Hepatic involvement is common in disseminated forms of tuberculosis but it rarely causes marked impairment of hepatic functions. A person having pre-existent chronic liver disease may also develop tuberculosis. Moreover, a patient undergoing treatment for tuberculosis may develop hepatotoxicity as an adverse reaction to drugs or may develop fresh liver disease like acute viral hepatitis. The presence of co-existent hepatic disease poses a challenge in the treatment of tuberculosis. Hepatic dysfunction can alter absorption and distribution of drugs that are metabolized or excreted in the liver. Therefore, in the presence of severe liver disease, it is advisable to include fewer hepatotoxic drugs and to extend the period of treatment. Since many of the potent anti-tubercular drugs are hepatotoxic, drug regimens may need modification or stoppage of anti-tubercular drugs for varying periods may be required. Rifampicin, Pyrazinamide, Isoniazid, Ethionamide, and PAS are all hepatotoxic drugs.

Transient elevation of hepatitis enzymes are however routinely observed in the patients being treated with Rifampicin. However, these return to normal on continuation of therapy. The various factors which predispose to hepatotoxicity during treatment with anti-TB drugs include old age, history of liver disease and excessive use of alcohol. Slow acetylators of Isoniazid are at a higher risk of hepatotoxicity. Frequency of liver damage increases with age and in general is less than 2%. Stead et al observed INH hepatitis in 4.5% of approximately 2000 elderly patients. Risk of hepatitis due to Rifampicin appears small. Yee et al reported a rate of 0.05 per 100 person-months for hepatitis caused by Rifampicin, whereas reported rates for Pyrazinamid and INH were ten and three times respectively. Moreover, metabolism of hepatically metabolized drugs such as Isoniazid and Rifampicin is diminished among persons with severe liver disease. The hepatotoxic effect of Rifampicin and Isoniazide are additive whereas the hepatic damage due to Pyrazinamide is related to dose and duration. Higher doses of Pyrazinamide may predispose to hepatotoxicity affecting as many as 15% of patients receiving 40-50mg/kg daily. Current recommended dose of 15-30mg/kg has, however, significantly less risk of hepatotoxicity. Since frequency of hepatotoxicity in patients who received Pyrazinamide in doses of 25-35mg/kg along with Rifampicin and Isoniazid was found to be same among those who received only Rifampicin and Isoniazid.

The adverse drug reactions are, however, lesser with intermittent drug regimens as in DOTS under RNTCP. In a study conducted at New Delhi Tuberculosis Centre the incidence of hepatotoxicity during DOTS therapy was observed to be only 1 out of 1195 patients, while in Hong Kong study 2% of the patients were reported to have hepatitis.

Most patients with pre-existent liver disease will tolerate standard tuberculosis treatment regimens with careful monitoring for hepatotoxicity. However, during treatment of tuberculosis the patient may present with jaundice which may be either due to drug toxicity or development of fresh disease e.g. acute viral hepatitis or worsening pre-existent liver disease. The hepatic function tests should be done and all the anti-tubercular treatment should be stopped. In presence of symptoms, raised transaminase levels more than three times upper normal limit signify drug induced hepatitis. The criteria for stopping ATT as recommended by American Thoracic Society and CDC-US include:

a) Serum transaminases i.e. SGOT/SGPT raised

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more than five times the upper normal limit even if the patient is asymptomatic. b) Raised serum transaminases i.e. SGOT/SGPT accompanied by symptoms of hepatitis. c) Raised serum bilirubin level. Although Pyrazinamide is considered to be most hepatotoxic and Rifampicin the least\(^1\), it would be prudent to avoid all the potential hepatotoxic first line drugs i.e. Rifampicin, Isoniazid and Pyrazinamide in this situation.

The treatment can be restarted after serum bilirubin and transaminase enzymes return to normal. The drugs should be restarted in a sequential fashion, if the symptoms have improved and transaminase levels fall to less than two times the upper normal limit\(^1\).\(^2\).\(^3\).

If, however, in serious situations, it is considered necessary to continue anti-tubercular drugs, special precautions need to be taken. The drugs which can be safely used during liver disease include aminoglycosides, Ethambutol, quinolones and cycloserine\(^4\). The treatment may be started with an aminoglycoside, a quinolone and Ethambutol. If further addition of drugs is considered necessary Rifampicin may be added. Isoniazid may be substituted for Rifampicin, if Rifampicin cannot be given\(^5\). Pyrazinamide is better avoided in chronic liver disease. Close monitoring of these patients for symptoms and repeat liver function tests at intervals is of paramount importance for the management of these patients.

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REFERENCES