

The Effect of Liv.52 on Liver Functions of Tubercular Patients Receiving Second Line Anti-Tubercular Drugs

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AIMS AND OBJECTS

1. To study the effect of second line anti-tubercular drugs on liver functions.
2. To study the effect of Liv.52 in preventing intolerance or derangement of liver function caused by second line anti-tubercular drugs.

MATERIAL AND METHODS

A total of 81 cases were studied. The cases selected for the study comprised of pulmonary tuberculosis and tubercular meningitis without any clinical or biochemical evidence of liver dysfunction.

All the cases were thoroughly investigated and only established cases of tubercular pathology were taken for the present study. The diagnosis of pulmonary tuberculosis was established by radiological examination of chest and demonstration of acid fast bacilli in the sputum while cases of tubercular meningitis were diagnosed by CSF examination.

Only resistant cases were given second line treatment along with one to two first line anti-tubercular drugs.

The following second line anti-tubercular drugs were used in the present study:

1. Ethionamide 500-750 mg/day.
2. Pyrazinamide 750-1000 mg/day.

The Pyrazinamide was given to the patients during the first 9 months of study and was not used in the last three months.

The cases were divided into two groups.

Group I — Control Group

In this group liver functions tests were done before starting the second line of anti-tubercular treatment. The liver function tests were repeated at intervals of 4 weeks and 8 weeks. Any resultant side effects were noted. No Liv.52 was given to this group.

Group II — Study Group

This group consisted of patients of the same age and sex group as Group I and received similar second line anti-tubercular drugs. The liver function tests were done before and 4 weeks after starting second line anti-tubercular treatment.

Liv.52 two tabs. thrice a day was administered along with second line anti-tubercular treatment in cases showing evidence of G.I.T. (Gastrointestinal tract) deranged liver function tests. After four weeks, liver function tests were repeated and Liv.52 was stopped. The LFT (Liver Function test) were again done 4 weeks later. Cases who then developed gastrointestinal, dermatological or deranged liver functions were again put on Liv.52 two tablets three times a day after four weeks. Liver function tests were again done and results noted.

A battery of liver function tests was done in each case.

1. Serum bilirubin,
2. Van den Bergh reaction,
3. Thymol turbidity, thymol flocculation, zinc sulphate turbidity,
4. Serum proteins and A/G ratio,
5. Prothrombin time,
6. Serum alkaline phosphatase,
7. SGOT and SGPT,
8. Liver biopsy (wherever needed and possible).

OBSERVATIONS

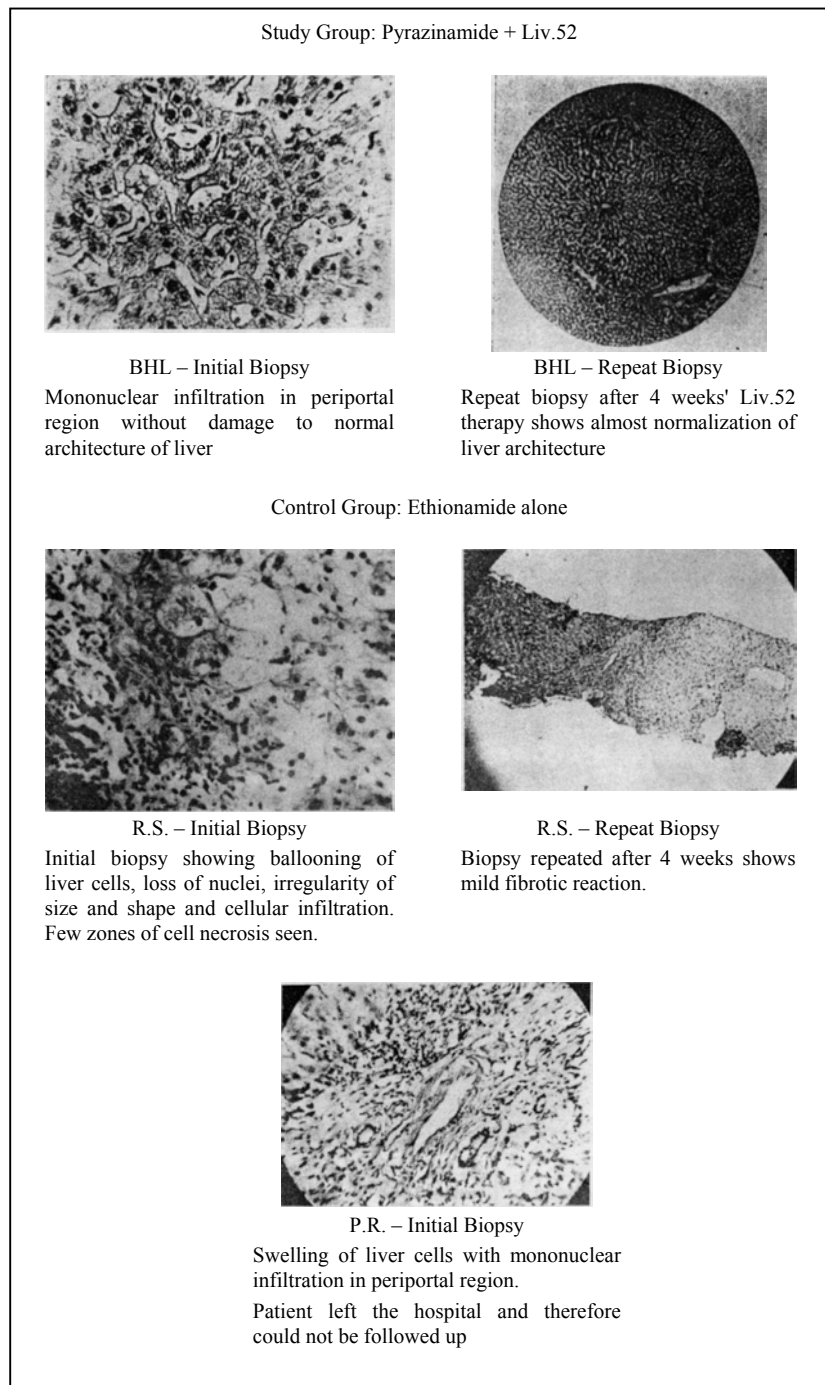
In all, 81 cases were studied. Out of them 32 were kept as control (Group I) and the remaining 49 were in study group (Group II).

