Incidence Of Hepatitis In Patients Taking Anti Tuberculous Treatment.

M U HAQ S RASUL Z H IQBAL M K CHAUDHARY A H BHATTI N ANWAR NASIR
Institute Of Chest Medicine, Mayo Hospital/King Edward Medical College,Lahore
Correspondance to:Dr. *Masood ul Haq*.

In present study, incidence of hepatitis has been studied in patients taking Anti tuberculous treatment (ATT) who were admitted in Institute of Chest Medicine, Mayo Hospital, Lahore during the months of June, July & August 97. During this period, 133 patients were put on ATT and among those 68(51.13%) were male and 65 patients (48.87% were female. Out of 133 patients, 11 (8.27%) developed jaundice (Male 7 & female 4). Age range was 16-80 years but 8 out of 11 (72.72%) were above 35 years of age. Time interval between start of ATT & appearance of jaundice varied between 3 days to 92 days. All the patients were on Rafampicin (R), INH (H), Ethambutol (E) and Pyrazinamide (Z). On appearance of jaundice, RHZ were stopped and patients were continued on Streptomycin (S), Ethambutol (E) and ciprofloxacin (cipro). Two out of 11 patients died during the treatment although their liver function tests were showing favourable response. Eight patients are being followed to-date. Jaundice disappeared in all eight patients in 12-60 days. ATT is generally well tolerated. In the present study the incidence of jaundice is 8.2% which is higher than previously reported studies. Secondly majority of those who developed jaundice (8 out of 11 i.e. 72.7%) are above 35 years. Therefore, it is recommended that patients who are more than 35 years of age and receiving ATT should be closely watched for evidence of drug induced hepatitis.

Hepatitis is a well known adverse effect of various antituberculous drugs. Girling [1] has studied various antituberculous regimens containing isonaizid, rifampicin and pyrazinamide and concluded that all the first line antituberculous drugs with the possible exception of streptomycin can cause hepatitis. Although ethambutol do cause transient derangement of liver function tests but it is generally considered safe as for as liver is concerned. Incidence of hepatitis induced by INH alone is less than 1% [2] but it varies with age, being uncommon below the age of 35 years but may approach a frequency of 2% when used chemoprophylactically in adults over the age of 35 years[3]. Jaundice is seen in 1% of patients taking rifampicin [4]. Pyrazinamide induced hepatitis was commoner when higher doses were used than are now recommended. It occurs in about 1% of cases but milder subclinical derangement of liver function test is common[3]. Obviously when these drugs are combined in various regimens, incidence of hepatitis will increase. We have studied the incidence of hepatitis in drug regimen containing rifampicin, isoniazid, ethambutol and pyrazinamide, being commonly used in our institute.

Materials and Methods

A total of 215 patients were admitted in Institute of Chest Medicine, Mayo Hospital, Lahore during the months of June, July & August 1997. Out of these, 133 patients were diagnosed as cases of pulmonary and/or extra pulmonary Tuberculosis. These 133 patients were the subjects of this study. They all were prescribed following drug regimen:

Rifampicin	10 mg/kg body wt.
Isoniazid	5 mg/kg body wt.
Ethambuol	25 mg/kg body wt.
Pyrazinamide	35 mg/kg body wt.

Besides history and thorough clinical examination patients were investigated for levels of serum bilirubin, S. alkaline Phosphatase, SGOT and SGPT at the start of treatment. All the patients were observed for clinical evidence of jaundice during the course of treatment and liver function tests repeated when indicated.

Extent of disease on chest X-ray was recorded in each case and labeled as

Normal when there is no detectable lesion in lungs i.e. extra pulmonary T.B.
Minimal (M)
Moderately Advanced (MA)
Far Advanced (FA)

Patients were interviewed carefully and divided into various categories on the basis of treatment history. Those who have no previous exposure to anti-tuberculosis drugs are labeled as Newly diagnosed (N). Those who have completed ATT and were cured but later developed disease again were labeled as Relapse (R). Those who were taking ATT irregularly or who had discontinued drugs ≥ 2 months were considered as Defaulters (D). Those who failed to respond to ATT clinically or bacteriorolgically fall in the category of failure (F). Incidence of hepatitis is being studied in the subjects of this study in relation with the age, sex, extent of disease, duration of anti-tuberculous treatment and chemotherapeutic status.

Results

Out of total 215 admissions, 133 patients had the diagnosis of tuberculosis, 108 patients were having pulmonary tuberculosis and 25 were having extra pulmonary tuberculosis. Out of 108 pulmonary cases, 72 patients had lesions limited to lungs only while 36 patients had concurrent T.B. of some other part of body or some other complicating factor in addition to lung lesion.

Prevalence of drug induced hepatitis in different patterns of tuberculosis is shown in table-I which clearly shows that jaundice is more common in patients with pulmonary tuberculosis.

Table II shows the relationship of jaundice with radiological extent of disease. It shows that the incidence

of jaundice is highest in those having far advance (FA) disease (16.66%) as compared with overall incidence in this study 8.27%.

