazid hepatotoxicity risk associated with hepatitis C infection while Hepatitis C was an independent risk factor for the development of hepatotoxicity in treating TB disease, elevating the risk fivefold. Coinfection with both hepatitis C and HIV elevated the risk of hepatotoxicity more than 14-fold in the treatment of the TB disease (31).

INVESTIGATIONS:

A benefit of ALT and/or bilirubin monitoring in preventing or alleviating DILI has not been rigorously tested both in children and adults but the benefit seems very little due to questionable cost efficacy of frequent testing for rare adverse events, development and progression of injury between testing events, unclear enzyme thresholds for medication discontinuation (31). The normal values for transaminase in children are lower as compared to adults (31). Routine liver function testing is not recommended for prepubescent children (45, 46). Until we have further data, the LFT are only indicated if there is clinical suspicion of hepatitis, chronic liver disease or those taking medications in addition to anti-TB drugs that may cause liver toxicity, such as many of the antiepileptic drugs (47). ALT is preferred for detecting and tracking hepatocellular injury while measurements of bilirubin, and alkaline phosphatase are adjunctive for monitoring chronic liver disease, cholestasis, or severe hepatocellular injury (31). Hepatitis B surface antigen-seropositive individuals with elevated ALT should have HBeAg testing. If positive, rifampicin may be preferred over isoniazid. In HBeAg-seropositive individuals, clinical and ALT monitoring should be done every 2 to 4 weeks (48).

MANAGEMENT OF TUBERCULOSIS IN CHILDREN WITH PRE-EXISTING LIVER DISORDERS:

The crucial efficacy of isoniazid, and particularly rifampicin, warrants their use and retention, if at all possible, even in the face of preexisting liver disease (49). In adults with chronic liver diseases the inclusion of pyrazinamide in the regimen does substantially increase the incidence of DILI (50). However in serious situations where it is considered necessary to continue anti-TB drugs, special precautions need to be taken. The drugs which can be safely used in liver diseases include aminoglycosides, ethambutol, quinolones and cycloserine. The treatment may be started with an aminoglycoside, a quinolone and Ethambutol (46). If further addition of drugs is considered necessary rifampicin may be added. Isoniazid may be substituted for rifampicin if later cannot be given. Close monitoring of these patients for symptoms and repeat liver function tests at intervals is of paramount importance for the management of these patients. (34) Several regimens are recommended if baseline serum ALT is more than three times the ULN, and TB is not believed to be the cause (49). Saigal S et al (51)

Compared regimen A (isoniazid, rifampicin and ethambutol for 2 months, followed by isoniazid and rifampicin for a further 7 months) and regimen B (isoniazid, pyrazinamide, ethambutol and ofloxacin for 2 months, followed by isoniazid, ethambutol and ofloxacin for a further 10 months) in adults with chronic liver disease. It was found that an ofloxacin-based antitubercular regimen without rifampicin is as effective as a rifampicin-based regimen and a combination of isoniazid with rifampicin is more hepatotoxic than a combination with ofloxacin and pyrazinamide. Fluoroquinolones e.g. Trovafloxacin (52) and gatifloxacin (53) are also effective in meningitis. It seems that fluoroquinolones will have a promising role in near future where first line anti-TB drugs are contraindicated.

1. Treatment without pyrazinamide might utilize isoniazid and rifampin for 9 months with ethambutol until drug susceptibility testing of the *M. tuberculosis* isolate is completed (31).
2. In patients with cirrhosis, rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered.
3. For patients with encephalopathic liver disease, ethambutol combined with a fluoroquinolone, cycloserine, and capreomycin or aminoglycoside for 18 to 24 months may be an option (31). However, these regimens have not been tested systematically (49).
4. Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected medication in patients with thrombocytopenia and/or coagulopathy.

