Original Article

Determination of safe anti-tubercular therapy regimen following anti-tubercular drug induced hepatitis in patients with active tuberculosis

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To determine the safety of restarting isoniazid and rifampicin and etambutol or isoniazid pyrazinamid and ethambutol in patients who develop antitubercular drug induced hepatitis. In 22 tuberculosis patients, who developed antitubercular drug induced hepatitis were analysed, for reintroduction of antitubercular drugs, isoniazid, rifampicin and ethambutol in 11 patients (Group A) and isoniazid, pyrazinamide and ethambutol in another 11 patients (Group B), following clinical and biochemical (liver function test) normalization. During antitubercular drug induced period, hepatotoxic antitubercular drugs were withdrawn till clinical and biochemical normalization and non-hepatotoxic antitubercular drugs like streptomycin, ethambutol were given. Jaundice appeared at variable interval of 2-13 weeks after starting the antitubercular treatment and before enrolling into the study. All 22 patients with abnormal liver function on close followup, came back to normal within 2 weeks of stoppage of antitubercular drug. On rechallange, 4 out of 11 patients receiving isoniazid and rifampicin developed hepatitis within 2-4 weeks of restart of therapy and 1 out of 11 developed (receiving isoniazid and pyrazinamide) in 4th week. Though the study sample size was small, the combination of isoniazid and pyrazinamide was apparently safer compared to isoniazid and rifampicin combination though it was statistically insignificant (p<0.155). [*J Indian Med Assoc* 2019; **117:** 13-9]

Key words **: Anti-tubercular agents, hepatitis, restart safe anti-tubercular regimen, active tuberculosis.**

Tuberculosis (TB) continues to be a major public health problem in India. Globally TB has remained a therapeutic challenge. Prevalence of TB cases per 1,00,000 population is 12-20 in developed countries, as against 250-500 in developing countries, so also is the mortality due to TB 1-2 per 1,00,000 population in the developed countries, as against 60-100 in developing countries. Nearly 5,00,000 people die of this disease in India every year[1]. According to conservative estimate, there are 15-20 million cases of infectious TB in the world. This infectious pool is maintained by the occurrence of 4-5 million new cases and 3 million deaths per year[1]. Inspite of these deluding statistics, TB is a curable disease. With modern chemotherapy cure rates of upto 99% can be achieved. However, unfortunately almost all the antitubercular drugs can cause hepatitis. Among these drugs, hepatitis is more common with isoniazid, rifampicin, and pyrazinamide when used either alone or in combination.

The risk of hepatitis with 2 months of isoniazid administration is about 5.2 per 1000 subjects having an age less than 35 years to 7.7 per 1000 for those aged 55 years or more[2]. The risk is similar in both sexes and the cumulative risk increases during the first 15-20 weeks of isoniazid administration[2,3]. About 15% of cases of symptomatic isoniazid induced hepatic injury appear within the first month of therapy and about 50% within first two months. In the remaining 50% of cases it may be delayed from three to twelve months[4-6].

Clinically isoniazid induced hepatitis resembles viral hepatitis[4,7-10]. If treatment is continued in patients with isoniazid induced hepatitis, fulminant hepatic damage can result; this has a very high mortality[2]. The fatality rate for clinically jaundiced patients is in the excess of 10% and most fatal cases have bilirubin level over 20mg/dl[16]. There are reports of patients of developing cirrhosis and portal hypertension following isoniazid induced hepatitis[2,11].

Rifampicin alone also can cause hepatocellular damage besides aggravating isoniazid toxicity through activation of hepatic microsomal enzyme systems[2]. Though rifampicin is well tolerated, transient elevation in AST levels are common (14-40% of patients) and of no clinical significance. Rifampicin induced hepatic injury usually appears, during the first month of therapy[30]. Major elevation of AST >150 units occurs in 4% and hepatitis with jaundice in about 1%[12]. Although considerable evidence exists regarding the rifampicin and isoniazid together causing more hepatotoxicity than either drug alone, lack of potentiation has also been reported[13-15].