Table –I: Prevalence of Jaundice in different Patterns of Tuberculosis

7	n=	Those who developed jaundice	%age
Pulmonary Tuberculosis	108	10	9.26%
ExtraPulmonary Tuberculosis	25	1	4.00%
Total	133	11	8.27%

Table-II: Relationship of Radiological Extent of Disease and A.T.T. induced Jaundice.

Extent of Disease on Chest Radiograph	n=	Those who developed jaundice	%age
Normal (Extra-Pulmonary)	25	1	4%
Minimal	14	1	7.14%
Moderately Advanced	46	1	2.17%
Far Advanced	48	8	16.66%
Total	133	11	8.27%

Table – III shows relationship of jaundice with age and sex. Jaundice is more common in male (10.29%) as compared with female (6.15%) 8 out of 11 (72.72%) patients who developed jaundice were above the age of 35 years.

Table –III: Relation of Jaundice with Age and Sex

Age (years)	Male			Female		
	n =	Jaundiced pts	%age	n=	Jaundiced pts.	%age
< 18	3	0	-	8	0	-
18-25	17	2	11.76%	23	0	-
26 – 36	12	1	8.33%	12	0	-
36 – 45	14	2	14.280%	5	0	-
46 – 55	8	1	12.50%	7	2	28.57 %
56 – 55	11	1	9.09%	6	1	16.66 %
> 65	3	0	-	4	1	25.00 %
Total	68	7	10.29%	65	4	6.15%

Table IV shows that among those who had ATT induced hepatitis, 7 out of 11 (63.63%) had some complicating factor in addition to lung lesion 2 had Diabetes Mellitus, 2 had corpulmonale, 2 had pyopneumothorax one of which had bilateral & recurrent & one had carries spine)

Table IV: Comparison between various groups of patients.

	N=	Jaundice pts.	% age
Pulmonary T.B.	72	3	4.16%
PTB + Some Complicating factor	36	7	19.44%
Extra Pulmonary T.B.	25	1	4.0%
Total	133	11	8.27%

Time interval between the start of ATT and appearance of jaundice varied between 3-92 days but 6 out of 11 patients (54.55%) had jaundice within 4 weeks and 8 out of 11 (72.73%) had jaundice within 8 weeks of start of ATT as shown in Table V

Table V: Relationship of development of Jaundice and Duration of A.T.T

Duration of Treatment	No of Patients who had Jaundice	%age
< 4 weeks	6	54.55%
5 – 8 weeks	2	18.18%
9-12 weeks	2	18.18%
>12 week	1	9.09%

It is clear from table VI that jaundice is less common among those who never reviews ATT previously (5.17%) than those who were previously exposed (8 out of 65 i.e. 12.31%)

Table –VI : Type of patients and ATT induced Jaundice

Type of patients	Total Patients	Jaundiced	%age
Newly diagnosed (N)	58	3	5.17%
Relapse (R)	15	3	20.00%
Defaulter /Irregular	38	4	10.52%
Failure (F)	4	-	-

On appearance of jaundice, rifampicin, INH & pyrazinamide were stopped and patients were continued on ethambutol, streptomycine and ciprofloxacin. Out of 11 patients, two died during the treatment , although their liver function were improving; one patients absconded, and 8 patients being followed up to-date. Jaundice cleared in all patients in 12- 60 days. INH & rifampicin were then added to the regimen sequentially, starting with small doses and then gradually increasing to full dose. All the eight patients tolerated both. It was not attempted to reintroduce pyrazinamide in any patients as a satisfactory regimen containing streptomycin, ethambutol, INH rifampicin had already evolved.

DISCUSSION:

Hepatotoxicity is a well known adverse effect of anti-tuberculous drugs. In the present study, incidence of ATT induced hepatitis is 8.27%. which is much higher than that cited in Harrison's Principles of internal medicine[4] where it is less than 2%. However, much higher incidence is being reported in various other studies e.g. more than 10% is reported by Kallan B.M. et al [5]. A comparison with some other studies has been given in Table VII

Table-VII:

Reference	Year	n=	Regimens	%Developed Jaundiced
Present study	1997	133	RHEZ	8.27%
Dubey et al (10)	1985	110	HREZ	17%
Gupta et al (11)	1983	105	SHRZ	12.3%
TRC Madras Study (2)	1983	552	3SHRZ/ $S_2H_2Z_2$	8%
Tripathy (12)				

It is difficult to conclude definite cause of hepatitis in patients taking A.T.T because liver functions may be deranged due to actual involvement of liver in tuberculous process. The drugs given to treat T.B. may improve the liver function by crubing the disease. On the other hand these drugs, being potentially hepatotoxic can themselves cause hepatitis. Then there are certain other variable which influence the incidence of A.T.T induced hepatitis like age, extent of disease, H/o A.T.T previously etc.

It is evident from this study that hepatotoxicity due to A.T.T varies with age. In present study 72.72% of those who developed jaundice were more than 35 years of age.

