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Medicine

A REVIEW ON HEPATOTOXICITY OF ANTITUBERCULOSIS THERAPY

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ABSTRACT The correlation between serum anti-tuberculosis (TB) drug levels and the drug-induced hepatotoxicity (DIH) remains unclear. The purpose of this study was to investigate whether anti-TB DIH is associated with basal serum drug levels. Serum peak levels of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) were analyzed in blood samples 2 hr after the administration of anti-TB medication. Anti-TB DIH and mild liver function test abnormality were diagnosed on the basis of laboratory and clinical criteria. Serum anti-TB drug levels and other clinical factors were compared between the hepatotoxicity and non-hepatotoxicity groups. A total of 195 TB patients were included in the study, and the data were analyzed retrospectively. Seventeen (8.7%) of the 195 patients showed hepatotoxicity, and the mean aspartate aminotransferase/alanine aminotransferase levels in the hepatotoxicity group were 249/249 IU/L, respectively. Among the 17 patients with hepatotoxicity,12 showed anti-TB DIH. Ten patients showed PZA-related hepatotoxicity and 2 showed INH- or RMP-related hepatotoxicity. However, intergroup differences in the serum levels of the 4 anti-TB drugs were not statistically significant. Basal serum drug concentration was not associated with the risk anti-TB DIH in patients being treated with the currently recommended doses of first-line anti-TB treatment drugs.

GRAPHICALABSTRACT

Drug concentration 2h after drug ingestion, µg/ml	Hepatotoxicity N=12	Mild LFT abnormality N=30	No Hepatotoxicity N=148	P-value
INH	25 ± 1.0	2.5 ± 1.4	2.5 ± 1.6	0.995
RMP	10.4 ± 5.0	9.5 ± 4.0	9.0 ± 3.5	0.371
EMB	3.6 ± 1.7	3.2 ± 1.6	3.3 ± 2.1	0.876
PZA	34.6 ± 13.4	36.8 ± 12.9	34.8 ± 12.6	0.736
Acetyl-INH/INH*	0.27 ± 0.20	0.62 ± 0.51	0.59 ± 0.50	0.102

KEYWORDS : Therapeutic Drug Monitoring, Hepatotoxicity, Tuberculosis

THE LIVER: STRUCTURE AND FUNCTION

The liver is situated between the alimentary tract and the sys-temic circulation to maximize processing of absorbed nutrients And to minimize exposure of the body to toxins and foreign chemicals. Consequently, the liver may be exposed to large con-centrations of exogenous substances and their metabolites.

Hepatic Drug Metabolism: Transporters, Enzymes, and Excretion The splanchnic circulation carries ingested drugs directly into the liver, a phenomenon known as the “first pass” through the liver. Metabolic enzymes convert these chemicals through phase 1 pathways of oxidation, reduction, or hydrolysis, which are carried out principally by the cytochrome P450 class of en-zymes. Phase 2 pathways include glucuronidation sulfation, ace-tylation, and glutathione conjugation to form compounds that are readily excreted from the body. Other subsequent steps include deacetylation and deaminidation. Many drugs may be metabolized through alternative pathways, and their relative contributions may explain some differences in toxicity between individuals. In phase 3 pathways, cellular transporter proteins facilitate excretion of these compounds into bile or the systemic circulation.Transporters and enzyme activities are influenced by endogenous factors such as circadian rhythms, hormones,cytokines, disease states, genetic factors, sex, ethnicity, age, and nutritional status, as well as by exogenous drugs or chemicals Bile is the major excretory route for hepatic metabolites.Compounds excreted in bile may undergo enterohepatic circula-tion, being reabsorbed in the small intestine and re-entering the portal circulation.

DRUG-INDUCED LIVER INJURY: GENERAL CONCEPTS DEFINITION

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. Histologic specimens of the liver are often not obtained. Other causes of liver injury, such as acute viral hepatitis,should be methodically sought, and their absence makes the diag-nosis plausible. Usually, the time of onset to acute injury is within months of initiating a drug. Rechallenge with the suspected of-fending agent with more than twofold serum alanine aminotrans-ferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis . Rechal-lenge may, in some instances, endanger the patient and is usually confined to essential drugs or used when multiple potentially hepa-totoxic drugs have been administered concomitantly.

