

## CLINICAL PRACTICE

# Treatment of tuberculosis in patients with pre-existing liver disease or following hepatotoxic drug reactions

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**T**reatment schedules for the majority of patients with pulmonary tuberculosis are now standard and highly effective.<sup>1</sup> There are, however, important considerations which we feel require clarification with regard to the initiation of treatment in patients with evidence of acute or chronic liver disease. The management of tuberculosis following drug-induced severe hepatitis remains a vexed problem because of increasing mycobacterial drug resistance and the poor response of many patients to suboptimal second-line therapy. We feel that the guidelines from our institution published in 1986<sup>2</sup> should be revised in the light of these difficulties.

Abnormalities of drug metabolism that occur in liver disease result from portal systemic shunting and hepatocyte dysfunction. These result in significant abnormalities in the pharmacokinetics and pharmacodynamics of several commonly used antituberculosis drugs.<sup>3</sup>

The overall incidence of drug-induced hepatitis after rifampicin, isoniazid or pyrazinamide therapy in all patients is considered acceptably low (less than 0.1%).<sup>4</sup> Patients with liver disease are subject, however, to a greater incidence of idiosyncratic and direct hepatotoxicity.<sup>5</sup> This is considered significant by the British National Formulary, which advises that isoniazid and pyrazinamide be avoided in patients with liver disease wherever possible.<sup>6</sup> Rifampicin, the most potent of the bactericidal antituberculosis agents, is a vital component of all short-course chemotherapy regimens. Precise dosage is important because there is a narrow margin between the minimum effective dose and toxic levels.<sup>7</sup> Hepatitis is associated with higher blood levels and longer periods of exposure.<sup>8</sup> In liver disease, rifampicin induction of P450 enzyme systems may be less efficient and dose reduction should be considered.<sup>9</sup> Rifampicin is excreted in high concentrations in bile. In cholestasis with jaundice, therefore, further dose reductions may be required.<sup>9,10</sup>

Patients with decompensated liver disease and active pulmonary tuberculosis should receive antituberculosis therapy in hospital under close supervision. These patients should not receive pyrazinamide at the onset of therapy, but may be started on rifampicin at 5 mg/kg/day (standard dose 9 mg/kg/day), isoniazid 5 mg/kg/day (up to 300 mg if well tolerated), and ethambutol 25 mg/kg/day. Streptomycin may be used if the patient has well-preserved renal function, adequate muscle bulk and no haemostatic problems. Quinolones should not be considered as first-line drugs.<sup>11</sup>

Malnourished patients with extensive pulmonary tuberculosis with a background of alcohol abuse often have unrecognised liver dysfunction. Ideally, these patients should be stabilised in hospital and receive adequate nutritional support before the introduction of pyrazinamide.<sup>12</sup> Patients with a history of excessive alcohol consumption, chronic consumption of enzyme-inducing drugs such as anticonvulsants, chronic viral

hepatitis or clinical pointers to possible liver disease should be considered an 'at risk' group. Pre-therapy liver enzymes, albumin and prothrombin INR levels should be determined.<sup>5,13</sup> Regular clinical evaluation is imperative and repeat liver enzyme level assessments should be performed at 2, 4 and 6 months.

Antituberculosis drug-induced liver injury usually occurs on an idiosyncratic basis.<sup>14</sup> It is usually impossible confidently to predict the guilty agent where multiple drug regimens have been employed. There are few controlled data to direct rational and safe drug substitution and rechallenge.<sup>3-5,14</sup> Minor elevations in transaminase levels due to isoniazid and unassociated with clinical disease occur in up to 20% of patients treated and may be associated with patchy necrosis of liver cells.<sup>15</sup> Severe reactions to isoniazid usually occur with concurrent administration of antituberculosis drugs which induce microsomal P450 enzyme systems, such as rifampicin or pyrazinamide.<sup>7,12,16</sup> However, in a survey of 13 838 patients treated only with 300 mg isoniazid daily, 114 cases of jaundice and 13 deaths occurred.<sup>17</sup> Liver disease was noticeable between 2 and 11 months after commencing therapy. Late onset of jaundice with serum bilirubin levels greater than 340 µmol/l were associated with a poor prognosis. High mortality rates were noted in blacks, women and patients over 30 years of age.<sup>17</sup> There are no consistent data that increased risks of isoniazid drug reactions occur in patients with rapid acetylator status.<sup>14,18</sup> Whether or not isoniazid causes drug-induced chronic active hepatitis remains controversial.<sup>19</sup>

