ARTHRALGIA IN SOUTH INDIAN PATIENTS WITH PULMONARY TUBERCULOSIS DURING TREATMENT WITH PYRAZINAMIDE AND RIFAMPICIN

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(Received for publication. May 1984)

ABSTRACT

Arthralgia was the major adverse reaction encountered in a clinical trial of the treatment of pulmonary tuberculosis with three short-course regimens containing pyrazinamide in South Indian patients. The first regimen was of rifampicin, streptomycin, isoniazid and pyrazinamide given daily for three months; the second was of the same four drugs daily for three months followed by streptomycin, isoniazid and pyrazinamide twice-weekly for two months, and the third was the same as the second except that rifampicin was not administered. Arthralgia was reported in 36% of 353 rifampicin patients and 66% of 179 non-rifampicin patients, a highly significant difference ($p<0.001$). The onset of arthralgia was mostly during the first two months of chemotherapy. The knees were affected in about 90% followed by the ankles in about 50% of the patients with arthralgia, and about 60% of these patients had one or more of the signs, swelling, tenderness and limitation of joint movement. Chemotherapy was modified in 10 rifampicin and 15 non-rifampicin patients; the rest of the patients were managed with symptomatic treatment with analgesics. There was a two to three fold increase in serum uric acid concentrations by the end of the first month and the concentrations were more or less stationary throughout the rest of the daily phase of treatment. The mean concentration during the daily phase of treatment in patients with arthralgia (0.482 mmoles/litre) was similar to that in those without arthralgia (0.484 mmoles/litre), while that in the rifampicin patients (0.476 mmoles/litre) was significantly lower ($p=0.03$) than that in the non-rifampicin patients (0.495 mmoles/litre).

Introduction

Arthralgia is a common adverse reaction associated with daily pyrazinamide therapy, especially in South Indian patients (Velu *et al,* 1961[1], 1964[2], Iyer and Srinivasan, 1978[3], Tuberculosis Research Centre, Madras, 1983[4]). This adverse reaction is probably due to the deposition of uric acid in joints caused by hyperuricaemia resulting from an inhibition of the excretion of uric acid by pyrazinoic acid (Cullen *et al,* 1956[5], Yu *et al,* 1957[6], Weiner and Tinker, 1972[7], Fanelli and Weiner, 1973[8], Ellard and Haslam, 1976[9]). a major metabolite of the drug (Weiner and Tinker, 1972[7], Ellard, 1969[10]). Two controlled clinical trials of the treatment of pulmonary tuberculosis with short-course regimens were undertaken in the Centre; the findings of arthralgia during therapy in the first trial were reported earlier (Tuberculosis Research Centre, Madras, 1983[4]). More detailed observations were made during the second trial (Tripathy, 1982[11]) and the findings are now presented.

Materials and Methods

Treatment regimens: Patients with sputum positive pulmonary tuberculosis were allocated at random to one of the following regimens:

R3: Rifampicin plus streptomycin plus isoniazid plus pyrazinamide daily for three months.

R5: The same as R3 followed by streptomycin, isoniazid and pyrazinamide twice-weekly for two months.

Z5: The same as the R5 regimen, but without rifampicin.

The dosages of the drugs during the daily phase were rifampicin 12 mg/kg body-weight, streptomycin 0.75 g, isoniazid 400 mg and pyrazinamide 35 mg/kg; the dosages during the twice-weekly phase were streptomycin 0.75 g, isoniazid 15 mg/kg and pyrazinamide 70 mg/kg.

The patients were not questioned to elicit symptoms of any adverse reactions, but any spontaneous complaint by the patient was followed by careful questioning by a physician, who recorded the full details.

Serum uric acid concentrations

Serum uric acid concentrations were determined by a phosphotungstate reduction method (Henry *et al,* 1957[12]) before the start of treatment, and at monthly intervals till the end of treatment. The determinations were undertaken approximately 24 hours after the previous dose of drugs during the daily phase, and 72-96 hours during the twice-weekly phase.

Results

In all, 532 patients were admitted to the study (173 R3, 180 R5, and 179 Z5). The incidence and the time of onset of arthralgia in these patients are presented in Table-I.