RIFAMPIN:

Rifampin, and similarly rifapentine, may occasionally cause dose-dependent interference with bilirubin uptake, resulting in sub-clinical, unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. This may be transient and occur early in treatment or in some individuals with preexisting liver disease. Rifampin occasionally can cause hepatocellular injury and potentiate hepatotoxicities of other anti-TB medications. In a study of patients with brucellosis treated with the combination of rifampin and minocycline, rifampin-attributed ALT increases of at least 250 IU/L were seen in approximately 5% of patients . In two small series of patients with primary biliary cirrhosis, in whom baseline transaminases were signifi-cantly elevated, clinically significant hepatitis was attributed to rifampin in 7.3 and 12.5% of patients .

MECHANISMS OF HEPATOTOXICITY:

Conjugated hyperbilirubinemia probably is caused by rifampin inhibiting the major bile salt exporter pump. Asymptomatic elevated bilirubin may also result from dose-dependent competition with bilirubin for clear-ance at the sinusoidal membrane or from impeded secretion at the canalicular level

Rare hepatocellular injury appears to be a hypersensitivity reaction, and it may be more common with large, intermittent doses . Hypersensitivity reactions have been reported in combination with renal dysfunction, hemolytic anemia, or “flu- like syndrome”.

PYRAZINAMIDE:

Pyrazinamide has been used with rifampin, ethambutol, or a fluoroquinolone for treatment of LTBI. Transaminase elevation more than four times the ULN was seen in 7 of 12 (58%) LTBI cases treated with pyrazinamide and ethambutol . Three of 17 (18%) patients prescribed levofloxacin and pyrazinamide for treatment of LTBI after exposure to MDR TB developed transaminase elevation more than four times the ULN. Nine of 22 (41%) patients treated with ofloxacin and pyrazinamide developed transaminase elevation of at least five times the ULN . Because these fluoroquinolones and ethambutol alone rarely cause hepatotoxicity, pyrazinamide is believed to be the

offending agent in most cases of hepatotoxicity associated with these regimens.

MECHANISM OF INJURY.

Pyrazinamide may exhibit both dose-dependent and idiosyncratic hepatotoxicity. Several decades ago,daily doses of pyrazinamide at 40 to 50 mg/kg commonly caused hepatotoxicity, and a relationship to dose was noted . Pyrazi-namide alters nicotinamide acetyl dehydr oge nase levels in rat liver , which might result in generation of free radical spe-cies. There may be shared mechanisms of injury for isoniazidand pyrazinamide, because there is some similarity in molecular structure. Patients who previously had hepatotoxic reactions with isoniazid have had more severe reactions with rifampin and pyrazinamide given for LTBI . Pyrazinamide may induce hyperse nsitivity reactions with eosinophilia and liver injury or granulo matous hepatitis

HEPATOTOXICITY DURING TREATMENT OF TB DISEASE:

The use of multiple regimens, vastly different study populations, varying definitions of hepatotoxicity, and different monitoring and reporting practices make it difficult to reach definitive con- clusions regarding risks of individual regimens. Overall, the risk of TB DILI in these diverse studies ranges from 5 to as high as 33%.

AGE OVER 35:

Several studies suggest that increasing age is a risk factor for TB DILI, but often statistical significance was not achieved or hepatotoxicity was not treatment limiting . One study reported a TB DILI rate ranging from 2 to 8% as age increased, with an average of 5% . Other studies have reported that hepatotoxicity ranges from 22 to 33% in those older than 35 years, compared with 8 to 17% in those younger than 35 years.

CHILDREN:

In a retrospective study, severe TB DILI was diagnosed in 8% of pediatric patients, and was associated with age younger than 5 years, extrapulmonary TB, and use of pyrazinamide . In another study of children with a mean age of 4.5 years treated with isoniazid and rifampin, 82% experienced an ALT elevation greater than 100 IU/L, and more than 40% had symptomatic hepatitis with jaundice. In a study of South Indian patients with TB of all ages, 16 to 39% of children with tuberculous meningitis developed hepatitis "nearly always with jaundice." These rates were substantially more than the 2 to 8% seen in the multiage cohorts with pulmonary or spinal TB . There are some data suggesting that doses of isoniazid greater than 15 to 20 mg/kg may be associated with a greater risk of hepatotoxicity .

