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Liver function tests during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin & pyrazinamide

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Serial liver function tests (aspartate amino transferase–AST, alanine amino transferase–ALT and total bilirubin) were undertaken in patients admitted to controlled clinical trials for the treatment of tuberculous meningitis and pulmonary tuberculosis. In patients with tuberculous meningitis, daily treatment with isoniazid 20 mg/kg in addition to rifampicin 12 mg/kg resulted in a significant increase in the activities of both AST and ALT; there was no appreciable change with regimens containing isoniazid 12 mg/kg. In two studies on pulmonary tuberculosis, there was a significant increase in the activities of both enzymes following 2 or 3 months of treatment with daily streptomycin, isoniazid and pyrazinamide with or without rifampicin. No appreciable differences were observed between patients who received rifampicin and those who did not and also between slow and rapid acetylators of isoniazid. Serum total bilirubin showed a significant decrease following treatment for 2 months with a daily regimen containing rifampicin in patients with tuberculous meningitis and also in those with pulmonary tuberculosis. A comparison of patients who developed jaundice during treatment with anti-tuberculosis drugs and others who had jaundice presumably due to infective hepatitis revealed lower mean values for total bilirubin, AST and ALT in the former group (by 48–64%) than in the latter ($P \leq 0.02$). There was, however, considerable overlap between the two groups in the distributions of all parameters.

A recent report from the Tuberculosis Research Centre (TRC), Madras gave the incidence of hepatitis, nearly always with jaundice, in patients in clinical trials of the treatment of tuberculous meningitis and of pulmonary tuberculosis with regimens containing isoniazid, rifampicin. streptomycin and pyrazinamide[1]. The incidence was high in patients treated with daily regimens containing isoniazid and rifampicin, being 16-39 per cent in children with tuberculous meningitis and 2-8 per cent in those with pulmonary tuberculosis. Further, hepatitis in those receiving rifampicin occurred more often in slow than in rapid acetylators. Liver function tests were undertaken routinely in patients admitted to these studies, and this report presents the findings of these investigations.

Material & Methods

These studies were undertaken in south Indian tuberculous patients usually drawn from the poorest sections of the population of Madras City. Tuberculosis was diagnosed on the basis of clinical and biochemical findings in cerebrospinal fluid in patients with tuberculous meningitis, and on results of direct smear and culture examination of sputum from those with pulmonary tuberculosis.

Children aged 1-12 yr were admitted to the studies on tuberculous meningitis while patients aged 12 yr or more were admitted to the clinical trials on pulmonary tuberculosis.

Studies and regimens :

(i) Tuberculous meningitis–The regimens and dosages of drugs employed during an initial intensive phase of 2 months are listed in Table I. Further, in all studies, the children were treated for 10 more months with daily ethambutol (17.5 mg/kg) and isoniazid (12 mg/kg); patients admitted to study I received, in addition, streptomycin (40 mg/kg) twice weekly from the 3rd to the 6th month. Almost all children received phenobarbitone 3-5 mg for varying periods and all received steroids.

(ii) Pulmonary tuberculosis–The regimens and dosages of drugs employed in the two studies on pulmonary tuberculosis

Table I. Studies, regimens and dosages of drugs

Study no.	Regimen	Description
		TB meningitis
I	2 RSH $(_{high})_7$	R (12 mg/kg), S (40 mg/kg) and H (20 mg/kg) daily for 2 months
	2 RSH_7	——— do ——— but with H 12 mg/kg
II	2 $RSHZ_7$	——— do ——— plus Z 30 mg/kg
III	2 R_2SHZ_7	——— do ——— except that R was given twice weekly
		Pulmonary TB
I	2 $RSHZ_7$/3 SHZ_2	R (12 mg/kg), S (0.75 g), H (400 mg) and Z (40 mg/kg) daily for 2 months followed by S (0.75 g), H (15 mg/kg) and Z (70 mg/kg) twice weekly for 3 months
	2 $RSHZ_7$/5 SHZ_2	——— do ——— except that the twice weekly phase was for 5 months
	2 SHZ_7/5 SHZ_2	——— do ——— but without R
II	3 $RSHZ_7$	R (12 mg/kg), S (0.75 g), H (400 mg) and Z (35 mg/kg) daily for 3 months
	3 $RSHZ_7$/2 SHZ_2	——— do ——— plus S (0.75 g), H (15 mg/kg) and Z (70 mg/kg) twice weekly for 2 months
	3 SHZ_7/2 SHZ_2	——— do ——— but without R

