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INDUCTION OF RIFAMPICIN METABOLISM DURING TREATMENT OF TUBERCULOUS PATIENTS WITH DAILY AND FULLY INTERMITTENT REGIMENS CONTAINING THE DRUG

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Self-induction of rifampicin metabolism during daily and intermittent chemotherapy was studied by monitoring the changes in the serum half-life of the drug over a 4-week period in patients with pulmonary tuberculosis. Rifampicin 450 mg was administered to 8 patients who received treatment daily, 7 on thrice-weekly and 7 others on twice-weekly treatment. Serum half-life was computed from concentrations of the drug determined at 3, 4½ and 6 hours after drug administration, on admission and at 1, 2 and 4 weeks after start of treatment. In the daily series, the mean serum half-life decreased from 4.9 hours on admission to 3.6 hours at 1 week ($P = 0.02$), and treatment beyond this had no further effect. In the thrice-weekly series, maximal induction was observed at the 2nd week, the mean values on admission and at 2 weeks being 5.8 and 3.7 hours, respectively ($P < 0.01$). In the twiceweekly series, maximal induction was observed only at the 4th week, the mean values on admission and at 4 weeks being 4.9 and 3.7 hours, respectively ($P < 0.01$).

Serum activity of gamma glutamyl transferase was not found to be a suitable *in vivo* marker to monitor induction of the hepatic microsomal enzymes as no significant changes were observed in the activity of this enzyme in any of the 3 series during the 4-week period.

Treatment of tuberculosis with fully intermittent short-course regimens containing rifampicin in addition to isoniazid, pyrazinamide and streptomycin has been shown to be as

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Table 1. *Dosages of drugs*

Drugs	Regimens		
	R_7	R_3	R_2
Rifampicin (mg)	450	450	450
Isoniazid (mg)	300	450	600
Ethambutol (mg)	800	1200	1600
Pyrazinamide (g)	1.5	1.5	2.0

6 hours according to the method of Dickinson *et al*[7] employing a strain of *Staphylococcus Aureus* (Sub group I, NCTC 10702) resistant to streptomycin and other antibiotics. Rifampicin standards ranging from 0.04 to 1.28 µg/ml were set up in quadruplicate and the concentrations of the drug in the samples (set up in quadruplicate in dilutions of 1 in 5 and 1 in 10) were obtained from the regression line of the log concentration of the standard on the diameter of the zone of inhibition. Serum activity of GGT was determined in the samples collected at 0 hour employing a standard procedure[8]. All determinations were undertaken after randomizing the samples.

Assuming first order kinetics, the disposition rate constant (K) was calculated from the regression of log rifampicin concentrations in serum on time, and the half-life ($t_{½}$) was obtained from the equation $t_{½} = 0.693/K$.

Student's t-test (paired) was employed for testing the differences between the mean values at the different weeks in each group.

Results

A total of 36 patients (12 each in R_7, R_3 and R_2) were selected for the study. Of them, 3 patients (2 R_7 and 1 R_3) were excluded from analysis due to inadequate chemotherapy (missed more than 10% of their scheduled chemotherapy) or had missed their doses on the occasion prior to the test-day on any of the 4 occasions, and 2 patients (1 R_3 and 1 R_2) were withdrawn from the study on clinical grounds. Further, serum half-life of rifampicin could not be calculated in 9 patients and-were excluded; in 7 of these (3 R_3 and 4 R_2), the peak concentrations were attained at the 6th hour, while there was practically no change in the concentrations at. the 3 time-points in the remaining 2 patients (both R_7). The analysis is, therefore, based on 22 patients (8 R_7, 7 R_3 and 7 R_2). The GGT values and certain pre-treatment disease characteristics such as the radiographic extent of lung lesions and results of sputum smear examination were similar in the exclusions and those retained in the analysis. The mean body-weight of the 22 patients in the analysis was 42 kg (range : 32- 54 kg), and the mean dosages of rifampicin administered were 10.7, 10.7, and 11.3 mg/kg in R_7, R_3 and R_2 series, respectively.

The mean serum rifampicin concentrations at 3, 4½ and 6 hours on admission (0 week)

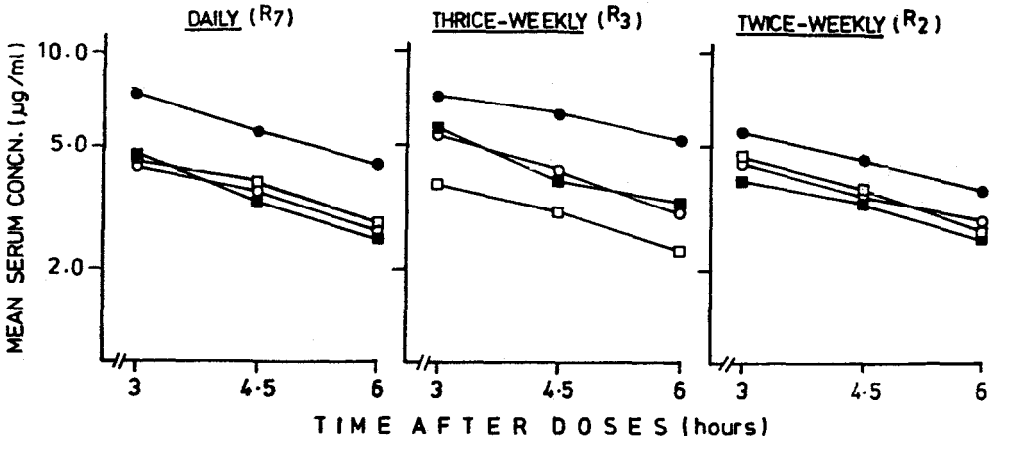

Fig.1. Mean serum rifampicin concentrations at 3, 4½ and 6 hours on admission (● ——●), and 1 week (○——○), 2 weeks (■——■), and 4 weeks (□ ——□) of treatment with daily, thrice-weekly and twice-weekly regimens containing rifampicin

and at 1, 2 and 4 weeks after start of treatment in the 3 groups are presented in figure 1; the mean serum half-lives are presented in table 2.

