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REVIEW

Anti-tuberculosis medication and the liver: dangers and recommendations in management

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ABSTRACT: In the light of three deaths due to liver failure secondary to anti-tuberculosis therapy at the Royal Free Hospital, we have reviewed the current literature, and asked - How common is liver dysfunction with anti-tuberculosis medications and how might it be prevented?

Anti-tuberculosis chemotherapy is associated with abnormalities in liver function tests in 10–25% of patients. Clinical hepatitis develops in about 3%, though estimates vary, and in these patients there is likely to be significant morbidity and mortality. On the basis of reported cases of tuberculosis, 160 patients in England and Wales can be expected to develop drug-induced hepatitis due to anti-tuberculosis therapy each year. There are published guidelines from the British and American Thoracic Societies regarding the choice of drug therapy for tuberculosis. Current recommendations with regard to monitoring liver function, and what to do when these tests become abnormal, vary considerably.

We suggest a protocol for using liver function tests to monitor for liver damage, and give recommendations on what action to take when these become abnormal.
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In England and Wales, in 1992, 5,798 patients with tuberculosis were notified to the Office of Population Census and Surveys [1]. There has been a 12% increase in incidence over the period 1988–1992. The current recommended treatment regimens for tuberculosis involve drugs which are potentially hepatotoxic. Recommendations with regard to monitoring for liver damage and the action to take when there is evidence of hepatic dysfunction vary considerably. In a recent survey [2] of 20 fatal cases of isoniazid-induced hepatitis, there was a management error in at least 35%, usually failure to stop the drug when the patient presented with symptoms (this survey was criticized in an accompanying editorial on the basis of rather haphazard case-ascertainment, a lack of rigorous diagnostic criteria, and no information regarding the frequency of significant hepatitis [3]).

The Hepato-Biliary Unit at the Royal Free Hospital has recently treated three patients with fulminant liver failure induced by anti-tuberculosis treatment, all of whom unfortunately died. In two cases, drug therapy was not stopped when the patient presented with symptoms and signs of liver failure. This prompted us to review the literature on the hepatotoxicity of anti-tuberculosis treatment and on current recommendations for monitoring liver damage. Finally, we suggest a protocol for the practical management of this important clinical problem.

How common is liver dysfunction with anti-tuberculosis chemotherapy?

The Joint Tuberculosis Committee of the British Thoracic Society recommends that initial therapy should consist of at least three drugs for 2 months; isoniazid, rifampicin and pyrazinamide are the drugs of choice, with ethambutol being added if resistance is suspected [4]. Streptomycin is now used rarely in the UK, unless the organism is resistant to isoniazid. After two months, a further 4 months of isoniazid and rifampicin are recommended, with more prolonged therapy for bone, joint and meningeal disease, or for resistant organisms.

Several anti-tuberculosis agents have been implicated as being hepatotoxic. Isoniazid (particularly in association with rifampicin) and pyrazinamide cause hepatic dysfunction more frequently than ethambutol and streptomycin, which cause hepatitis problems rarely, if at all.

Isoniazid (INH). Injury is mostly acute hepatocellular in type, though a mixed hepatocellular-cholestatic

picture has been reported [5]. There are various metabolic products of isoniazid, including monoacetyl hydrazine, hydrazine and isonicotinic acid, which have been suggested as being hepatotoxic. The onset of injury is usually after 6 weeks, and maybe up to 1 year after beginning [2, 6, 7]. Concomitant use of rifampicin leads to earlier and more frequent injury, some in less than 10 days [8]. The incidence of impaired liver function tests, with raised transaminases, varies from 10–25% [9–12].

Symptomatic liver disease occurs less commonly, being reported in 0.5–3% [6, 13–15]. A recent meta-analysis revealed a clinical hepatitis rate of 0.6% when isoniazid was used alone, and 1.6% when used in multidrug regimens not including rifampicin [16]. When rifampicin was also given, symptomatic liver disease was found in 2.7% [16], a figure lower than previous reports of 7–10% [13, 17]. It has been suggested that the elderly [18], pregnant women [2], malnourished patients [14] and black people (in the United States) [7] are more prone to liver damage due to isoniazid. In an analysis of seven studies, children seemed to be less susceptible to isoniazid hepatoxicity when it was used alone (clinical hepatitis in 0.2%) but to be more susceptible to a combination of isoniazid and rifampicin (clinical hepatitis in 6.9%) [16].

In those who develop clinical evidence of liver disturbance the morality is up to 13% [5]. The most common indications are "flu"-like symptoms and nonspecific gastrointestinal upset [2, 5]. Poor prognostic factors include onset more than 2 months after starting anti-tuberculosis therapy and a bilirubin level over 200 $\mu mol \cdot L^{-1}$ [5]. A dose-dependent effect has been observed, particularly in children; the hepatitis rate being less than half with an isoniazid dose of 12 $mg \cdot kg^{-1}$ as compared to 20 $mg \cdot kg^{-1}$ [17].