Hepatotoxicity is not enhanced when pyrazinamid is

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added to isoniazid and rifampicin[16]. Reports from Madras indicate that a combination of isoniazid and rifampicin causes biochemical hepatitis in over 8% of patients[18]. The incidence of hepatitis was higher ie, 16-30% when treatment was given on daily basis as compared to 5% with twice a week regime[2]. Ramakrishna CV *et al* while reviewing the adverse effect of rifampicin, quoted the report of Asim Dutt *et al* in which chemical hepatitis observed in 12 (1.5%) of 781 patients receiving short course antitubercular chemotherapy, attributed to rifampicin in daily phase in four, and to isoniazid in six and could not assign a reason in two[19].

Pyrazinamide hepatotoxicity is dose related, it is around to 6% when the pyrazinamid dose is 40mg/kg. Pyrazinamide toxicity in lower doses (30mg/kg body weight), prescribed today shows no report of hepatitis (Fox 1978). Hepatitis is more common when higher doses of the drug are used[2].

Continuation of drug after symptoms of hepatic dysfunction have appeared tends to increase the severity of damage. Stoppage of antitubercular drugs and institution of supportive therapy are mandatory, if the patient on antitubercular treatment develops drug induced hepatitis[2,21].

The literature is silent as to which antitubercular drug should be started after liver function tests become normal following antitubercular drug induced hepatitis. Girling mentions that treatment with same drugs which caused hepatitis can often be resumed uneventfully[2,21-25] with close monitoring of liver function. Richard J O'Brien advocates stoppage of all drugs in a setup of serious hepatotoxicity eg. high transaminases and symptoms of hepatitis and to continue ethambutol and streptomycin and rechallenge the patients after introducing one drug at a time, preferably rifampicin first and then isoniazid and later followed by pyrazinamid[26].

Data regarding the safety of restarting antitubercular therapy after drug induced hepatitis is scanty. Since for any effective bactericidal antitubercular drugs like isoniazid, rifampicin, and pyrazinamide are essential, this study was proposed to determine safe readministration of isoniazid, ethambutol and rifampicin and its comparison with isoniazid, ethambutol and pyrazinamide after drug induced hepatitis.

Aim and Objective

To determine the safety of restarting isoniazid and rifampicin and ethambutol or isoniazid, pyrazinamide and ethambutol in patients who develop antitubercular drug induced hepatitis.

Materials and Method

This study was conducted on twenty two patients who developed antitubercular drug induced hepatitis. On the basis of international consensus meeting on definitions on drug induced liver disorders (Paris 12-13 June,1989),63 the patients were considered to be having drug induced hepatitis if there was :- (1) An increase above twice the upper limit of normal of alanine aminotransferase OR (2) An increase in conjugated bilirubin twice above the normal upper limit OR (3) Combined abnormality of aspertate aminotransferase, alkaline phosphatase and total bilirubin provided one of them is above the twice of the upper limit of normal.

Inclusion Criteria — Patients who develop hepatitis within three months of start of antitubercular drugs, were included in the study. Hepatitis was considered to be due to antitubercular therapy if the liver functions return to normal within 2 weeks of stoppage of drugs.

Exclusion criteria — (1) Hepatitis B surface antigen positive patients. (2) Patients with history of chronic alcoholism. (3) Patients with chronic liver disease. (4) Patients with previous history of jaundice. (5) Pregnancy. (6) Patients with history of blood transfusion within 2 weeks to 6 months of onset of hepatitis. (7) Patients with recent episode of hypotension. (8) Patients suffering from gall stones, choledocholithiasis or pancreatic disease.

Methodology

After the patients developed antitubercular drug induced hepatitis, all drugs were stopped and nonhepatotoxic drugs injection streptomycin and tablet ethambutol were started. Patients were closely monitored clinically and biochemically with liver functions till these became normal, then patients were randomly allocated to the following groups of antitubercular regimen.