Rifampicin is the cause of drug-induced hepatitis in 1 - 4% of patients treated solely with this drug. Patients who develop symptoms within 3 weeks of starting therapy are particularly likely to show evidence of severe disease.<sup>16,20</sup> Although continuation or reintroduction of rifampicin therapy may be compatible with a full recovery from hepatitis and liver injury,<sup>20</sup> this course of action may also be fatal.

Pyrazinamide appears to be more frequently implicated in hepatotoxic reactions than the other antituberculosis drugs and should be used with caution.<sup>21</sup> The underlying mechanisms are uncertain but hepatitis is often severe enough to cause death if the drug is not discontinued.<sup>21,22</sup> The onset of hepatitis may either be rapid or more commonly, delayed for up to 5 - 6 months from the start of therapy. Ethionamide has also been linked with late-onset hepatitis, which may even be fatal.<sup>23</sup> Ethambutol and streptomycin are infrequently, if ever, hepatotoxic.<sup>3</sup>

At Brooklyn Chest Hospital in Cape Town, there are on average 4 cases of significant drug-induced hepatitis per 1 000 cases treated for tuberculosis.<sup>21</sup> About half of severe liver reactions secondary to drug therapy at Groote Schuur Hospital are thought to be caused by antituberculosis therapy.<sup>24</sup> Approximately 40% of patients with hepatitis, jaundice and encephalopathy secondary to antituberculosis therapy die.<sup>21,24</sup>

When a patient develops jaundice while taking antituberculosis drugs, these should be discontinued. A decision then has to be made whether to continue treatment with non-hepatotoxic drugs or whether to wait until clinical and biochemical recovery has taken place and rechallenge.<sup>3,8</sup> In all instances careful risk-benefit analyses are mandatory.

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It is important to recognise that patients who develop jaundice on antituberculosis therapy do not always have drug-induced liver disease. Other causes of jaundice such as extrahepatic biliary obstruction, viral hepatitis, alcohol abuse, and heart failure must be considered. A liver biopsy may be necessary to confirm or exclude these other diagnoses. It is self-evident that the diagnosis of tuberculosis should be re-examined in those patients where there is no initial bacteriological proof of the diagnosis.

For practical purposes the issues of antituberculosis drug substitution and challenge following drug-induced liver injury can be classified into three major groups.

Firstly, there are patients who develop minimal jaundice or develop abnormal transaminase levels (in excess of fivefold normal range). Although these patients may not be acutely ill from tuberculosis, reconsideration should be given to admission and monitoring in hospital at the time liver injury is recognised. Antituberculosis therapy should be discontinued until the clinical condition improves, bilirubin levels return to the normal range, and the serum transaminase values are on a downward trend.

We recommend that selected patients who require effective antituberculosis therapy then be rechallenged with isoniazid in standard dosage (day 1). Liver function tests should be checked 48 - 72 hours after drug exposure. If this initial test dose is well tolerated the drug may be continued for a further 5 days with repeat liver function tests on day 8. If there are no further untoward effects, after a further break of 3 days, rifampicin may be introduced at standard dosage (day 12). No drugs are administered for the next 2 days after which liver function tests are re-checked (day 15). Rifampicin is then administered daily for a further 5 days and liver function tests again checked at the end of this treatment (day 21). After this isoniazid is reintroduced with rifampicin and again liver function tests should be monitored. These patients also receive ethambutol in standard dosages, which may be conveniently initiated at the introduction of isoniazid therapy. We do not recommend the reintroduction of pyrazinamide except under highly unusual circumstances. Patients with pulmonary tuberculosis should receive triple drug therapy for a total of 9 months unless they have already received at least 2 months' therapy with pyrazinamide, rifampicin and isoniazid.