Those with pre-existing liver disease seem to be more likely to develop liver injury. Alcoholism is associated with an increased risk of symptomatic liver dysfunction [18]. Patients with hepatitis B viral infection may be more susceptible to drug-induced liver dysfunction (increased in transaminases occurring in 50% in one recent series [19]). Such patients may have a worse prognosis if symptomatic liver disease develops [15], though this was not found in another study [20].

Rifampicin. This may cause transient hyperbilirubinaemia, due to interference with bilirubin excretion, and a rise in gamma-glutamyl transferase. Serious liver injury due to rifampicin *per se* is rare (and is associated with zone 3 centrilobular necrosis [21]) but rifampicin does increase the hepatotoxicity of isoniazid [12, 15]. This effect is thought to be due to enzyme induction, leading to an increase in hepatotoxic metabolites of isoniazid. There is evidence that the dose regimen appears important; in one series of patients treated with rifampicin and isoniazid, the rate of drug-induced hepatitis was 21% when rifampicin was given daily and 5% when given twice weekly [17].

Pyrazinamide. Studies in the 1950s suggested that elevated transaminases occurred in 20%, and overt hepatitis in 8%, of those treated with pyrazinamide, which has some structural resemblance to isoniazid. Experience with lower dose regimens, in combination with other agents, suggests that there is only a small risk of hepatocellular injury [22], though cases of fatal hepatic necrosis have been described [23].

Para-aminosalicyclic acid (PAS). Hypersensitivity to PAS. Hypersensitivity to PAS has been recorded in up to 5% of recipients from the largest published series of 277 cases [24]. Jaundice occurred in 23% of these cases, with the onset usually between 2–6 weeks after commencing treatment. Rechallenge may result in recurrence of the abnormal response.

Streptomycin, ethambutol and cycloserine. Hepatic injury due to these agents occurs rarely, if at all [25]. These drugs, of course, do have other side-effects, *e.g.* ototoxicity and nephrotoxicity with streptomycin (which also requires daily intramuscular injections), optic neuritis with ethambutol, and psychosis with cycloserine.

Prothionamide and ethionamide. These similar agents may produce elevated serum transaminases in about 10% of recipients, usually after 8–12 weeks [25]. Some series have suggested that hepatic injury may be higher, though definition of injury varies between studies and other potentially hepatotoxic drugs were also involved.

Current recommendations regarding monitoring liver function with anti-tuberculosis medication

There are few specific guidelines available concerning the screening for and management of hepatic dysfunction due to anti-tuberculosis therapy. ABPI Data Sheet Compendium recommendations vary. Marrion Merrell Dow Ltd (manufacturers of isoniazid, rifampicin and pyrazinamide) suggest liver function tests prior to starting therapy with rifampicin and isoniazid, and then every 2–4 weeks for the duration of therapy for those with impaired liver function. The company also recommends that caution should be exercised with the elderly, malnourished, and children under 2 yrs of age. It is recommended therapy should be withdrawn if there are "signs" of hepatocellular damage, but that tests should be repeated if there is an isolated, "moderate" rise in bilirubin or transaminases (these terms are not quantified) [26]. Cambridge Laboratories (manufacturers of isoniazid) recommended that liver function tests should be performed monthly, and that treatment with isoniazid should be stopped if transaminase levels exceed three times the upper limit of normal [27]. Ciba Laboratories (manufacturers of isoniazid and rifampicin) identify the same high risk groups as Marrion Merrell Dow Ltd, but give less specific recommendations with regard to checking liver function tests, suggesting that these should be done "periodically". It is recommended that any detrioration in liver function in patients undergoing prolonged therapy is an indication to stop treatment [28]. Lederle

Laboratories give no specific recommendation when prescribing a combination of isoniazid and ethambutol [29]. Merck Sharpe and Dohme Ltd recommend that liver function tests should be performed every 2–4 weeks, and that pyrazinamide should be withdrawn and not reinstated if signs of hepatocellular damage occur [30].

Advice from the United States Pharmacopeial Convention is similar with regard to monitoring liver function tests. These should commence before starting therapy and then monthly "or more frequently" [31]. Patients should be advised of the importance of hepatitis prodromal symptoms, and drugs stopped if signs of hepatotoxicity occur; however, no advice is given on how to act following abnormal liver function tests.

