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Detection of Isoniazid Induced Hepatitis after 12 Weeks and Its Management

Authors

Dr. Jitesh Dhingra[1], Dr. Sanjay Rajpal[2], Dr. K.K Chopra[3]

[1]Junior Resident,Lal Bahadur Shastri Hospital, Dehli
Email: *jitesh.dhingra.ucms@gmail.com*
[2,3]New Delhi Tuberculosis Center
Emails: sanjayrajpalin@yahoo.com, chopra_drkk@yahoo.co.in

Abstract

Hepatotoxicity is a common complication of anti-tuberculosis therapy ranging in severity fromasymptomatic elevation of hepatic transaminases to hepatic failure necessitating liver transplantation. Thistoxicity is caused by most anti-tuberculosis drugs but appears to represent an idiosyncratic response and isusually seen in the first six weeks of starting anti-tuberculosis treatment (ATT) mainly due toIsoniazid(INH) and Rifampicin. The hepatotoxicity seen after twelve weeks is majorly due to Pyrazinamide.However sometimes Isoniazid can be an offending agent after 12 weeks.

DISCUSSION

Since 1952, Isoniazid has been used as a front-line antimicrobial for tuberculosis (TB).

It interferes with mycobacterial cell wall synthesis, though its exact mechanism of action is unknown. INH is commonly used in combination with other medications for active disease.

INH hepatotoxicity is a common complication of anti-tuberculosis therapy, ranging in severity from asymptomatic elevation of serum transaminases to hepatic failure necessitating liver transplantation. This toxicity is not caused by high plasma INH levels but appears to represent an idiosyncratic response.

INH hepatotoxicity presents a difficult management problem, for several reasons:

- Patients who are affected often are taking other potentially hepatotoxic drugs, such as Rifampicin; Pyrazinamide or protease inhibitors; this makes it difficult to determine which drug is causing the liver damage.
- Most cases of INH hepatotoxicity are mild and commonly resolve despite continued therapy with INH; however, a small number of adult patients taking INH develop severe hepatitis that may progress to liver failure and death if the drug is not stopped promptly as in our case.
- Lack of effective alternative drugs often necessitates that INH be continued despite low-grade hepatotoxicity.
- Patients who are severely affected may have few symptoms until potentially lethal liver damage has occurred.

The hepatotoxicity of anti-tuberculosis treatment can be divided into 2 types:

1. Predictable or Direct toxicity: This is dose related, has a higher attack rate and occurs rapidly.

2. Unpredictable (idiosyncratic): This is an immunologic response and independent of dose.

There are three signals of liver toxicity in clinical trials: (i) a statistically significant doubling (or more) in the incidence of serum alanine aminotransferase (ALT) elevation >3 x the upper limit of normal (ULN); (ii) any incidence of serum ALT elevation >8-10 x ULN; and (iii) any incidence of serum ALT elevation >3 x ULN accompanied by a serum bilirubin elevation >2 x ULN.

The management of drug induced hepatitis in anti-tuberculosis management revolves around these rules:

If the patient has mild gastrointestinal complaints with liver function tests being less than 5 times the upper normal limit without symptoms or liver function rests being less than 3 times in symptomatic patients we should continue the first line management.

We should stop the first line treatment if the liver function tests are more than 5 times the upper normal limit and patients is without symptoms or more than 3 times the upper normal limit with the patient having symptoms.

The reintroduction of therapy is begun with at least three least toxic drugs, Ethambutol, Sulfonamides, Fluoroquinolones (EMB, SM, FQ). These drugs should be reintroduced when the liver function tests reveal an ALT and AST < 2 of the upper normal limit.

The reintroduction of first line anti-tuberculosis treatment should be begun with stepwise increase in the dose and a subsequent liver function test to monitor for a recurrence of drug induced hepatotoxicity.

In the meanwhile we also evaluate patient for hepatitis A, B and C virus, biliary disease,

alcoholic liver disease , and other potentially hepatotoxic drugs.

Genetic predisposition is an important factor, but no clinical test for this predisposition is currently

available. Age is an important risk factor, presumably reflecting aging-related changes in hepatic metabolism. Female gender increases both the risk of developing INH hepatitis and the risk of death once hepatitis develops. Animal studies suggest that low levels of certain antioxidants (e.g., glutathione), which are associated with poor nutrition, increase risk; however, human studies are lacking.

CONCLUSION

Hepatotoxicity is a common complication of anti-tuberculosis therapy ranging in severity from asymptomatic elevation of hepatic transaminases to hepatic failure which can cause mortality or necessitate liver transplantation in order to save the patient's life. Hepatotoxicity is caused by most anti-TB drugs but appears to represent an idiosyncratic response and is usually seen in the first six weeks of starting anti-tuberculosis therapy (ATT) and is mainly due to Isoniazid(INH) and Rifampicin. The hepatotoxicity seen after twelve weeks is majorly due to Pyrazinamide.

However rarely Isoniazid is also the offending agent, so it is important to keep a close eye on Isoniazid induced hepatotoxicity as a possible presentation after 12 weeks of ATT. The impending hepatic failure can be avoided by early detection of the symptoms stopping ATT at the first presentation of symptoms in the patient.