TABLE–1

ONSET OF ARTHRALGIA DURING TREATMENT

Regimen	Total No. of patients	Patients with arthralgia		Occurrence of arthralgia at the following months							
				1 (Daily phase)		2		3		*4-5* (Twice-weekly phase)	
		No.	%	No.	%	No.	%	No.	%	No.	%
R3	173	67	*39*	25	*14*	38	*22*	3	*2*	1*	*1*
R5	180	66	*37*	17	*9*	40	*22*	5	*3*	4	*2*
R3+R5	353	133	*38*	*42*	*12*	78	*22*	8	*2*	5	*1*
Z5	179	118	*66*	49	*27*	60	*34*	7	*4*	2	1

'This patient first complained of arthralgia in the 15th week.

In the great majority of the patients with arthralgia, the onset occurred during the initial daily phase during which the two rifampicin regimens were identical and the results, which were also similar, have been amalgamated subsequently. The proportions of patients who complained of arthralgia were 38% of 353 rifampicin patients and 66% of 179 non-rifampicin patients, a highly significant difference ($p<0.001$). Most of the cases occurred in the first two months, particularly the second, and there were hardly any during the third month or the subsequent twice-weekly phase.

The proportions of the 133 rifampicin patients with arthralgia during the first nine weeks and beyond were 2%, 5%, 6%, 13%, 12%, 19%, 14%, 11%, 9% and 9%, respectively; the proportions of the 118 non-rifampicin patients were 3%, 4%, 7%, 20%, 22%, 18%, 12%, 3%, 5% and 6%, respectively. The over-all proportions in the two groups were similar during the first three weeks, higher in the non-rifampicin patients during the period four to six weeks, and higher in the rifampicin patients during the last three weeks.

Joints involved: The joints most frequently affected (Table–2) were of the lower limbs, the knees being involved in over 90%. the ankles in about 50% and the feet and hips in about 15-20% of the patients.

TABLE-2

JOINTS INVOLVED IN ARTHRALGIA

Joints	Regimen			
	R3 + R5		Z5	
	NO.	%	No.	%
Shoulders	15	*11*	17	*14*
Elbows	22	*17*	17	*14*
Wrists	26	*20*	38	*32*
Hands	32	*24*	46	*39*
Hips	20	*15*	19	*16*
Knees	123	*92*	112	*95*
Ankles	58	*44*	62	*53*
Feet	23	*17*	23	*19*
Vertebrae	2	*2*	3	*3*
No. of patients with arthralgia	133		118	

The upper limbs were less frequently involved, the order of frequency being the hands, the wrists, the elbows and the shoulders, and vertebral involvement was rare. Only one type of joint was affected in 36% of the 133 rifampicin patients and 25% of the 118 non-rifampicin patients, two types of joints were involved in 28% and 29%. and three or more in 36% and 47%. respectively. The joint involvement was bilaterally symmetrical in a great majority of the patients (nearly 98%) in both groups. One or more large joints were affected in 90% of the rifampicin patients and in all the non-rifampicin patients. There was a suggestion that small joints were more frequently affected in the non-rifampicin patients than

in the rifampicin patients, the proportions being 46% and 32%. respectively (p=0.03).

Symptoms and signs: In addition to joint pain, joint swelling was observed in 36% of the rifampicin patients and 47% of the non-rifampicin patients, joint tenderness in 32% and 42%, and limitation of movement in 30% and 36%, respectively. Of the rifampicin patients with arthralgia, 40% had pain only, 33% had one sign in addition, 16% had two signs and 11% had three signs; the corresponding proportions in the non-rifampicin patients were 37%, 25%, 13% and 25%. respectively. The proportion of patients with pain plus three signs was lower in the rifampicin patients than in the non-rifampicin patients (p<0.01).

Management of arthralgia: Details of the management of arthralgia in patients are presented in Table-3.