The patients suffering from pulmonary tuberculosis have more chances of hepatitis than those with extra pulmonary T.B. In present study, 9.26% of those with Pul. T.B. and 4% of those with extra pulmonary T.B. developed hepatitis. In a similar study, V.K. Arora reported that none of 25 extrapulmonary T.B. cases developed hepatitis [6].

It is also observed that those with prior history of A.T.T have more chances (12.31%) of hepatitis as compared to those never exposed before (5.17%)

Chronic malnutrition and catabolism due to disease make the liver more vulnerable to toxicity [7]. Hypoxia has been suggested to be another factor by Refsum [8]. Extensive pulmonary T.B. lowers PaO_2 so renders the patients more susceptible to liver toxicity. In the present study, those patients with extensive (F.A) tuberculosis have higher incidence of hepatitis 16.66% as compared to those with minimal disease (7.14%)

72.73% of those who developed hepatitis in present study, did so within first 2 months of start of therapy while it is cited in Harison's Principles of internal Medicine that approximately half of cases of INH hepatotoxicity occurs within first 2 months [9].

Prevalence of viral hepatitis in community also affect the incidence of drug induced jaundice. It is documented that 5-20% of normal population of Far East and tropical countries are carriers of hepatitis B virus[9]. It is possible that such people might be suffering from sub clinical derangement of liver function which get worse under antituberculous chemotherapy. Unfortu-nately, we could not determine the hepatitis carrier status of our patients as the facility for the investigation was not available in the hospital and patients were unable to get it done privately.

After the disappearance of jaundice, rifampicin and INH was introduced sequentially, starting with smaller dose and gradually increasing to full dose. All the eight patients tolerated it well as have been reported in other studies[9]. This may be due to fact that disease is controlled to certain extent, the toxaemia become less and hypoxaemia improve, so the patients were able to tolerate these drugs when reintroduced. Same factors may explain the lesser incidence of hepatitis beyond the first two months of ani-tuberculous chemotherapy.

Conclusion

It may be concluded that A.T.T. is generally well tolerated but there is definite risk of drug induced hepatitis which may prove fatal if not detected and dealt earlier. Certain groups of people are more prone to this adverse effect and are needed to be closely watched for. They are:

1. Those more than 35 years of age.
2. Those having extensive (F.A) pulmonary tuberculosis
3. Those having some other complicating factors as COPD, Diabetes Mellitus, corpulmonale in addition to PTB.
4. Those who are malnourished.
5. Those who had taken anti-tuberculous drugs previously.
6. Especially during the initial phase of .A.T.T.

Reference:

1. Girling D.J. (1978) The Hepatic toxicity of anti-tuberculous regimens cotaining isoniazed, refampicin and pyrazinamide Tubercle 59, 13.
2. Davies R.J. Tuberculosis, in Kaumar P, Clark M, eds. Clinical Medicine 3rd edns ELBS with Bialliere Tindall, 1994: 683- 687.
3. Seation A., Seaton D., Leitch A.G. Crofton and Douglas's Respiratory Disease. 4th ed. Blackwell scientific Publications 1989, 426- 427.
4. Stead W.W., Bates J.H, Tuberculosis in Harison's Principles of Internal Medicine 10th ed. McGraw Hill International Book company 1983; 1019-1029.
5. Kallen B.M., Mohinder Sing, Aggarwal N.P., Khanna S.L, Jain R.K. Hepatitis in patients on anti-tuberculous chemotherapy in Proceedings of XV Eastern Regional conference of IUAT & LD Lahore Pakistan 1987; 245-8.
6. Arora V.K. Hepatotoxicty with rifampicin and pyrazinamide containing regimen at moderate altitude (2200 meters) in Himachal Pardesh, India in Proceedings of XV Estern Regional conference of IUAT & LD Lahore Pakistan 1987; 254-7
7. Marang R.K. and Sarin J.N. (1996) Jaundice due to thiacetazone. Ind. J. Tub. 13:77
8. Refsum H.R. (1963) Arterial hypoxaemia serum activities of SGOT, SGPT,, and LDH and centrilobular liver cell necrosis in pulmonary insufficiency. Clin Scc. 25; 369
9. Dienstag J.L,. Wands J.R, Koff R.S. Acute Hepatitis in Harisons Principles of Internal Medicine 10th ed Mc Graw Hill International Book company 1983; 1798-1801
10. Dubey G.R. Shah R.C, Kamat SR et al, A study of efficacy and toxicity of short course chemotherapy with ethambutal, refampicin, pyrazinamide and isoniazid in pulmonary tuberculosis, lung India, 1985, 3; 272-275.
11. Gupta P.R., Purohit S.D,. Sharma TN e t al. Hepatoxicity of isoniazid, refampicin, and pyrazinamide therapy. Lung India 1983, 1; 245-247.
12. Tripathy S.P. Controlled clinical trial of 3 months and 2 months regimens in pulmonary tuberculosis- second Madras short course study. Bull IUAT & LD 1983,58;97-100.