Group A- Isoniazid, Rifampicin and Ethambutol. Group B- Isoniazid, Pyrazinamide and Ethambutol

Doses (daily)

-	Isoniazid	300 mg
-	Rifampicin (for patients)	<50 kg - 450mg, >50kg - 600mg
-	Pyrazinamid (for patients)	<50 kg – 1.5gm, 50-74kg – 2 gm, >75 kg – 2.5 gm

The doses were given to the patients according to the recommendations of International Union against tuberculosis and lung diseases[25].

As soon as the liver functions became normal, tablet isoniazid was added to each group of patient gradually increasing doses, starting 100 mg per day to reach maximum dose of 300 mg within seven days, after liver function monitoring. If liver function test remained normal after 300 mg of isoniazid, rifampicin and pyrazinamide, in the above mentioned doses was added to isoniazid, ethambutol in group A and group B respectively. The liver function tests were monitored every two weeks for a total period of three months and the group with highest hepatotoxicity following resumption of antitubercular therapy was determined. The drugs were stopped once patient observed

evidence of hepatitis either clinically or biochemically and restarted on injection streptomycin, tablet ciprofloxacin with continuation of ethambutol.

The liver function tests done, were (a) Aspertate amino transferase (SGOT). Normal value (2-20) IU (by the method spectrophotometry, Reitman and Frankel). (b) Alanine amino transferase (SGPT). Normal value (2-15) IU. (by the method of spectrophotometry, Reitman & Frankel). (c) Alkaline phosphatase. Normal value (70-140 IU / 3-13 KAU). (d) Serum bilirubin, total and conjugated. Normal value (0-0.8 mg%) (by the method of Vandenbergh & Muller). (e) Serum protein, total, albumin and globulin. Normal value- total protein- 5.5-7 gm%, albumin- 3.5- 5 gm%, globulin- 2- 3 gm%, (by the method of Biuret). Hepatitis B surface antigen from blood by ELISA was done when the patient was first detected to have hepatitis. Ultrasound study of liver, gall bladder, biliary tract and pancreas was done at the time of hepatitis to exclude extrahepatic biliary obstruction as a cause of jaundice.

Statistical Analysis

Comparison of safety between two antitubercular therapy groups was done by Chi-sqare test and fisher table.

Ethical Consideration

The study involved taking 5ml of blood in the beginning and 5ml of blood every 2 weeks or more frequently as was necessary, over a period of 3 months by venepuncture from the subjects. Study also included doing an Ultrasound study of abdomen, a non-invasive procedure. The ethical justification for restarting the same regimen ie, Isoniazid, Rifampicin, Ethambutol and Isoniazid, Pyrazinamid, Ethambutol, was based on the recommendation from the Committee on Treatment of the International Union against Tuberculosis and Lung Disease[25]. In all cases, informed consent were taken.

Observation

(A) The demographic profile of the two groups of patients are as

(1) Group A had a total of 11 patients, (4 males & 7 females) with an age range of 15-65 years (34.18 ± 15.33). Out of these 11 patients, 4 had pulmonary parenchymal lesion, 3 had pleural effusion (2 had associated pneumothorax), 1had skin TB (Tubercular verrucus cutis, lymphnodal tuberculosis), 2 had tubercular meningitis (1 had associated pulmonary parenchymal lesion), 1 had parietal lobe tuberculoma. These group of patients were rechallenged with rifampicin and isoniazid.

(2) Group B had a total of 11 patients, (male 5 & 6 female), with an age range of 15-60 years (30.09 +- 14.20). Out these 11 patients, 3 had pulmonary parenchymal lesion, 2 had disseminated tuberculosis (1 had associated pulmonary parenchymal lesion and 1had pleural effusion), 1 had TB spine (spinal TB), 1 had cold abscess back, 2 had lymphnodal tuberculosis (1 had associated pulmonary parenchymal lesion), 2 had abdominal TB.

Clinical profile of patients in 2 groups.

