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Rifampicin Toxicity and Liv.52

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ABSTRACT
One hundred fresh patients of pulmonary tuberculosis were divided in two groups of 50 each. To Group I, streptomycin, isoniazid, ethambutol and rifampicin were given daily for 30 days, while Group II received Liv.52 in addition to these drugs for one month. In all the patients, the initial and subsequent clinical responses were recorded every week for a period of one month.

Patients on Liv.52 gained weight better than those of the control group. Gastrointestinal disturbances and hepatitis were negligible in the Liv.52 group in comparison with the control group. Serum rifampicin levels in both the groups were equal.

The addition of Liv.52 to the regimen containing rifampicin is helpful in reducing rifampicin-induced side-effects.

INTRODUCTION
Hepatitis is the most frequent side-effect of isoniazid and rifampicin combination. Various workers (Decroiz *et al.,* 1971, Lal *et al.,* 1972, Less *et al.,* 1971 and Purohit *et al.,* 1983) have reported that rifampicin induced hepatitis ranging from 2 to 13% of patients. Purohit *et al.,* (1983) have reported raised alanine amino-transferase (ALT) levels in the 3rd week of rifampicin therapy. Purohit *et al.,* (1986) reported that the addition of Vitamin C to rifampicin may reduce the incidence of rifampicin-induced hepatitis.

Prasad *et al.,* (1976), while studying the protective effect of Liv.52 on degeneration and fibrotic changes produced by CCl_4 could document signs of regeneration of endoplasmic reticulum, mitochondria and also some glycogen granules.

AIMS AND OBJECTIVES
The present study was, therefore, undertaken to assess:

a) The influence of Liv.52 on the incidence of hepatitis in a patient treated with isoniazid and rifampicin, and

b) whether the addition of Liv.52 in any way influences the serum rifampicin levels or not.

MATERIAL AND METHODS
Fresh patients of pulmonary tuberculosis admitted to the Chest Hospital, Jaipur were scrutinised for inclusion in the present study. Patients having cardiac, renal, hepatic and neurological involvement or having a history of alcohol intake were excluded from the study. A total of 100 patients were included in the study and were divided into two groups of 50 each. All the patients were subjected to routine investigations including sputum for A.F.B., X-ray chest, routine haematocrit examination and urine examination.

Serum rifampicin levels were estimated by the method of Sunahara and Hakagug, three times during the study (initial, 15th and 30th day). Patients were closely watched with special reference to

weight gain, sense of well-being and development of any untoward reaction to anti-tubercular drugs.

The development of anorexia, nausea, vomiting, jaundice, fever and malaise were recorded during the therapy. These manifestations were considered as clinical parameters of hepatitis and were followed by enzyme estimations. In situation where suggestive clinical symptoms were associated with abnormal enzyme levels, it was considered as specific of hepatitis and an indication for withdrawal of drugs. Hepatitis was labeled as severe, if it was associated with ALT levels over 125 units.

ALT levels (SGOT and SGPT) were estimated initially and subsequently on the 15th and 30th day. All the patients were randomly put on two regimens:

Group I (50 patients): On SIER (Inj. Streptomycin 0.75 gm I.M., O.D., Tab. INH 300 mg/day, Tab. Ethambutol 20 mg/kg daily, Rifampicin 10–12 mg/kg daily for 30 days).

Group II (50 patients): In addition to SIER, they were given Liv.52, two tablets twice daily for 30 days.

OBSERVATIONS

Sixty-eight males and 32 females were studied. The mean age was 31.3 years (± 6.7) for Group I (Control) and 35.4 years (± 5.7) for Group II (Liv.52) patients ($p<0.05$).

Table 1 shows the initial and subsequent serum rifampicin levels in both the groups. There is a falling trend in the levels if one compares the initial and subsequent readings, but its range was negligible and statistically not significant. While comparing the levels in Group I (Control) and Group II (Liv.52), they were found nearly similar. It appears that the process of enzymatic induction witnessed with rifampicin metabolism is not influenced by the addition of Liv.52.