TABLE-3

MANAGEMENT OF ARTHRALGIA

Action taken	Regimen			
	R3 + R5		Z5	
	No.	%	No.	%
Modification of chemotherapy*				
Interruption	3	*2*	9	*8*
Reduction of dosage	1	*1*	0	*0*
Interruption + reduction	1	*1*	4	*3*
Termination	5	*4*	2	*2*
Total	10	*8*	15	*13*
Analgesics administered				
Aspirin	95	*71*	77	*65*
Oxyphenylbutazone	80	*60*	96	*81*
Phenylbutazone	32	*24*	36	*31*
Ibuprofen	19	*14*	22	*19*
Others	23	*17*	35	*30*
No. of patients with arthralgia	133		118	

*With respect to pyrazinamide administration

The mean duration of arthralgia was 47 days in the rifampicin patients and 54 days in the non-rifampicin patients. It was only in a small proportion of the patients, namely in 10 of 133 rifampicin patients and 15 of 118 non-rifampicin patients that chemotherapy was modified through interruption, reduction or termination of pyrazinamide. In the rest of the patients, arthralgia was managed mainly by the use of analgesics such as aspirin (1.8 g/day), oxyphenylbutazone, phenylbutazone or ibuprofen (300 mg/day), either singly or in combination. The mean duration of treatment with analgesics was 22 days in the rifampicin patients and 26 days in the non-rifampicin patients. A combination of two analgesics to relieve symptoms was used in 18% of the rifampicin and 30% of the non-rifampicin patients (p=0.03); however, the mean duration of such treatment was 11 days in the former and seven days in the latter (p=0.04).

Serum uric acid concentrations: Since the onset of arthralgia was mainly during the daily phase and since rifampicin was also administered only during this phase, comparisons were made of uric acid concentrations on admission and during the daily phase of treatment (Table-4.)

TABLE-4

MEAN SERUM URIC ACID CONCENTRATIONS BEFORE AND DURING DAILY TREATMENT

Group	Total patients	Mean ± S.D. serum uric acid concentrations (mmoles/l)	
		Before treatment	During daily treatment*
Arthralgia[a]	237	0.184 ± 0.062	0.482 ± 0.137
No arthralgia[a]	247	0.197 ± 0.073	0.484 ± 0.134
Rifampicin[b]	319	0.193 ± 0.071	0.476 ± 0.136
No rifampicin[b]	165	0.187 ± 0.062	0.495 ± 0.133

*Mean of determinations at 1, 2 and 3 months

[a]Amalgamating patients in the rifampicin and the non-rifampicin groups

[b]Amalgamating patients with and without arthralgia

The mean values at one, two and three months within each group were similar, the mean concentrations being 0.472, 0.467 and 0.488 mmoles/litre, respectively in the rifampicin patients, and 0.497, 0.490 and 0.497 mmoles/litre, in the non-rifampicin patients; the mean of the three values was therefore taken for subsequent analysis.

There was a two to three fold increase in the serum uric acid concentration during daily treatment with pyrazinamide with or without rifampicin. The differences between the mean concentrations during treatment in patients with and without arthralgia and for those in the rifampicin and the non-rifampicin groups were tested after adjusting for pre-treatment differences in serum uric acid concentrations (by

analysis of co-variance). It was observed that the difference in the mean concentrations between patients with and without arthralgia was not significant (p>0.2); however, the mean concentration in the rifampicin group was significantly lower (p=0.03) than that in the non-rifampicin group.

Of the 247 patients without arthralgia at any time (included in the serum uric acid analysis), 194 belonged to the rifampicin group and 53 to the non-rifampicin group; the mean serum uric acid concentrations during the daily phase of treatment in these two groups were 0.476 and 0.510 mmoles/litre, respectively (p=0.03). Of the 237 patients who had complained of arthralgia, the corresponding mean values in 125 rifampicin and 112 non-rifampicin patients were 0.476 and 0.488 mmoles/litre, respectively (p > 0.2).

The mean serum uric acid concentrations during the twice-weekly phase (not tabulated) were similar in patients with and without arthralgia. and for those in the rifampicin and the non-rifampicin groups, and have been amalgamated; the mean values at four and five months were 0.293 and 0.279 mmoles/litre, respectively. These concentrations, though significantly higher than the pretreatment values (p<0.001), are well within normal limits (0.090 to 0.420 mmoles/ litre), and appreciably lower than those during daily treatment (p<0.001).