R, rifampicin; S, streptomycin; H, isoniaxid; Z, pyrazinamide

are listed in Table I. Further, half the patients admitted to study I, selected at random, received prednisolone 20 mg thrice a day during the first week; the dose was then tapered off over the next 7 wk.

Determination of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities[2], and serum total bilirubin concentrations[3] was undertaken on admission, at 1 and 2 months and at the end ofchemotherapy in patients with tuberculous meningitis ; and on admission, at the end of the daily phase of treatment and at the end of treatment in those with pulmonary tuberculosis. These tests and the determination of alkaline phosphatase (AP) activity[4] were also undertaken in patients with symptoms suggestive of hepatic toxicity. The acetylator phenotype of patients admitted to study I of pulmonary tuberculosis was determined by methods described earlier[5,6].

The differences between the mean values within each series were tested by t-test (paired), while t-test (unpaired) was employed for testing the differences between the series.

Results

Tuberculous meningitis : The liver function tests on admission and at 1 and 2 months in patients for whom values at all the 3 time points are available are presented in Table II (values at the end of treatment have not been presented due to paucity of numbers; moreover, jaundice occurred almost always during the initial intensive phase of treatment for 2 months when rifampicin was administered as one of the drugs).

There was a significant increase in the activities of both the aminotransferases following daily treatment for 1 month with the 2 RSH (high), regimen ($P \leq 0.04$). There was a slight fall there-

Table II. Liver function tests during treatment in children with tuberculous meningitis

Regimen	Total patients	Geometric mean values in serum according to month of determination								
		AST (Karmen units)			ALT (Karmen units)			Total bilirubin (μmoles/l)*		
		0 month	1 month	2 months	0 month	1 month	2 months	0 month	1 month	2 months
2 RSH $(_{high})_7$	16	21.5	32.4	29.6	12.7	21.6	18.3	–	–	–
2 RSH_7	35–38	22.2	23.3	24.0	6.6	10.5	10.8	6.7	6.8	5.1
2 RSH_7	12–17	29.3	22.4	24.6	8.7	13.0	12.4	6.2	6.8	4.4
2 R_2SHZ_7	52–55	28.3	24.2	28.2	12.6	14.1	16.1	5.1	5.1	5.5

*17.1 μmoles/l = 1 mg/dl

after and the mean values at 2 months were not significantly different from those on admission. The changes in the activities of the two enzymes during 2 months of treatment were minor with the other three regimens. Serum bilirubin concentrations were not determined in patients admitted to the 2 RSH $(high)_7$ regimen; with the other 3 regimens the mean values at 1 month were similar to those on admission. The mean concentrations at 2 months, however. were about 24 and 29 per cent lower than those on admission with the two daily regimens (P=0.02 and 0.08, respectively).

Pulmonary tuberculosis :

Study I–Of the total of 683 patients admitted to the study, test results at all 3 points (0, 2 and 5/7 months) were available in 616; the findings are presented in Table III.

Two months of daily treatment resulted in a significant increase in the activities of both the aminotransferases with all regimens (P<0.001). The mean activities of both enzymes at the end of treatment, while similar to those at the end of the daily phase, were higher than those before start of treatment (P<0.001) for all regimens. At 2 months (end of daily phase), serum AST levels of 40 Karmen units or more were encountered in 32 of 312 rifampicin patients and 18 of 304 non-rifampicin patients (P=0.07), while similarly elevated ALT levels were observed in 13 rifampicin and 5 non-rifampicin patients (P=0.1).