Control Group

In the control group, 10 cases were given Pyrazinamide tablets while 22 cases were given Ethionamide tablets.

Out of 22 cases who were included in the Ethionamide tablets.

Out of 22 cases who were included in the Ethionamide group, 13 cases did not show any gastrointestinal disturbances or deterioration of liver function. Out of the remaining 9 cases, 5 cases developed gastrointestinal disturbances in the form of nausea, vomiting and anorexia but liver function tests were within normal limits. The remaining four cases, along with above-mentioned symptoms, developed bad taste, sialorrhoea, stomatitis and derangement of liver function tests as borne out by raised SGOT and SGPT levels, after 8 weeks of second line treatment with Ethionamide. Later, biopsy of 2 cases revealed hepatitis-like changes of varying severity from



cellular infiltration in periportal regions to liver cell necrosis. In one case, repeat liver biopsy after 4 weeks showed increase in cellular infiltration and necrosis and hence Ethionamide was withdrawn.

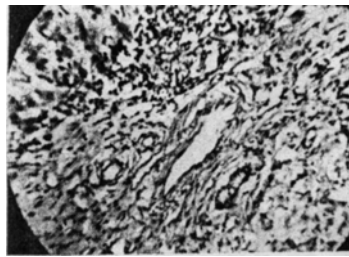
In the Pyrazinamide group, 10 cases were included in the study. Six cases did not show any toxic manifestation of any kind while 3 cases showed gastrointestinal symptoms in the form of anorexia, nausea and metallic taste in the mouth. Only one case showed features of hepatotoxicity as evident from deranged liver functions. Liver biopsy could not be done in this case.

Liv.52 Group

In this study group on Liv.52, out of 49 patients, 37 received Thionamide and 12 received pyrazinamide tablets.

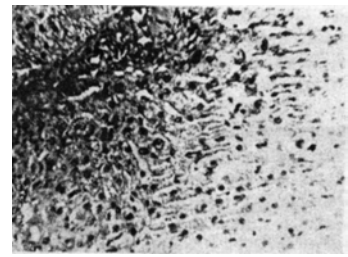
Out of 37 patients who were on Ethionamide therapy, 26 patients did not show any toxic features either gastrointestinal or hepatic, upto 8 weeks. Therefore, these cases were not given Liv.52 therapy. Out of the remaining 11 patients, 6 showed gastrointestinal and dermatological symptoms, including skin rashes. Most of these cases showed toxic manifestations within 4 weeks of starting the anti-tubercular drugs. Besides, these 5 cases showed features of hepato-toxicity; their liver function tests were deranged. The SGOT and SGPT elevations were regarded as the earliest indication of hepato-toxicity. Other causes of raised transaminases were strictly ruled out. Liver biopsy performed in 4 cases out of 5, revealed features of hepatitis. In 2 cases, there was liver cell necrosis of mild to moderate severity while 2 cases showed mononuclear cell infiltration in periportal regions.

