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Uric acid disposition during intermittent chemotherapy of pulmonary tuberculosis with regimens containing pyrazinamide & rifampicin

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Uric acid disposition during intermittent chemotherapy of pulmonary tuberculosis was studied in 13 patients allocated to a thrice-weekly regimen containing pyrazinamide in addition to rifampicin, isoniazid and streptomycin and in 19 patients allocated to a twice-weekly regimen of the same four drugs; the dosage of pyrazinamide was 50 mg/kg in the former and 70 mg/kg in the latter. In the thrice-weekly series, the mean serum uric acid concentration ½ h before drug administration at 2 months (5.5 mg/dl) was significantly higher (P< 0.001) than that on admission (3.2 mg/dl); hyperuricaemia (>7 mg/dl) was observed in none of the patients on admission and in 3 at 2 months. In the twice-weekly series, the two values (3.4 and 3.1 mg/dl, respectively) were similar, and none of the patients bad hyperuricaemia. The mean concentrations 5 h after drug administration at 2 months were significantly higher (P< 0.001) than those before drug administration in both the series (6.6 and 4.8 mg/dl, respectively), and hyperuricaemia was observed in 4 patients, all in the thrice weekly series.

The incidence of arthralgia has been reported to be high during treatment of pulmonary tuberculosis patients with regimens containing pyrazinamide which had a daily phase followed by a twice-weekly phase; and the onset in the great majority of patients was during the daily phase[1,2]. In a current clinical study, intermittent regimens containing pyrazinamide during an initial, intensive phase of 2 months are being investigated. Since there is circumstantial evidence implicating altered disposition of uric acid in the development of arthralgia in patients receiving pyrazinamide[3,4], a detailed investigation was undertaken to study these alterations during intermittent chemotherapy; this report presents the findings.

Material & Methods

Treatment regimens : Patients with pulmonary tuberculosis are being allocated at random to one of the following two regimens (during the initial intensive phase of 2 months) in a clinical study currently in progress at our Centre.

$RSHZ_3$: Rifampicin (R), streptomycin (S), isoniazid (H) and pyrazinamide (Z) thrice weekly for 2 months.

$RSHZ_2$: R, S, H and *Z* twice weekly for 2 months.

The dosages are : rifampicin 15 mg/kg body weight, streptomycin 0.75 g, isoniazid 15 mg/kg, and pyrazinamide 50 mg/kg in the $RSHZ_3$ regimen and 70 mg/kg in the $RSHZ_2$ regimen.

The rate of urinary excretion (based on a 1 h urine collection) and serum concentration of uric acid (at the mid-point of the urine collection period) were determined in 13 $RSHZ_3$ and 19 $RSHZ_2$ patients before the start of treatment and before drug administration on the last day of the initial intensive phase of treatment, *i.e.*, at 2 months (all the. patients had received their penultimate dose of drugs). These patients were then administered their scheduled chemotherapy inclusive of pyrazinamide, and the rate of urinary excretion, based on a 4½-5½ h urine collection, and the serum concentration of uric acid at 5 h were determined. None of the patients was receiving any analgesic at the time of the tests, and they were not given beverages (such as coffee or tea) containing methylated purines on the days of the test.

Uric acid concentrations in serum and urine were determined by a phosphotungstate reduction method[5], and hyperuricaemia[6,7] has been defined as a serum concentration greater than 7 mg/dl.

The differences between the mean values within each series were tested by t test (paired), while analysis of co-variance (adjusting for pre-treatment differences) was employed for testing the differences in the mean values at 2 months between the two series.

Results

The mean rates of urinary excretion and the serum concentration of uric acid before the start of treatment and at the end of the initial intensive phase of treatment are presented in the Table.