The mean total bilirubin concentration at 2 months was about 15 per cent lower than the pre-treatment value in the rifampicin series (P=0.02); subsequent twice weekly treatment, however, resulted in a significant increase, and the mean value at the end of treatment was about 29 per cent higher than on admission (P<0.001). In the non-rifampicin series, the mean value at 2 months was similar to that on admission; however, the value at the end of treatment was about 32 per cent higher than on admission (P<0.001).

Table III. Liver function tests during treatment in patients with pulmonary tuberculosis-study I

Regimen	Total patients	Geometric mean values in serum according to month of determination								
		AST (Karmen units)			ALT (Karmen units)			Total bilirubin (μmoles/l)		
		0 month	2 months	5/7 months	0 month	2 months	5/7 months	0 month	2 months	5/7 months
2 $RSHZ_7$/3 SHZ_2	159	15.9	21.6	22.4	8.9	12.0	12.3	5.3	4.3	6.7
2 $RSHZ_7$/5 SHZ_2	153	16.4	22.3	20.8	9.0	12.0	11.9	5.1	4.8	6.7
Rifampicin regimens	312	16.1	21.9	21.6	8.9	12.0	12.0	5.2	4.4	6.7
2 SHZ_7/5 SHZ_2	304	15.4	19.6	18.2	8.6	12.1	11.0	5.3	5.5	7.0

The mean serum values of AST, ALT and total bilirubin were similar in the rifampicin and the non-rifampicin patients before start of treatment. At 2 months, the mean total bilirubin concentration was lower (P<0.001) and the mean AST activity higher (P=0.03) in the rifampicin series than in the non-rifampicin series. At the end of treatment, the mean total bilirubin and ALT values were similar in the two groups while the mean AST activity was higher in the rifampicin series than in the non-rifampicin series (P=0.05).

Study II–Three months of daily treatment (results not tabulated) resulted in a significant increase, ranging from 42-80 per cent, in the activities of both aminotransferases with all regimens (P<0.001). The mean values for both the enzymes at 5 months were, however, 25-40 per cent higher than those on admission in both the rifampicin and the non-rifampicin series (P<0.001 for both).

The mean total bilirubin concentration at 3 months was about 14 per cent lower than the pre-treatment value in the rifampicin series (P<0.001) whereas the two values were similar in the non-rifampicin series. Subsequent twice weekly treatment for 2 months resulted in a significant increase ranging from 21-27 per cent in both series, and the mean values at the end of treatment were 8 per cent higher in patients in the 3 $RSHZ_7/2SHZ_2$ regimen (P=0.08) and 14 per cent higher in the non-rifampicin series (P<0.01) than on admission.

Acetylator phenotype and liver function tests : The influence of acetylator phenotype on the hepatic function was also examined in the first study on patients with pulmonary tuberculosis (Table IV). The proportions of slow acetylators among the 312 rifampicin and 304 non-rifampicin patients were 57 and 59 per cent, respectively. The mean activities of AST and ALT were similar in slow and rapid acetyrators in both the rifampicin and the non-rifampicin series at 0, 2 and 5/7 months. In the rifampicin series, the mean serum total bilirubin concentration at 2 months was similar