HEPATITIS B:

Several studies from Asia have addressed DILI during treatment of TB disease in patients with hepatitis B infection. In Taiwan, 42 (2.4%) of 1,783 patients with TB treated with isoniazid, rifam-pin, and ethambutol had symptomatic hepatitis. Fifteen were hepatitis B carriers (had hepatitis B surface antigen), and 7 of 15 died of hepatic failure. Of the other 27 patients with symptomatic hepatitis who were not hepatitis B carriers, one died of hepatic failure . The severity of hepatotoxicity appears to have been increased in the hepatitis B carrier population.Also in Taiwan, hepatitis B carriers with TB who received isoniazid, rifampin, pyrazinamide, and ethambutol had a hepato-toxicity rate of 29%, similar to the 26% experienced by hepatitis B–seronegative individuals. Patients were excluded if alco-hol ingestion exceeded 60 g/day or if baseline serum transami-nase concentrations were greater than the ULN.In a study from Hong Kong , which excluded alcoholic and nonviral liver diseases, 16% of patients with TB with hepati-tis B surface antigen developed symptomatic hepatitis compared with 4.7% in those without hepatitis B infection. Patients who had hepatitis B surface antigen also had more severe liver injury and were more likely to have a permanent treatment discontinu-ation, 4.7 compared with 2.5%.A retrospective case-control study from Seoul, Korea, of 110 patients with hepatitis B surface antigen and normal pretreat-ment transaminases found a trend toward transminase elevations of at least five times the ULN more frequently in the hepatitis B carrier group than in the control subjects .However, isoniazid and rifampin were successfully reintroduced in five of the nine carriers . In summary, notable variations in study designs and the po-tential for confounding reasons preclude firm conclusions about the contribution of hepatitis B carriage alone to the incidence of liver injury for patients being treated for TB disease. Two of these four studies indicate that there may be increased incidence of TB DILI in hepatitis B carriers, whereas one does not . Two studies suggest that hepatitis B carriers may incur more severe hepatic disease from treatment-associated liver injury, and the extent of underlying liver disease could be a determinant. These studies did not stratify patients according to evidence of active hepatitis B viral replication, such as HBeAg or hepatitis B viral DNA. Additional studies are needed, but the limited data leave sufficient concern that hepatitis B may be a risk factor for more frequent or severe hepatotoxicity during treatment of TB disease.

RECOMMENDATIONS REGARDING TB DILI:

Program Infrastructure Standardized approaches to developing safe treatment of LTBI and TB disease should be implemented in an effort to prevent TB DILI. Optimal care requires the following:

1. Clear and recurring communications with patients in the preferred language
2. Accurate medical evaluation, treatment, and monitoring
3. Convenient access to care and rapid responses to suspected drug adverse events

TREATMENT OF LTBI:

Patient and regimen selection. The clinician and patient decide on treatment of LTBI based on the benefits of treatment relative to its risks

1. Isoniazid taken for 9 months remains the preferred regimen.
2. Rifampin is an option for patients who may not tolerate isoniazid, but potential drug interactions should be considered.
3. Because isoniazid with rifampin is more hepatotoxic than either alone , this combination should be used with caution in patients at risk for hepatotoxicity.
4. For those with ALT elevation more than 2.5 to 3 times the ULN, chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits. If LTBI treatment is undertaken, close monitoring is indicated.
5. RZ is no longer generally recommended for treatment of LTBI

INTERVENTIONS FOR HEPATOTOXICITY :

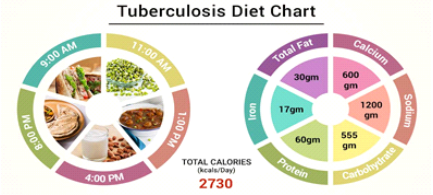
1. Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms .
2. A rapid increase in ALT may be an indication for more frequent monitoring, every 2 weeks instead of monthly, particularly if one of these treatment-limiting ALT thresh- olds is being approached, or if the patient has previously identified risk factors for hepatotoxicity.
3. For the few patients who may begin isoniazid LTBI treat- ment with a baseline ALT more than three times the ULN, some experts recommend, in the absence of adequate clini- cal data, that treatment should be discontinued if there is more than a two- to threefold increase above baseline or if there is a mental status change, jaundice, or significant increase in bilirubin or INR

TREATMENT OF TB DISEASE:

Regimen selection.The crucial efficacy of isoniazid, and particu-larly rifampin, warrants their use and retention, if at all possible,even in the face of preexisting liver disease. Several regi-mens are recommended if baseline serum ALT is more than three times the ULN, and TB is not believed to be the cause

1. Treatment without pyrazinamide might utilize isoniazid and rifampin for 9 months with ethambutol until drug suscepti- bility testing of the M. Tuberculosis isolate is completed.
2. In patients with cirrhosis, rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered.
3. For patients with encephalopathic liver disease, ethambu- tol combined with a fluoroquinolone, cycloserine, and ca- preomycin or aminoglycoside for 18 to 24 months may be an option. However, these regimens have not been tested systematically.
4. Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected medication in patients with throm- bocytopenia and/or coagulopathy.

DIET :



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