Table. Uric acid disposition during intermittent chemotherapy

(Data are mean ± SD)

Period of urine collection	Rate of urinary excretion of uric acid (μg/min)		Serum concentrations of uric acid (mg/dl) at mid-point of period	
	$RSHZ_3$	$RSHZ_2$	$RSHZ_3$	$RSHZ_2$
1 h prior to start of chemotherapy	324 ± 201	378 ± 163	3.2 ± 1.0	3.l ± 1.3
At 2 months :				
1 h prior to drug administration	442 ± 190	376 ± 112	5.5 ± 2.1	3.4 ± 1.2
4½ to 5½ h after drug administration	214 ± 96	160 ± 53	6.6 ± 2.0	4.8 ± 1.2

$RSHZ_3$ – Rifampicin, streptomycin, isoniazid and pyrazinamide thrice-weekly for 2 months (13 patients)
$RSHZ_2$ – Rifampicin, streptomycin, isoniazid and pyrazinamide twice-weekly for 2 months (19 patients)

In the thrice-weekly series, the mean rate of urinary excretion of uric acid before drug administration at 2 months (approximately 48 h after the previous dose of drugs) was about 36 per cent higher than that before start of treatment (P=0.07), while in the twice-weekly series (approximately 72 h after the previous dose of drugs), the 2 values were similar. Administration of pyrazinamide caused a significant decrease in the rate of excretion (based on urine collected over the period 4½- 5½ h) in both groups of patients (P<0.01); the decrease was of the order of 55 per cent in each. The mean rate of excretion at 2 months appeared to be higher in the thrice-weekly series than in the twice-weekly series; the difference before drug administration was not significant (P=0.09), and that after administration of drugs just attained statistical significance (P=0.05).

The mean serum uric acid concentration about 4 h before drug administration at 2 months was 72 per cent higher (P<0.001) than the pretreatment value in the thrice-weekly series, while the 2 values were similar in the twice-weekly series. The mean concentration 5 h after drug administration was 20 per cent higher in the thrice-weekly series and 40 per cent higher in the twice weekly series than the respective mean values before drug administration (P<0.001). The mean concentrations in the thrice-weekly series were higher than in the twice-weekly series both before and after drug administration at 2 months (62 and 38%, respectively; P<0.01, for both).

None of the patients in either group had concentrations higher than the 7 mg/dl before start of treatment (Fig.). At 2 months, hyperuricaemia was observed

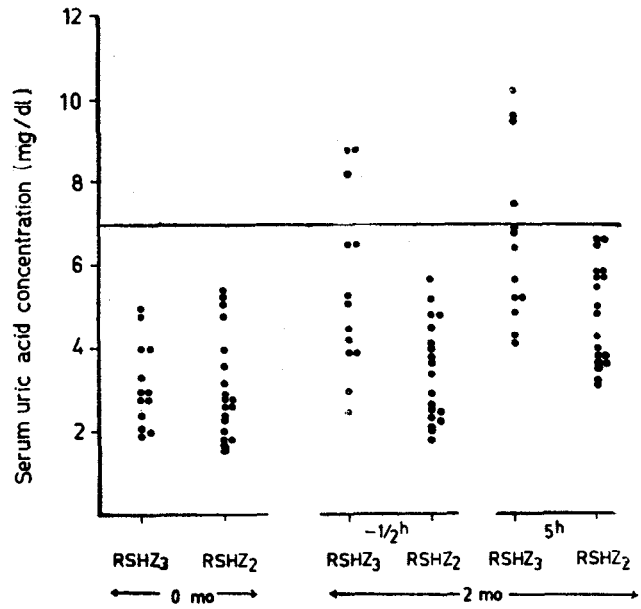

Fig. Distribution of serum uric acid concentrations in 13 $RSHZ_3$ and 19 $RSHZ_2$ patients.

in 3 of 13 $RSHZ_3$ patients and in none of the 19 $RSHZ_2$ patients ½ h before drug administration (P=0.06); the proportions were 4 of 13 and none of 19, respectively 5 h after drug administration (P=0.02).