British Thoracic Society (BTS) guidelines state that all patients should have liver function checked before treatment but that only those with liver disease and alcoholics require regular monitoring thereafter [4]. Patients with pre-existing liver disease should receive regular treatment. Transient increases in hepatic transaminases are noted to be common, but no action is required unless the patient has symptoms of hepatitis and jaundice, when all drugs must be stopped. Similar recommendations are made in "Modern Drug Treatments of Tuberculosis" [32] and in the Oxford Textbook of Medicine [33]. The American Thoracic Society (ATS) guidelines are similar to those of the BTS, with all patients recommended to have baseline liver function tests and only those with known liver disease or abnormalities of initial tests requiring regular liver function tests [34].

The most specific published guidelines on how to act following abnormalities of liver function tests come from R.J. O'Brien of the Center for Disease Control (CDC), Atlanta, USA. He suggested that a rise in transaminases greater than three times normal warrants discontinuation of isoniazid. When liver function has returned to normal, rechallenge can be performed; if hepatitis recurs, ethambutol should be substituted in place of isoniazid. If serious liver dysfunction occurs, then all drugs should be withdrawn and, if necessary, ethambutol and streptomycin should be given. Rechallenge should be with one drug at a time; as pyrazinamide hepatotoxicity is dose-dependent, this should be with a lower dose, *e.g.* 20 $\mu g \cdot kg^{-1}$ [35].

Revised recommendations regarding monitoring liver function with anti-tuberculosis medication

Anti-tuberculosis medication frequently causes disturbance to liver function tests and may cause serious liver function dysfunction [13, 16, 17]. With 5,800 cases of tuberculosis reported in England and Wales each year, 160 patients with clinically significant drug-induced hepatitis can be expected [1, 16]. We feel that there is a need for clearer guidelines for monitoring and managing abnormalities in liver function arising during anti-tuberculosis chemotherapy. These guidelines should address certain problems.

What information should be given to patients?

All patients should be made aware of the potential problem of hepatotoxicity. Those who drink more alcohol than the maximum that is currently recommended [36] should be advised to reduce their intake. Patients must be told that if they feel nonspecifically unwell, particularly with gastrointestinal upset or the presence of jaundice, they should seek urgent medical advice. Previous studies [2, 5] have shown that such symptoms are experienced by most of those with clinical drug-induced hepatitis.

How often should one perform liver function tests (LFTs)?

We recommend that liver function tests should be performed before starting anti-tuberculosis therapy (fig. 1). These should then be performed every 2 weeks for the first 8 weeks, and monthly thereafter. With the use of rifampicin and isoniazid, the onset of liver damage may be as soon as 10 days after commencing therapy [8], and for this reason we recommend fortnightly liver function tests initially. There is no point at which it is safe to stop performing routine liver function tests whilst prescribing anti-tuberculosis treatment, as the onset of liver injury mat be up to 1 year after starting therapy [2, 6, 7]. By the time a patient complains of hepatic symptoms or jaundice there is significant morbidity and risk of mortality (of up to 13%) [5]. We feel that more frequent testing is not a practical proposition.

Which groups are at high risk and should patients in these groups be monitored differently?

Particular risk groups seem to be those with known or suspected liver disease [15, 18, 19], the malnourished [14], and possibly the elderly [18] and children [16]. However, patients who are in these high risk groups are also those at particular risk of acquiring tuberculosis. Suspicion of liver disease includes those with a high alcohol intake, a family history of liver disease and those with risk factors for hepatitis B and C infection (in these cases viral serology should be performed). There is evidence that hepatitis B co-infection predisposes to drug-induced hepatotoxicity [19], and when symptomatic hepatitis develops the clinical outcome appears to be worse [15]. There is no documented evidence that hepatitis C infection predisposes to drug-induced hepatitis. However, it would seem sensible to take similar precautions with hepatitis B and C virus infections, both of which are known to produce chronic liver disease.

Patients in these high risk groups will require standard anti-tuberculosis therapy; divergence from this will risk either undertreatment or unacceptable side-effects from second-line agents. The standard regimen for monitoring patients in high risk groups can be followed, but, the clinician and the patient should be particularly aware of the risk of drug-induced hepatitis with low threshold of suspicion for this problem.