MANAGEMENT OF TUBERCULOSIS IF HEPATOXICITY DEVELOPS WHILE ON ANTI-TB DRUGS:

Consensus guidelines for the management of patients with anti-TB drugs hepatotoxicity are yet to be evolved in children. The published guidelines are mainly concerned with adults. Careful assessment of all other potential causes of liver injury needs to be done in every case, because the diagnosis of DILI is one of exclusion. The usual assessment includes serologies for viral liver disorders, ruling out metabolic liver disorders, abdominal ultrasonography while heterophile Epstein-Barr virus antibody and antibodies to cytomegalovirus and herpes simplex in immunosuppressed patients and identification of potential confounders such as hypotension, sepsis, heart failure, and use of total parenteral nutrition or hepatotoxic drugs. Concomitant diseases such as HIV and malnutrition should be given their due importance because their presence could affect the outcome negatively. In severe cases or in those in whom ALT did not recover with drug withdrawal, additional testing for autoimmune disease may also be considered: anti-nuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody, and immunoglobulin profile (31).

ALT may be an indication for more frequent monitoring, every 2 weeks instead of monthly, particularly if one of these treatment-limiting ALT thresholds is being approached, or if the patient has previously identified risk factors for hepatotoxicity. Hepatology consultation is recommended for unusual or severe cases of hepatitis particularly those who become sufficiently ill to require hospital admission or who may require liver transplantation (31).

WHEN TO STOP HEPATOTOXIC ANTI-TUBERCULOUS DRUGS?

The answer is that there is no diagnostic criteria based on abnormal liver functions when to stop antituberculosis therapy in children and adults. The criteria for stopping anti-TB drugs may be: ((31, 41, 46, 54, 55)

- a) Serum transaminases i.e. ALT/AST raised more than five times the upper normal limit even if the patient is asymptomatic.
- b) Raised serum transaminases i.e. ALT/AST above three times of the UNL accompanied by symptoms of hepatitis such as anorexia, nausea, vomiting or abdominal pain, dark coloured urine and jaundice.
- c) Total bilirubin to 4.2 mg/dl with or without rise in transaminase is also accepted as "hepatotoxicity"

The most cost effective criteria seem to be 'b' if any to be used. The bilirubin rise may also be due to other causes like hemolytic anemia, so it is the least cost effective. The first-line anti-TB drugs, especially rifampicin, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-TB treatment. Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy.

RECHALLENGE TEST:

If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity. If no alternative drugs are available then the hepatotoxic drugs may be reintroduced by a method called "rechallenge test".

The reintroduction of antituberculosis drugs has seldom been systematically studied even in adults, and a great deal of controversy exists regarding the sequence in which the drugs are to be reintroduced, i.e. whether the reintroduction should be done in full dosages or in gradually escalating dosages. It was found that the recurrence rate of hepatotoxicity in the retreatment of tuberculosis is higher in the reintroduction of a full-dose regimen including pyrazinamide of a regimen without pyrazinamide (56). Rechallenge may endanger the patient and is usually confined to essential drugs or used when multiple potentially hepatotoxic drugs have been administered concomitantly (31). So it should be considered relative to its potential benefit and is only considered when it is unclear which medication was the cause of symptoms or of transaminase increases. Rechallenge with the suspected offending agent with more than threefold serum ALT elevation and discontinuation leading to a fall in ALT is the strongest confirmation of the diagnosis (57). While the Joint Tuberculosis Committee of The British Thoracic Society recommendations () suggest that the first-line drugs can be reintroduced sequentially in the order isoniazid, rifampicin and pyrazinamide in an escalating dosage schedule, But the more recent guidelines published by the American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society of America () suggest that rifampicin is to be restarted first. The following protocol may be adopted for recallange (31).

- 1 Stop all hepatotoxic drugs (isoniazid, rifampicin and pyrazinamide) if serum ALT levels rise to more than three times with symptome or five times without symptoms above normal or if serum bilirubin is elevated.
- 2 Reintroduce them only if the patient's liver function has returned to normal and if no other satisfactory treatment is available (60).
- 3 Rechallenged patients should be told to stop medication in case of hepatitis symptoms appear.
- 4 After ALT returns to less than two times the ULN, rifampin may be restarted with or without ethambutol.
- 5 After 3 to 7 days, isoniazid may be reintroduced, subsequently rechecking ALT.
- 6 If symptoms recur or ALT increases, the last drug added should be stopped.
- 7 Measure serum transaminases every 2 weeks for the next 6 weeks. If hepatotoxicity is to recur, the rise in transaminases will probably occur earlier than it did after the first exposure (60).