Discussion

Pyrazinamide is metabolised to pyrazinoic acid by hepatic microsomal pyrazinamide deamidase[8,9], and the latter suppresses urinary excretion of uric acid by inhibiting its tubular secretion[9-12]. This suppression is probably independent of the dosage of pyrazinamide, as investigations undertaken earlier at our Centre (unpublished data based on 20 patients) have shown that the decrease in the rate of excretion of uric acid (based on a 4½-5½ h urine collection after drug administration) with a 70 mg/kg dose (44%) was similar to that with a 35 mg/kg dose (41%).

During daily treatment with regimens containing pyrazinamide 35 mg/kg, uric acid excretion is suppressed for a long duration of time (> 12 h), but returns to normal (pre-treatment) levels by about 24 h after drug administration[13]. Results presented in this paper also show a marked suppression in the urinary excretion of uric acid initially during treatment with intermittent regimens containing pyrazinamide 50 or 70 mg/kg; however, the rate of excretion at approximately 48 h after the previous dose of drugs (in the thrice weekly series) is higher than that on admission, while that at 72 h (in the twice weekly series) is similar to the pre-treatment value. This suggests that after release of inhibition of uric acid excretion, the urinary excretion rate exceeds the normal rate for a period of time to enable the system to eliminate the retained uric acid. When this phase is over (between 48 and 72 h), the excretion rate returns to normal as is seen in the twice-weekly series. These findings are consistent with those of Ellard and Haslam[12] who estimated that urinary excretion of uric acid will be suppressed 80 per cent of the time with daily regimens containing pyraziaamide, 40-50 per cent of the time with thrice-weekly regimens and only 30-40 per cent of the time with twice-weekly regimens.

The mean serum uric acid concentration about ½ h before drug administration 2 months after start of treatment was significantly higher than the pre-treatment value in the thrice-weekly series, while the difference between the two values was not significant in the twice-weekly series. This suggests that the retained uric acid is not completely eliminated by 48 h, and that an interval of at least 3 days between successive doses is necessary to enable the serum concentrations to return to the pre-treatment levels.

Hyperuricaemia was observed in 3 (9%) of 32 patients who received intermittent chemotherapy with regimens containing pyrazinamide and rifampicin for 2 months. In contrast, serum concentrations of greater than 7 mg/dl were observed in 65 per cent of 319 patients during treatment with daily regimens containing the two drugs for 2 months[2]. It is therefore to be expected that arthralgia during treatment with pyrazinamide would be appreciably lower with intermittent regimens than with daily regimens. Since hyperuricaemia during intermittent treatment, either before or at 5 h after drug administration, was not observed in the twice-weekly series, it is also likely that

Occurrence of arthralgia would be less frequent in these patients than in those receiving thrice-weekly treatment. Indeed, preliminary findings in patients admitted to the current clinical study indicate that the incidence of arthralgia during the. initial intensive phase of 2 months is of the order of 10-15 per cent with intermittent regimens, while it was 34 per cent during the same period in patients on daily treatment[2]. There is also a suggestion that arthralgia is more frequently encountered among patients in the thrice-weekly series than among those in the twice-weekly series.

During daily treatment of pulmonary tuberculosis with short-course regimens containing pyrazinamide, it was observed that the incidence of arthralgia was appreciably less in patients who also received rifampicin than in those who did not[1,2]. Rifampicin has been shown to enhance the urinary excretion of uric acid[13], and the serum concentrations of uric acid during daily treatment have been shown to be slightly but significantly lower in patients who received this drug than in those who did not[2]. Both the intermittent regimens employed in the present study contain rifampicin in addition to pyrazinamide, and uric acid disposition with intermittent non-rifampicin regimens has therefore not been studied. It is, however, possible that hyperuricaemia, and consequently arthralgia, could be higher during treatment with fully intermittent short-course regimens which do not contain rifampicin than with those which include this drug.

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