Anti-tubercular Drugs Induced Hepatotoxicity

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INTRODUCTION

The linchpin of tuberculosis eradication is the anti-tuberculous drugs (ATD) predominantly isoniazid, rifampicin, pyrazinamide and ethambutol. The major adverse effects of ATD is hepatotoxicity, and the minor ones being dermatological, gastrointestinal and neurological manifestations. Antituberculosis drug-induced hepatotoxicity (ATDH) can range from asymptomatic rise in transaminases (AST: and ALT:) to fatal outcomes. The incidence of ATDH in India is 15 % and most of them are transient and asymptomatic rise in AST and ALT, which resolve spontaneously, called hepatic adaptation. (1) Significant adverse reactions may lead to non-compliance resulting in treatment failure, relapse or the emergence of drug-resistance, or switching to second line drugs leading to sub optimal treatment. ATD which are metabolised in liver are chiefly hepatotoxic as isoniazid, rifampicin and pyrazinamide. Ethambutol and streptomycin are not known to produce hepatotoxicity. (2) Among the second line agents, hepatotoxicity is recognised (2%) with ethionomide, prothionamide, moxifloxacin and para-aminosalicylic acid. (1)

DEFINITION

ATDH which warrants cessation of drugs is defined as:

1. Elevation of liver enzymes (AST/ ALT) to more than three times the upper limit of normal (ULN) along with symptoms as nausea, vomiting, abdominal pain and jaundice, or elevation more than five times the ULN with or without symptoms.
2. Rise in total bilirubin more than 2 mg/dL with or without rise in liver enzymes or symptoms.

RISK FACTORS

ATDH is seen more frequently in children with hypoalbuminemia probably due to depletion of glutathione stores thus making them vulnerable to oxidative injuries, and those with co-medication with hepatotoxic drugs as phenytoin, phenobarbital, paracetamol, omeprazole and ranitidine. For some unknown reasons children with tubercular meningitis are at higher risk of ATDH. Also, in some studies younger age, female gender, low BMI, underlying chronic liver disorder and HIV seropositivity have been reported as risk factors. So, these groups of children on ATD should be monitored closely. (4, 5) The risk of developing ATDH with isoniazid prophylaxis at a dose of 10mg/kg is very low but when administered in combination with other drugs as rifampicin, the combined effect may be more marked. (6)

CLINICAL FEATURES

ATDH can occur at any age or with any dose of ATD. It occurs mainly in the initial two months of treatment but can occur anytime during the course. Most frequent symptoms are jaundice, nausea, vomiting, anorexia and abdominal pain. Almost one third may remain asymptomatic with only biochemical derangements including those with severe hepatotoxicity. Few cases may progress to acute liver failure requiring transplant. (3) However, routine monitoring during treatment is not mandatory according to WHO guidelines unless there is jaundice, hepatomegaly or hepatic tenderness. (7) Poor prognosis is associated with rising INR, encephalopathy, severe hypoalbuminemia or ascites. A characteristic feature of ATD induced hepatitis is hepatic adaptation or tolerance where the elevation in ALT resolves on its own without discontinuing the therapy. This condition should be kept in mind to avoid unnecessary stoppage of treatment.

MANAGEMENT

Investigations

Baseline blood tests are not recommended for healthy and not-at-risk individuals. Only for children with underlying chronic liver disease or cirrhosis, HIV seropositivity, children on any other hepatotoxic drugs and with any major risk factors, baseline liver function test should be obtained. ALT is enough for detecting hepatotoxicity, however serum bilirubin, AST, alkaline phosphatase and serum proteins can be utilised for identifying or for monitoring any underlying liver disease. Children with ALT more than three times ULN should be retested for complete liver function test,

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international normalised ratio (INR), viral markers or any other possible cause of hepatitis, and risk factors should be identified.

Treatment

As soon as ATDH is confirmed as per the definition, all the drugs should be should be withheld. Thereafter, ALT should be monitored every 2 weeks if there is rapid rise in ALT or there is some underlying risk factor, else monthly monitoring would suffice. After normalisation of ALT to less than two times ULN rechallenge can be considered and biochemical monitoring at 2-4 weeks should be done. For rechallenge rifampicin should be introduced first with or without ethambutol and monitor. If it is well tolerated then isoniazid should be added after 3-7 days. If it is not tolerated then last added drug should be withdrawn. If after introduction of isoniazid no rise in ALT is observed then treatment should be continued. If frequent, prolong or severe ATDH is experienced then second line drug as fluroquinolone or cycloserine along with pyrazinamide should be introduced. Drugs can be introduced in maximum or escalating doses. (2)

CONCLUSION

ATDH is fairly common and is the most common reason for cessation of treatment. Though most of the times it is mild but can also lead to liver failure and death. It is mostly seen in the first two months of therapy and there are various risk factors associated.With the ALT rising above the limit defined all drugs should be stopped and then gradually increased.

Further Reading:

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ALGORITHM FOR MANAGEMENT OF ATDH