Study group: Ethionamide + Liv.52



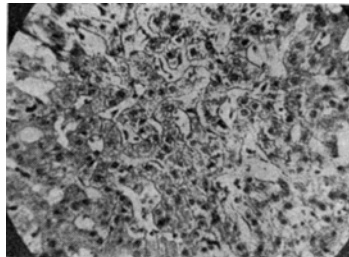
BNL – Initial Biopsy

Biopsy shows few zones of liver cell necrosis with inflammatory changes characterized by mononuclear cell infiltration in periportal region.



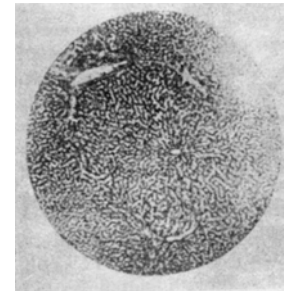
BNL – Repeat Biopsy

Repeat biopsy after 4 weeks shows diminution of infiltration with mild fibrotic reaction.



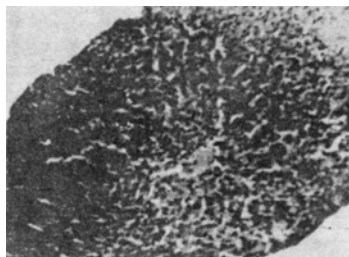
R.R. – Initial Biopsy

Biopsy reveals inflammation of liver cells with cellular infiltration chiefly in periportal region.



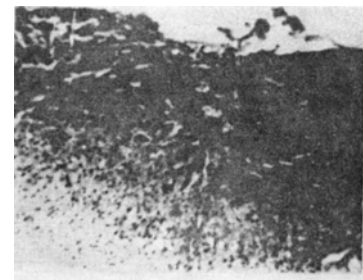
R.R. – Repeat Biopsy

Repeat biopsy after 4 weeks shows normal architecture of liver.



M.S. – Initial Biopsy

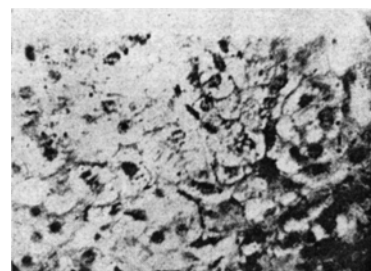
Initial biopsy shows infiltration of periportal areas by mononuclear cells.



M.S. – Repeat Biopsy

Repeat biopsy shows marked reduction of cellular infiltration with few zones of fibrosis also.

Study Group: Ethionamide + Liv.52



B.D. – Initial Biopsy

Initial biopsy shows advanced liver damage with areas of liver cell necrosis and cellular infiltration and loss of normal liver architecture.

Patient left the hospital and could not be

referred for further management.

All the patients showing toxic manifestations, either gastrointestinal or hepatic, were now given Liv.52, 2 tablets three times a day along with Ethionamide tablets. Patients with gastrointestinal symptoms and skin rashes showed marked relief of their symptoms, within 1-2 weeks of starting the Liv.52 tablets. All patients improved except one who developed jaundice. Ethionamide was withdrawn in this case. He was given only Liv.52, following which he improved. Rest of the cases were doing well on Ethionamide + Liv.52 therapy without showing toxic symptoms. When Liv.52 was withdrawn for 4 weeks, all the cases again showed gastrointestinal manifestations. These were again put on Liv.52 therapy and they were again free of their toxic symptoms.

The 4 cases on Ethionamide therapy who showed changes in their liver biopsy were followed up. After 4 weeks of Liv.52 therapy in doses of 2 tabs. t.i.d. biopsy was repeated after 4 weeks in 3 cases. In the 4th case, biopsy was not possible due to his discharge from hospital. In all the 3 cases there was marked reduction of cellular infiltration as compared to previous biopsy and necrosed area was replaced by fibrous tissue in 2 cases while in one case the liver showed more or less normal architecture. In this third case which was followed up, marked reduction of mononuclear infiltration was observed after 4 weeks of Liv.52 therapy. The liver function tests of all these 4 cases returned to normal after 4 weeks of Liv.52 therapy.