For those who have experienced prolonged or severe hepatotoxicity but tolerate reintroduction with rifampin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued as reintroduction of a full-dose regimen including pyrazinamide, causes more hepatotoxicity than gradual reintroduction of a regimen without pyrazinamide (57) and the treatment must be extended to 9 months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity (62), the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.

THE CHEMOPROPHYLAXIS OF TUBERCULOSIS IN CHILDREN WITH LIVER DISORDERS OR DEVELOPS HEPATOTOXICITY WHILE ON ANTI-TB DRUGS:

The only chemoprophylaxis regimens to be used in children is isoniazid and, to a lesser extent rifampicin. If these drugs are contraindicated then the close contacts should receive careful clinical follow-up for a period of at least 2 years for the development of active TB disease but the second-line drugs or pyrazinamide are not recommended for chemoprophylaxis (46). Because isoniazid with rifampicin is more hepatotoxic than either alone this combination should be used with caution in patients at risk for hepatotoxicity (31).

For those with ALT elevation more than 3 times the ULN or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits. If LTBI treatment is undertaken, close monitoring is indicated (31). The decision to treat LTBI, or more likely to defer, should be carefully made on a case-by-case basis, weighing the risk of progression to TB disease against the risk of isoniazid or rifampicin-related DILI. Factors influencing the latter include degree of baseline ALT elevation, malnutrition, severity of tuberculosis, age, and evidence of active replication of hepatitis virus. If treatment is started, some experts recommend measuring serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months, and as necessary. Some experts recommend monitoring transaminases in individuals treated with a combination of pyrazinamide and a fluoroquinolones or ethambutol for contact with a patient with MDR TB (31) but pyrazinamide is no longer generally recommended for treatment of LTBI. The American Academy of Pediatrics states that the 2-month revamping and pyrazinamide regimen is not recommended for children due to hepatotoxicity. (61)

MONITORING:

Clinical monitoring:

There is general recommendation that only clinical monitoring is necessary (46, 63, 64). Face-to-face monthly assessments, patient education for adverse drug and directly observed treatment (DOT) enhance treatment adherence and monitoring (49).

LABORATORY MONITORING:

It is being discussed under the heading of "INVESTIGATIONS"

PREVENTION:

- 1 Clear and recurring communications with patients in the preferred language
- 2 Accurate medical evaluation, treatment, and monitoring
- 2 Health providers should be made aware of TB diagnosis and treatment and adverse reactions of anti-TB drugs.
- 3 Providers without TB treatment experience should be asked to refer to a specialized clinic.
- 4 Initial evaluation of the patient includes
 - a A standardized history form which includes risk factors for hepatotoxicity.
 - b The physical examination should include evaluation for signs of liver disease, such as liver tenderness, hepatosplenomegaly, jaundice, caput medusa, spider angiomas, ascites, and edema.
 - c Previous laboratory values should be reviewed when available.
4. Screening for viral hepatitis should be considered in high risks e.g. child exposure to repeated blood, are chronic hemodialysis patients and infants born to HBsAg positive mothers.
5. Voluntary HIV counseling and testing are recommended for all patients with TB disease in HIV prevalent areas.
- 6 Patient Education should be in the form of printed instructions which should include signs and symptoms of hepatotoxicity and liver diseases and contact information if such symptoms develop in preferred language at a readable level.
- 7 Follow-up visits of the patient for monitoring of the disease as well as side effects of drugs
- 8 Isoniazid should be given in a dose of 5mg/kg/day while rifampicin in a dose of 10mg/kg/day. A 5 mg/kg oral dose once a day in children as recommended by WHO and IUATLD (46,64). This dose produces curative tissue levels that are 60 – 100 times the minimum inhibitory concentration (65, 66) even in neonates (67). Hepatotoxicity of antituberculous drugs is greatly reduced when isoniazid and rifampin are used in lower dosages regardless of acetylator phenotype (33). Two doses of rifampicin 19mg/kg/day and 7.5mg/kg/day were used tuberculous meningitis (TBM) in age group of 6 months to 10 years and it was found that mean serum and CSF concentration were many times higher than the MIC against *Mycobacterium tuberculosis* (68).

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