	Group A (n-11)	Group B (n-11)
Age in years :		
Mean ± SD	34.18 ± 15.33	30.09 ± 14.20
Range	18-65 years	!5-60 years
Below 50 years M:F	3:6	3:6
50 years or above M:F	1:1	2:0
Icterus	9	9
Liver enlargement	5	4
Splenomegaly	0	0
Ascites	0	0

Liver function test of patients in 2 groups at the time of antitubercular hepatitis.

	Group A (n=11)	Group B (n=11)
Serum Bilirubin (Mean+-SD) (mg%)	3.5 ± 1.8	2.12 ± 2.04
Range	0.8-7.7	0.8-5.7
SGOT	44-136	21-127
SGPT	21-141	26-127
Alkaline phosphatase	N-43	N-35
n = number of patients, N = normal		

(B) Hepatotoxicity to antitubercular drugs started from different specialities in the 22 patients, developed over a variable period of time i.e. 4-13 weeks. The drugs used in these patients before they were registered in this study were taking rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin. 4 patients (18.18%) developed hepatotoxicity within first week, 9 patients (40.9%) in second week, 2 in third week (9.08%), 1 in fourth week (4.54%), 1 in 8th week (4.54%), 4 in 12th week (18.18%), 1 in 13th week (4.54%).

(C) Time taken for the liver function test to come to normal.

	Group A(n=11)	Group B(n=11)
Duration taken to come back to normal	5-14 days (11.27 ± 3.69)	4-14 days 12.09 ± 3.23)

(D) Recurrence of hepatic biochemical abnormality on rechallenge

In Group A 4 patients (36.36%) out of 11 (2 M & 2 F) developed hepatic biochemical abnormalities. All showed an increase above 2 folds in SGOT/SGPT levels while 2 patients showed an increase in serum bilirubin level after 2-4 weeks of restart of isoniazid and rifampicin (1 patient in 2nd week & 1 patient in 4th week).

Group B only one male patient (9.09%) out of 11 developed hepatic biochemical abnormalities, in the form of raised bilirubin and SGOT/SGPT after 4 weeks of restart of isoniazid ($p<0.0155$).

None of the patient developed liver function abnormalities after 1 week of initial restart of isoniazid. All these patients who developed hepatic biochemical abnormality on rechallenge had anorexia, 4 of them had vague epigastric discomfort and dull pain over the right upper quadrant.

Correlation of time of onset of hepatotoxicity following rechallenge with drugs with time of onset of the initial hepatotoxicity.

				On rechallenge		On initial treatment	
Pt No	Sex	Gr	SB mg%	SGOT/ PT level IU	Duration of onset of increase	SGOT/ SGPT level IU	Duration of onset of increase
4	F	A	0.9	41/22	2nd week	44/30	2nd week
6	M	A	2.7	64/85	4th week	57/77	4th week
7	M	A	1.7	98/99	2nd week	65/28	3rd month
10	F	A	0.7	62/60	22nd week	65/21	9th day
4	M	B	2.7	98/124	4th week	102/127	End of 3rd month

p>0.5; SB- Serum Bilirubin

Occurrence of rechallenge hepatitis in pulmonary and extra-pulmonary tuberculosis patients.

Group A (n=11) :

8 (72.72%) patients were suffering from pulmonary tuberculosis – out of which 3 (27.27%) patients developed hepatitis on restart. 3 (27.27%) patients were suffering from extra-pulmonary tuberculosis – out of which one (9.09%) patient developed hepatitis on restart.

Group B (n=11) :

6 (54.54%) patients were suffering from pulmonary tuberculosis – out of which no patient had hepatitis on restart. 5 (45.15%) patients were suffering from extra-pulmonary tuberculosis – out of which one (9.09%) patient developed hepatitis on restart. In 3 patients developed hepatotoxicity after the same duration of rechallenge with antitubercular drug, compared with initial antitubercular therapy, before the patients were registered into the study.

Ultrasound abdomen study revealed no evidence of chronic liver disease, Gall bladder, biliary tract or pancreatic abnormality, though one patient had fatty liver and another had Gall bladder polyp.

Follow up after rechallenge hepatotoxicity.