Table 1: Initial and subsequent serum rifampicin levels in both the groups after 2 hours of rifampicin ingestion (in gm/ml)

Day of estimation	Group I (Control)	Group II (Liv.52)
1st day	8.5 ± 4.2	9.01 ± 5.3
15th day	7.6 ± 4.9	7.4 ± 4.7
30th day	7.1 ± 5.1	7.9 ± 4.5
		$p < 0.05$

Table 2 shows the ALT levels during the one month therapy. After 15 days of rifampicin, 7 patients of Group I (control) had abnormal ALT levels, out of which 3 had specific hepatitis, whereas 4 had signs of non-specific hepatitis.

Table 2: Alanine aminotransferase (ALT) levels recorded initially and during therapy

	Group I (Control)			Group II (Liv.52)		
ALT levels upto (units)	Initial N=50	After 15 days N=50	After 30 days N=50	Initial N=50	After 15 days N=50	After 30 days N=50
40	50	43	45	50	49	50
41-59	–	4	2	–	1	–
60	–	3	3	–	–	–

ALT levels in Group II (Liv.52) were just abnormal in one patient (2%) but termination of rifampicin therapy was not required.

After 30 days, when ALT levels were analysed, 2 patients (4.3%) out of 47 had raised ALT levels in Group I (Control), whereas it was normal in all the 50 patients of Group II (Liv.52).

Table 3 shows the weight gains during the one month therapy. In Group I (Control), the majority of patients, i.e. 36 out of 50 (72%), had gain in weight upto 2 kg, whereas in Group II (Liv.52), the majority of patients, i.e. 34 out of 50 (68%) had gained more than 2 kg weight in the first month. Two patients of Group I (Control) had no weight gain in contrast to nil such patients of Group II (Liv.52).

Table 3: Gain in weight

Gain in weight	Group I (Control)	Group II (Liv.52)
No gain	2	–
Upto 2 kg	36	9
Upto 4 kg	10	34
Upto 6 kg	1	3
Upto 8 kg	1	4

Table 4 shows that in Group I (Control), anorexia and nausea were recorded in 12 and 11 patients respectively, whereas in Group II (Liv.52) only 2 and 1 respectively had these symptoms. In Group II (Liv.52) jaundice, vomiting and pain in the abdomen were not recorded in any case, whereas these symptoms were present in 3 (6%), 9 (18%) and 1 (2%) patients of Group I (Control) respectively.

Table 4: Clinical symptoms related to hepatitis

Symptoms	Group I (Control)	Group II (Liv.52)
Jaundice	3	–
Nausea	11	1
Vomiting	9	–
Anorexia	12	2
Pain in the abdomen	1	–

Note: A few patients had more than one symptom.

DISCUSSION

The initial (1st) and subsequent (15th and 30th day) serum rifampicin levels were similar in both the groups. Though there was a fall in subsequent serum rifampicin levels in all the patients, their differences with the initial values were statistically significant. This fall in the subsequent (15th and 30th day) serum rifampicin levels in both the groups is due to microsomal changes induced by rifampicin [Robert O'Reilly (1975), Buffington *et al.,* (1976) and Skolnick *et al.,* (1976)] and it appears that the addition of Liv.52 does not influence this metabolic aspect of rifampicin.

ALT levels were raised in 7 (14%) patients of Group I (Control) in contrast to 1 (2%) patient in Group II (Liv.52). Why and how ALT levels were within normal limits in the Liv.52 group requires further probing.

Liv.52 has been used in cases of anorexia (Saxena S., 1971) with encouraging results. In our study anorexia was recorded in 4 percent of patients in Group II (Liv.52) in contrast to 24 percent of patients of Group I (Control). A similar high percentage (19%) of gastrointestinal disturbances has been reported by Gupta *et al.,* from the western part of Rajasthan. The better weight gain recorded in Group II (Liv.52) might be related to better appetite induced by Liv.52.

Many workers (Lal *et al.,* 1973 and Purohit *et al.,* 1985) reported rifampicin-induced hepatitis ranging from 2-13%. In our study this was observed in 8 percent of patients in the control group. There was no case of jaundice in Group II (Liv.52) indicating that Liv.52 may protect the liver

against the toxic effects of hepatitis caused by rifampicin. How and at what level this protective property is exerted are yet to be explored. As the side-effects recorded in Group I (Control) were more than those in Group II (Liv.52), one may infer that acceptability of rifampicin is better when it is given with Liv.52.

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