Table 2. *Serum half-life of rifampicin during treatment with daily, thrice-weekly and mice-weekly regimens containing the drug*

Week	Serum half-life of rifampicin (hours)		
	R_7	R_3	R_2
0	4.9* (2.9-9.8)	5.8 (4.5-7.1)	4.9 (3.1-9.1)
1	3.6 (1.9-6.7)	4.3 (2.4-9.4)	4.8 (3.5-6.3)
2	3.1 (1.9-5.0)	3.7 (2.8-5.1)	4.8 (3.1-8.0)
4	3.1 (1.7-5.7)	4.2 (2.7-8.4)	3.7 (3.0-4.5)
No. of patients	8	7	7

*Geometric mean with the range in parenthesis.

Serum concentrations of rifampicin were highest on admission in all the 3 groups of patients and there was an exponential fall between the 3rd and the 6th hour on all the test days. In the daily series, the mean serum half life of rifampicin at 1 week was significantly lower than that on admission ($P = 0.02$); subsequent treatment had no effect and the means at 1, 2 and 4 weeks were similar ($P > 0.2$). In the thrice-weekly series, the decrease at 1 week was not significant ($P > 0.1$); however, the mean value at 2 weeks was significantly lower than that on admission ($P < 0.01$). Further, thrice-weekly treatment had no effect and the difference in the mean values between the 2nd and the 4th weeks was not significant ($P > 0.2$). In the twice-weekly series, the values at 0, 1 and 2 weeks were similar; the mean value at the 4th week was, however, appreciably lower than those during the preceding weeks ($P < 0.01$).

The mean GGT values (not tabulated) on admission and at the end of 4 weeks of treatment were 33 and 38 IU/L in the R, series, 38 and 25 IU/L in the R_3 series and 37 and 25 IU/L in the R_2 series. The slight increase observed in the daily series and the decreases in the thrice-weekly and the twice-weekly series were not significant ($P > 0.1$ for all).

Discussion

The primary step in the metabolism of rifampicin is hydrolysis to desacetylrifampicin. Serum concentrations of rifampicin were determined by the plate diffusion assay employing *Staph. aureus*[7]. It has been demonstrated that the activity of desacetylrifampicin against this organism is only about 20-25% of that of rifampicin[7], and that the metabolite forms only a small proportion (< 15%) of the total circulating rifampicin in human subjects'. Thus, the changes observed in serum concentrations would almostentirely reflect those of unchanged rifampicin.

Investigations undertaken earlier at this Centre in healthy subjects had shown that the mean serum half-life of rifampicin was 4.9 hours at the start of rifampicin administration and that maximal induction of the metabolism of the drug, and presumably that of the hepatic microsomal enzyme system in general, was attained after 7 daily doses of the drug[5]. Similar findings have been reported by Acocella *et al*[4]. Results reported in this communication show that the maximal induction of rifampicin metabolism was observed after 1 week of treatment (7 doses) in the R_7 series, at 2 weeks (6 doses) in the R_3 series and at 4 weeks (8 doses) in the R_2 series. These findings suggest that maximal induction of the metabolism of this drug is attained with about 6-8 doses of the drug irrespective of the frequency of administration. However, the incidence of hepatitis, attributed to the release of hydrazine following induction of isoniazid hydrolase[3], was substantially higher during daily treatment with a combination of rifampicin and isoniazid than during thrice-weekly or twice-weekly treatment with regimens containing the same drugs[2], and hepatitis tended to occur early on during treatment[2,10]. It is, therefore, possible that occurrence of hepatitis is also related to the speed with which maximal induction of isoniazid hydrolase is attained.

The dosages of isoniazid, pyrazinamide and ethambutol administered to the 3 groups of patients were different for reasons of therapeutic efficacy and toxicity. It has been shown

that isoniazid does not affect the bio-disposition of rifampicin[11,12] and to the best of our knowledge, the effect of pyrazinamide and ethambutol have not been studied so far. It is unlikely that these two compounds will have any effect as they are not known to induce the hepatic microsomal enzyme system, and the pathways of metabolism and excretion are different. Further, all patients admitted to the study (by random allocation) were from the poorest socio-economic strata of the population of Madras City and as such, dietary factors and nutritional status, which could influence the biodisposition of drugs, would not be radically different in the 3 groups. In any case, the effect of the dosages of the companion drugs and dietary factors would be much less than the effect of the induction by rifampicin of the hepatic microsomal enzyme system on the metabolism of the drug.

The changes observed in the serum activities of GGT before and at the end of 4 weeks of treatment were not significant in any of the 3 series. Ohnhaus *et al*[13] also did not observe any significant increase in the GGT activity following 8 daily doses of 1200 mg (2 x 600 mg) of rifampicin, while there was a 7-fold increase in the excretion of 6- β -hydroxycortisol during the same period. It is thus obvious that GGT activity cannot be used to monitor enzyme induction in the hepatocyte during rifampicin treatment and that more sensitive markers such as the urinary excretion of 6- β -hydroqcortisol should be employed for this purpose.

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