The drugs were stopped as soon as the liver function showed an abnormality and second line antitubercular drugs started and ethambutol continued. These liver function abnormality reverted back to normal again within two weeks and patients instructed not to restart isoniazid, rifampicin and pyrazinamide again. No patients developed either prolonged hepatitis, subacute hepatic failure or fulminant hepatic failure.

Discussion

Rifampicin, isoniazid and pyrazinamide constitute the main armamentarium of anti-tubercular chemotherapy, although their potential hepatotoxicity in combination or alone, is well known. To evaluate the hepatotoxic potential of rifampicin, isoniazid versus pyrazinamide and isoniazid combination, when rechallanged following recovery of anti-tubercular drug induced hepatitis, the study was conducted on 22 patients. There is scanty literature on the restart of anti-tubercular drug following drug induced hepatitis, although Girling et al in his study had mentioned the safety of restart of these drugs[21]. Citron *et al* also mentions that "all drugs following antitubercular hepatotoxicity, must be stopped. It is usually safe to restart all drugs after liver functions have returned to pretreatment levels. If symptoms recur the drug should be introduced individually once the liver function test have returned to normal, at a lower dose, initially together with at least one drug that unlikely to cause hepatic dysfunction (streptomycin and ethambutol)[24].

All the patients in this study, who had initially had antitubercular drug induced hepatotoxicity had their liver functions returning to normal within 2 weeks of stoppage of all the offending drugs. There may be confusion whether this jaundice is due to viral hepatitis or chronic liver disease. To exclude these diseases the following test done like HbsAg, Ultrasonographic study of abdomen.

While the start of initial hepatotoxicity before the patients were entered into the study, was after variable interval of 4 days to 13 weeks, majority (40.9%) developed hepatotoxicity in the end of 2nd week of starting treatment. Ramesh R *et al* reported mean onset of jaundice in 4 patients out of 50 patients of tuberculosis treated with rifampicin and isoniazid of 16 days (range 1-22 days) and complete recovery within two weeks[55]. Rugmini *et al* reported the duration of hepatotoxicity in 32 (24.7%) of the 130 children treated isoniazid and rifampicin. In majority of patients this was recorded mostly within 2 months. Similar duration of onset of hepatotoxicity have been reported by O'Brien *et al* and Riska *et al* when these patients were initially put on anti-tubercular treatment[26,48].

Rechallenge of isoniazid and rifampicin lead to hepatotoxicity in 4/11 (36.36%) patients which was accompanied by vague ill health, anorexia, and dull ache in right hypochondrium. This was more, than in patients given a combination of isoniazd and pyrazinamide (1/11) (9.09%) though the difference was statistically insignificant ($p<0.155$). Three of the above five patients had pulmonary tuberculosis as against 2 with extra-pulmonary tuberculosis. The ages of these patients who on rechallenge developed hepatotoxicity was 18-55 years with no predilection for old age. (33.8±4.8 years). Onset of hepatitis on rechallenge occurred in 2 weeks to 4 weeks after start of drugs.

Purohit et al reported 40.3% of patients of pulmonary tuberculosis receiving isoniazid and rifampicin showed abnormal ALT levels and 70% had clinical hepatitis within first three months and resumption of therapy was possible within 7-10 days. On resumption of isoniazid and rifampicin following recovery of anti-tubercular drug induced hepatitis, was possible without hepatotoxicity in all 4 patients who had an abnormal ALT level with clinical symptoms as reported by Purohit *et al*. Ramesh *et al* also re-

ported no increase in serum bilirubin or enzymes after reintroduction of isonoazid. Rugmini et al reported in children suffering from different forms of tuberculosis, 16 out of 32 cases who had transient elevation of transaminase did not show further problem on continuing therapy, although later in one children drug had to be stopped due to jaundice. In the remaining 16 out of 32 children on reintroduction isoniazid in same or other combination was possible in 9 cases.