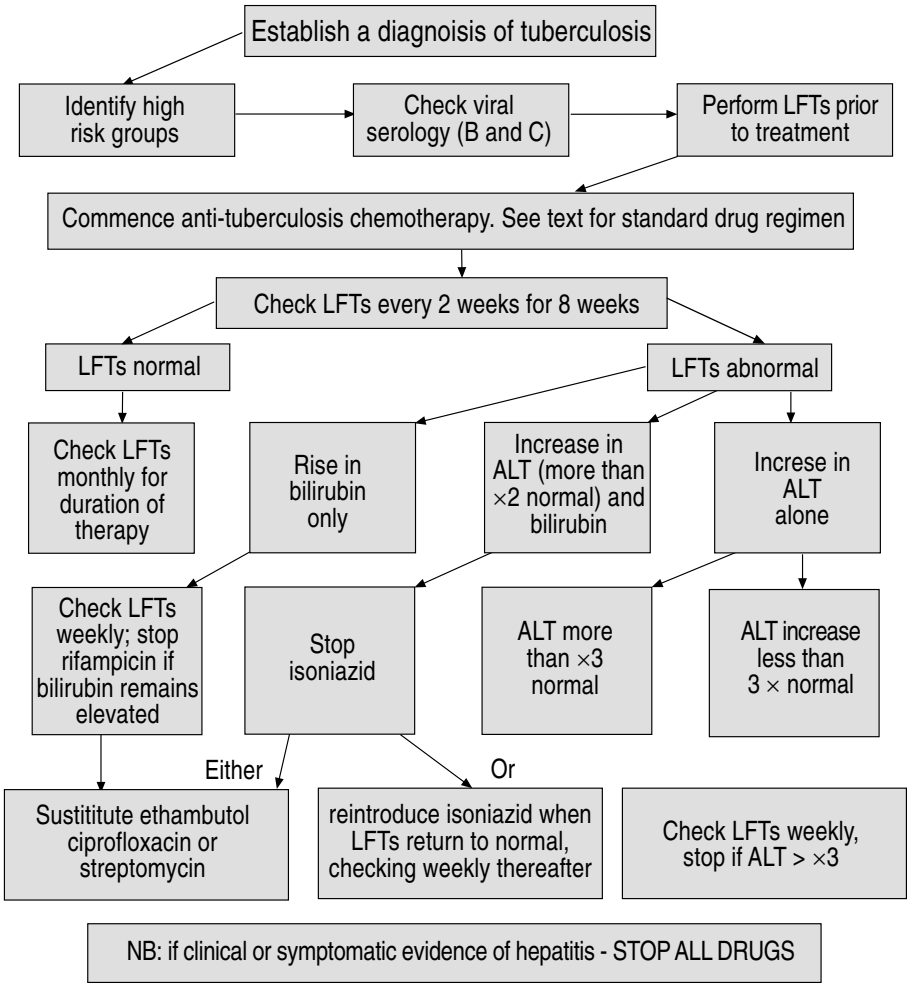

Fig. 1. – Protocol for anti-tuberculosis drugs and possible hepatotoxicity. LFTs: liver function tests; ALT: L-alanine aminotransferase.

At what level of hepatic dysfunction should treatment be changed and which drugs need to be withdrawn; all or specific drugs?

If there is clinical hepatitis or biochemical evidence of significant liver dysfunction due to anti-tuberculosis therapy, particularly impairment of synthetic function (most commonly a fall in serum albumin in prothrombin time) all medication should be stopped immediately.

If there is an isolated increase in bilirubin, without a concomitant rise in transaminase values, then therapy may be continued with repeat liver function tests being performed on a weekly basis. The hyperbilirubinaemia is usually transient and due to interference with bilirubin excretion by rifampicin; it rarely requires cessation of the drug. If, however, the bilirubin has not decreased after 2 weeks, it would be sensible to withdraw rifampicin. We recommend that if there is an associated rise in transaminase levels, greater than twice normal values, then hepatotoxicity should be suspected and isoniazid should be withdrawn on the basis that it is the most likely cause.

If there is an isolated rise in transaminase values, to a level less than three times normal, then liver function tests should be monitored weekly. If transaminase values rise to more than three times normal, isoniazid should be withdrawn. The cut-off of three times the normal limit is arbitrary but would seem to be sensible for clinical practice. This would not exclude the large number of patients who have only a relatively small rise in transaminases from taking isoniazid, but would allow early identification of those who are experiencing a significant drug-related hepatitis and withdrawal of the most likely offending agent, isoniazid.

On withdrawal of isoniazid, liver function tests should be performed weekly, if there is no decrease then all drugs should be withdrawn. If isoniazid is withdrawn then it can either be reintroduced when liver function tests have been returned to normal or another drug substituted for it. Substitution of isoniazid should be with ethambutol; streptomycin or a 4-quinolone (which has proven efficacy and safety [37–39]) are other possibilities.

Which should be reintroduced and when?

Reintroduction of isoniazid can be performed when liver function tests have returned to normal but not if there has been symptomatic evidence of liver impairment. Liver function tests should be performed on a weekly

basis for 4 weeks, and then according to the original protocol for monitoring. If all drugs have been withdrawn then "second line agents", such as ethambutol, streptomycin and ciprofloxacin, could be used with either rifampicin or low-dose pyrazinamide.

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