Secondly, there are patients who are severely ill with extensive pulmonary tuberculosis, miliary tuberculosis or tuberculous meningitis. In the event of suspected drug-induced hepatitis the offending drug regimen should be discontinued. These patients should however then receive 'interim therapy' while awaiting resolution of liver injury. An aminoglycoside (either streptomycin, or intravenous amikacin if the patient has a severe coagulopathy or has minimal muscle bulk), ethambutol and a quinolone (ofloxacin 400 mg twice daily) are our currently recommended drugs under these circumstances. Renal function should be monitored and dose adjustments made to all 3 drugs according to the serum creatinine levels. After normalisation of jaundice and liver injury, patients should be rechallenged as before with isoniazid and rifampicin and treated with 3- or 4-drug therapy for at least 9 months.

Finally, there are patients who develop severe acute or fulminant liver failure following antituberculosis therapy. If warranted these patients should receive interim antituberculosis therapy as described above. All patients should receive adequate supportive therapy for acute liver failure to facilitate hepatic regeneration and recovery which will occur in approximately 60% of cases. After normalisation of liver tests in those patients who survive, a careful risk-benefit analysis should be

undertaken. If deemed necessary patients may be cautiously rechallenged with isoniazid and rifampicin according to the schedule as described above. If this approach is not considered justified then ethambutol, streptomycin, ethionamide and ofloxacin should be administered. Treatment should continue for 18 months. If the pulmonary tuberculosis does not appear to respond to this regimen, then we would recommend either that these patients be challenged with isoniazid and rifampicin as described above, or receive an aminoglycoside or additional second-line drugs, viz. terizidone, kanamycin, amoxycillin with clavulanic acid.

If patients develop jaundice or are noted to have significant increases in transaminase values after administration of isoniazid or rifampicin, the offending drug must be discontinued immediately. Such information from a drug challenge may therefore help identify the agent responsible. These patients may then be started on 'interim therapy' as described above and receive additional second-line drugs. This therapy has a lower rate of success and needs to be administered for up to 18 months. The possibility of drug-resistant tuberculosis should be excluded in non-responsive cases by appropriate sputum culture techniques. Surgical options may need to be explored at a later point.

There are no readily available laboratory tests which may usefully predict the agent responsible for drug-induced hepatitis in the setting of multiple drug administration.<sup>3,5,14</sup>

Rechallenge after drug-induced hepatitis is dangerous. Wherever possible this should only be done in hospital after consultation with and under close supervision of clinicians experienced in the management of acute liver failure.<sup>24,25</sup> Even then fatalities may occur. After the reintroduction of antituberculosis therapy, all patients must be carefully monitored during the remainder of their course of therapy.

Severe drug-induced hepatitis during the treatment of tuberculosis is an unusual complication. However, because of the large numbers of patients treated for tuberculosis,<sup>26,27</sup> this remains an important medical problem. The prognosis of established severe drug-induced hepatitis is dismal, particularly if patients continue on the implicated drugs.<sup>4,21</sup> The predisposition of patients with alcohol abuse and established liver disease to tuberculosis<sup>28</sup> is further complicated by an increased likelihood of drug-induced hepatitis.<sup>3,5</sup> Antituberculosis chemotherapy according to standard schedules may lead to high rates of iatrogenic liver damage in patients who have diminished hepatic reserves.<sup>9,15</sup>

The above guidelines are intended to be practical and applicable to general clinical practice. In all cases, however, flexibility and individualised clinical judgement are most important.

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