Out of 12 cases receiving Pyrazinamide, 7 cases did not show either gastrointestinal disturbance or derangement of liver functions. Out of the remaining 5 cases, 4 cases showed gastrointestinal tract symptoms without deranged liver function tests and one case showed derangement of liver functions. The liver biopsy of this case revealed hepatitis-like changes without any zone of liver cell necrosis.

All those cases showing gastrointestinal symptoms and hepato-toxic features were put on Liv.52 therapy, 2 tabs. three times a day. The gastrointestinal symptoms of 2 patients were relieved within one week of Liv.52 therapy while the third case showed improvement after 2 weeks of Liv.52 therapy. The case showing hepato-toxicity improved within 4 weeks of Liv.52 therapy; his liver function tests became normal and his repeat biopsy after 4 weeks showed normal liver architecture. In only one case on Pyrazinamide therapy, the nausea and vomiting become troublesome in spite of Liv.52 therapy. In this case the drug was withdrawn. In rest of the 4 cases who improved on Liv.52 after 4 weeks, Liv.52 was stopped. In all such cases gastrointestinal symptoms reappeared and they were again put on Liv.52, following which they improved.

Table I: Showing number of cases on Ethionamide and Pyrazinamide in Control and Study Groups

Group	Ethionamide	Pyrazinamide	Total
I (Control)	22	10	32
II (Study)	37	12	81
Total	59	22	81

Table II: Showing incidence of G.I. symptoms and deranged liver function in control cases on Ethionamide and pyrazinamide

Drug	Total no. of cases	GI symptoms	Percentage	Deranged L.F.T.	Percentage
Ethionamide	22	5	22.7	4	18.18
Pyrazinamide	10	3	30.0	1	10.00

Table III: Showing incidence of G.I. symptoms and deranged liver function in study cases on Ethionamide and pyrazinamide					
Drug	Total no. of cases	GI symptoms	Percentage	Deranged L.F.T.	Percentage
Ethionamide	37	6	16.21	5	13.51
Pyrazinamide	12	4	33.33	1	8.33

Table IV: Showing the effect of Liv.52 in doses of 2 t.i.d. in patients developing GI, cutaneous and deranged liver function after Ethionamide and Pyrazinamide in Study Group					
	No. of Pts. With GI symptoms	Patients showing improvement	No. of Pts. With deranged L.F.T.	Patients showing improvement	
				Complete	Partially
Ethionamide	6	6	5	3	2
Pyrazinamide	4	3	1	1	–

SUMMARY AND CONCLUSIONS

The effect of Liv.52 on the liver function of tubercular patients receiving the second line of anti-tubercular drugs, was studied in this project. The study revealed that:

1. Both Ethionamide and Pyrazinamide are hepatotoxic drugs. In the control group 22.7% patients developed gastrointestinal symptoms and 18.18% cases showed hepato-toxicity on Ethionamide therapy. The biopsy of patients showing hepato-toxicity showed hepatitis-like features of mild to moderate severity. Liv.52 was able to reverse or modify these side effects in most cases.
2. In the study group, 16.2% patients developed gastrointestinal disturbances and 13.5% patients developed hepatotoxicity on Ethionamide therapy. Administration of Liv.52 two tabs. three times a day, along with Ethionamide, resulted in improvement in all cases, showing gastrointestinal symptoms and skin rashes. Sixty per cent cases showing hepato-toxicity improved completely with normalisation of liver, histologically, while 40% cases showed partial improvement. In the control group, 30% patients developed gastrointestinal symptoms and 10% developed deranged liver functions after Pyrazinamide therapy. In the study group, 33.3% patients developed gastrointestinal symptoms and 8.3% cases showed hepato-toxicity after Pyrazinamide therapy. The administration of Liv.52, 2 tablets three times a day along with Pyrazinamide in study group resulted in improvement of gastrointestinal symptoms in 75% cases and improvement of liver function test and histological picture in 100% cases.
3. Patients who do not tolerate well Ethionamide or Pyrazinamide therapy and manifest either gastrointestinal upset or deranged liver functions should therefore be put on Liv.52 which results in functional and histological improvement in such cases. In this study emphasis has been laid on histological changes. It is evident that when Liv.52 is given along with Ethionamide or Pyrazinamide therapy, liver damage due to drug toxicity may be prevented. If given at the earliest evidence of liver damage, Liv.52 may normalise liver histologically. Only a few biopsies were possible in this study due to the patients unwillingness for biopsy when they were already in distress due to troublesome gastrointestinal and hepatotoxic symptoms. Thus, the number of liver biopsies was limited in spite of best efforts, specially in the Pyrazinamide group.