Table IV. Liver function tests in slow and rapid acetylators of isoniazid

Regimen	Inactivator status	Total patients	Geometric mean values in serum according to month of determination								
			AST (Karmen units)			ALT (Karmen units)			Total bilirubin (µmoles/l)		
			0 month	2 mouths	5/7 months	0 month	2 months	5/7 months	0 month	2 months	5/7 months
Both rifampicin regimens	Slow	177	15.6	22.9	20.7	8.8	13.0	11.2	5.0	5.1	6.5
	Rapid	135	16.8	20.8	22.8	9.1	10.8	13.3	5.5	3.8	6.8
Non-rifampicin regimen	Slow	178	15.5	20.1	19.1	8.3	10.5	13.7	5.1	5.1	6.7
	Rapid	126	15.3	18.9	19.7	9.0	12.4	11.4	5.5	5.6	7.2

to that on admission in slow acetylators; in rapid acetylators, however, the mean value at 2 months was about 31 per cent lower than that on admission (P<0.001). In the non-rifampicin series, the mean values at 2 months were similar to those on admission in both slow and rapid acetylators. Subsequent twice-weekly treatment resulted in an appreciable increase in patients of both phenotypes in both the rifampicin and the non-rifampicin series. At the end of treatment, the mean total bilirubin values were fairly similar in both phenotypes in both the rifampicin and the non-rifampicin series, and 25-31 per cent higher than the respective pre-treatment values (P<0.05).

Comparison between the two groups of hepatitis patients : The liver function tests were also undertaken during episodes of hepatitis. These tests were done only once (on diagnosis) in some patients and more than once in the rest. During approximately the same period as the second study on pulmonary tuberculosis was in progress, a number of staff members or their relatives (who were not receiving any anti-tuberculosis drugs) had liver function tests at the TRC because of jaundice. Assuming that hepatitis in tuberculous patients during treatment is likely to be drug-induced, and that in the other group, it is likely to be infective hepatitis, a comparison of the various liver function tests was undertaken and the means are presented in Table V. In the case of subjects with two or more determinations, the set of values farthest from normal was chosen (the differences were of the same order when the values obtained at the first determination were compared).

The mean total bilirubin concentration was 48 per cent lower in tuberculosis

Table V. Liver function tests in patients with probable infective hepatitis alone and those who developed jaundice while on anti-tuberculosis treatment

Liver function test (serum values)	Geometric mean values	
	Hepatitis with tuberculosis	Infective hepatitis (?)
Total bilirubin (μmoles/l)	37·6 (6·8-379·7)	72.1 (5.1-355.7)
AST (Karmen units)	90 (19-620)	184 (36-890)
ALT (Karmen units)	89 (9-1140)	250 (47-1450)
ALT/AST ratio	0·99 (0·29-2·91)	1.36 (0.28-4.20)
AP (KA units)	12 (4-25)	12 (5-41)
No. of patients	33	25

Figures in parentheses are the ranges

patients who developed jaundice than in those with hepatitis alone (P=0.02). Concentrations of greater than 35 μmoles/I (2 mg/dl) were observed in 18 (55%) of 33 patients in the former and 20 (80%) of 25 patients in the latter. The mean AST value was 51 per cent lower (P<0.01) and the mean ALT value 64 per cent lower (P<0.001) in tuberculosis patients with jaundice than in those with infective hepatitis alone. AST values of greater than 200 units were encountered in 15 and 56 per cent respectively in the two groups (P<0.01), and the proportions of patients with similarly elevated ALT values were 24 and 60 per cent, respectively (P=0.01). The mean ratio of ALT to AST was 0.99 in patients with tuberculosis and jaundice and 1.36 in those with jaundice alone (P=0.05), and the proportion of patients with a ratio of 1 or more was 52 per cent in the former and 76 per cent in the latter (P=0.1). The mean alkaline phosphatase values were the same in the two groups. The proportion of patients with values above normal (≥ 14 KA units) was 37 per cent in tuberculosis patients with jaundice and 48 per cent in those with jaundice alone; values greater than 25 units were observed in 0 and 12 per cent respectively in the two groups (P>0.2).