In this study it is unique that liver function tests have been serially followed up for period of atleast three months. Three patients who developed hepatitis on restart, developed hepatitis at the same time as was the initial hepatitis, while 2 patients had it earlier compared to 3 months in the earlier episode of hepatotoxicity. The findings of this study could be subtle pointer against hypersensitivity type of adverse reaction with isoniazid and rifampicin / pyrazinamide, otherwise hepatotoxicity should have occurred faster and earlier and should have more severe[4].

None of study patients either on initial hepatotoxicity, at the time of entry into the study or on rechallenge, developed serious liver disease like fulminant hepatic failure or subacute hepatic failure. This strengthens the belief and general recommendation of stopping the drug as soon as the patient becomes symptomatic for liver disease or has abnormal liver function, which should be monitored for the initial 2 -3 months at least after the start of anti-tubercular therapy.

Hepatotoxicity complicates antituberculur chemotherapy mostly with rifampicin, isoniazid and pyrazinmide, which are bactericidal drugs and are essential for the effective short term treatment of tuberculosis. Mechanism of isoniazid induced hepatitis remains unclear and ambiguous but proposed mechanism is either metabolite induced immunoallergy or presence of toxic metabolite. Though it is reported that monoacetylhydrazine, an initial metabolite of isoniazid causes hepatic injury producing reactive acetyl radical following further acetylation, there are variable reports regarding the possible potentiation of hepatotoxicity of acetylator phenotype of patients (rapid or slow acetylator). Rifampicin, a hepatic microsomal enzyme inducer may alone itself cause hepatotoxicity or may potentiate the hepatotoxicity of isoniazid by increasing the level of isoniazid metabolite. Pyrazinamide hepatotoxicity, though uncommon, is usually dose related to high dose.

All 22 patients in this study, had normalization of liver function after stopping the drugs within 2 weeks which is consistent with the international consensus held in Paris 12-13 June 1989[63]. It may be concluded that while restarting isoniazid, rifampicin and pyrazinamide, isonazid combination, close monitoring of patients both clinically and biochemically, is necessary to avoid any serious untoward hepatotoxicity. From this study of small number of patients a conclusion could be drawn that on rechallenge isoniazid combinations have hepatotoxic potential. Liver function tests must be monitored every week or fortnightly for about 2 months.

Summary and Conclusion

There is scanty of literature on the safety on reintroduction of isoniazid and rifampicin / pyrazinamide, once the patient developed anti-tubercular drug induced hepatitis. In 22 patients of anti-tubercular drug induced hepatitis with the primary being pulmonary tuberculosis in 14 patients and 8 extrapulmonary tuberculosis patients were included in the study. The jaundice appeared in variable interval of 2-13 weeks after starting the anti-tubercular treatment and before enrolling into the study. All these 22 patients with abnormal liver function on close followup, came back tonormal within 2 weeks of stoppage of anti-tubercular drug. 22 patients were rechallanged with initially for a week with isoniazid (starting with 100 mg increase to reach maximum of 300 mg over a period of seven days monitoring liver function tests) and if the liver function was normal they were randomly allocated to either rifampicin or pyrazinamide (11 in Group A and 11 in Group B). The liver functions were assessed every weekly / fortnightly for a period of 3 months or / and the drugs discontinued if patient developed evidence of clinical or chemical hepatitis.

4 out of 11 patients receiving isoniazid and rifampicin developed hepatitis within 2-4 weeks of restart of therapy and 1 out of 11 patients, receiving isoniazid and pyrazinamide, developed in 4th week. This hepatitis was mild and subsided after discontinuation of the drug and these patients were put on non-hepatotoxic second line of drugs. They were continued on ethambutol and injection streptomycin during the recovery phase of initial and restart therapy.

In conclusion, this study sample size was small, the combination of isoniazid and pyrazinamide was apparently safer compared to isoniazid and rifampicin combination though it was statistically insignificant ($p<0.155$). None of this study patients with recurrence of hepatitis following rechallenge with isoniazid and rifampicin / pyrazinamide combination either developed prolonged hepatitis or subacute hepatic failure or fulminant hepatic failure.

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