Discussion

Hepatitis, nearly always with jaundice, occurred fairly frequently during daily treatment with regimens containing rifampicin and isoniazid in our patients, and the incidence was appreciably higher in slow than in rapid acetylators of isoniazid[1]. Hepatitis recurred in only a small proportion of patients when drugs were reintroduced, suggesting that a direct toxic effect and not a hyper-sensitivity mechanism was responsible.[1] Hepatitis during treatment with anti-tuberculosis drugs is also unlikely to be of the cholestatic type as none of the patients who developed hepatitis had a serum alkaline phosphatase value greater than 25 KA units; marked elevation of the activity of this enzyme, depending upon the drug and its dosage, is usually seen in drug-induced cholestatic hepatitis[7].

Two months of daily treatment with regimens containing rifampicin caused a significant decrease in the serum total bilirubin concentrations in patients with pulmonary tuberculosis as well as those with tuberculous meningitis; no such decrease was observed in patients who did not receive this drug. Other worker[8,9] have observed that daily administration of rifampicin caused an initial increase in the serum bilirubin levels followed by a return to normal limits within 7 days when treatment was continued: the initial increase was attributed to the competition between the two compounds for uptake and/or biliary excretion. Rifampicin, like phenobarbitone, is a potent inducer of the hepatic microsomal enzyme system, and phenobarbitone has been shown to cause a decrease in the total bilirubin levels, particularly in infants with neonatal jaundice, by induction of the hepatic glucuronidase which converts free bilirubin to conjugated bilirubin[10]. It is possible that prolonged daily administration of rifampicin exerts a similar effect and that bilirubin is cleared from serum through conjugation and subsequent biliary excretion. The decrease in total bilirubin concentration during rifampicin treatment was, however, observed in only the rapid acetylators of isoniazid; this

is an unexpected finding and it is not known whether isoniazid or any of its metabolites influence the hepatic bilirubin clearance.

A significant increase in the activities of both aminotransferases was observed during the initial stages of treatment; however, the differences between the rifampicin and the non-rifampicin series of patients were minor. The activities of the two enzymes were also similar in slow and rapid acetylators in both the rifampicin and the non-rifampicin series. Lack of difference in the aminotransferase activities between the two phenotypes before, during and at the end of chemotherapy was also observed in an earlier study of the treatment of pulmonary tuberculosis with once-weekly regimens containing streptomycin and a slow-release formulation of isoniazid at our Centre[11], in Singapore patients during treatment with twice weekly and once weekly regimens of isoniazid and rifampicin[12] and in Hong Kong patients during treatment with a twice weekly regimen of isoniazid, streptomycin and pyrazinamide[13]. Hepatitis tended to occur fairly early during treatment in our studies (most occurred within a month of the start of treatment in the second study on pulmonary tuberculosis)[1] and it is possible that the enzyme levels had stabilized by the time their activities were routinely determined, namely at 1 month in patients with tuberculous meningitis and at 2 or 3 months in patients with pulmonary tuberculosis.

Marked elevation of the aminotransferase activities is usually observed in patients with acute jaundice whereas the elevation is less pronounced and varies with the nature of the drug and its dosage in patients with drug-induced hepatitis; moreover, ALT levels usually exceed those of AST in patients with viral hepatitis while the converse has been reported in patients with drug-induced hepatitis[7]. In our studies, the frequency of the occurrence of grossly abnormal values for total bilirubin and the two aminotransferases was greater in patients with jaundice alone than in those with tuberculosis and jaundice, while the proportion of patients with ALT values higher than AST values was only slightly higher in patients with jaundice alone. However, there was *a* considerable overlap between the two groups in the distributions of all the parameters and it was not possible to establish a criterion to distinguish tuberculosis patients with presumed drug-induced hepatitis from those with presumed infective hepatitis alone. In the absence of HBs Ag studies, we could not prove that all the cases of hepatitis that occurred during treatment were due to the toxic effects of the drugs employed, particularly as Madras region in south India is endemic for infective hepatitis. We suggest that. the biochemical tests normally used to assess liver function are not capable of distinguishing between the two groups of hepatitis patients.

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