Discussion

The incidence of arthralgia in Madras patients on pyrazinamide regimens is high, 38% of 353 rifampicin and 66% of 179 non-rifampicin patients having complained of arthralgia during treatment. It is, therefore, evident that concomitant administration of rifampicin appreciably decreases the incidence of arthralgia. This confirms the findings of an earlier study undertaken at this Centre with short-course regimens containing streptomycin, isoniazid and pyrazinamide with or without rifampicin (Tuberculosis Research Centre, Madras, 1983[4]) where the incidence of arthralgia was 24% of 338 rifampicin patients and 46% of 345 non-rifampicin patients. The arthralgia-sparing effect of rifampicin was also observed by Sharma and others in Jaipur patients where the overall incidence of arthralgia was 16-19% (Sharma *et al.* 1981[13], 1983[14]), but not observed in Hong Kong patients where the incidence was low (Jenner *et al,* 1981[15], Hong Kong Tuberculosis Treatment Services/ British Medical Research Council, 1976[16]).

In the present study, in addition to joint pain, about 60% of patients with arthralgia had one or more of the signs, swelling, tenderness and/or limitation of joint movement. The proportion of patients having all three signs was significantly less in the rifampicin patients, suggesting that rifampicin also decreased the severity of arthralgia.

The onset of arthralgia in most of the patients was during the daily phase, particularly during the first two months, and daily treatment for an additional month did not result in an increase in the incidence; the onset during the intermittent phase was also low

Even though the incidence of arthralgia was high in our patients, modification of treatment such as interruption, reduction of dosage or termination of pyrazinamide was taken in only a small proportion of the patients, namely in 8% of the rifampicin and 13% of the non-rifampicin patients. The other patients with arthralgia continued their normal activities with symptomatic treatment with analgesics such as aspirin (1.8 g/day), oxyphenylbutazone, phenylbutazone or ibuprofen (300 mg/day).

Perusal of serum uric acid concentrations in the individual patients indicated that daily treatment with pyrazinamide, with or without rifampicin, resulted in a two to three fold increase in serum uric acid concentrations, and the values at one, two and three months were very similar. This suggests that serum is saturated at this concentration (approximately 0.48-0.50 mmoles/litre) and the retained uric acid is probably deposited in the joints leading to arthralgia. Susceptibility to arthralgia might, however, depend upon certain other factors such as the concentration of the urate-binding protein in the individual patients.

No association was observed between arthralgia and serum uric acid concentrations determined approximately 24 hours after drug administration-a finding similar to that reported earlier from this Centre (Tuberculosis Research Centre, Madras, 19834) and by other investigators (Jenner *et al* 1981 [15], Horsfall *et al,* 1979[17]). It has been demonstrated that the rate of urinary excretion of uric acid returns to pretreatment levels by about 24 hours after a dose of pyrazinamide 35 mg/kg (Raghupati Sarma *et al,* 1983[18]); this, however, is not reflected in the serum concentrations possibly on account of the dynamic equilibrium existing between the serum levels and the deposited uric acid. Serum concentrations would return to normal only after the tissue deposits are mobilized and depleted.

Administration of rifampicin has caused an appreciable decrease in the incidence of arthralgia, the

mean serum uric acid concentrations during the daily phase of treatment being slightly, but significantly less in patients receiving rifampicin, confirming findings of an earlier study in our Centre (Tuberculosis Research Centre, Madras, 1983[4]). In that study the mean serum uric acid concentrations before and at the end of daily treatment (two months) in 324 rifampicin patients were 0.185 and 0.461 mmoles/litre, and those in 333 non-rifampicin patients were 0.177 and 0.482 mmoles/litre, respectively; the difference in the mean concentrations at the end of the daily phase of treatment between the two groups (after adjusting for pre-treatment differences in serum uric acid concentrations) was significant (p=0.02). The slight difference observed in both studies is probably due to the effect of rifampicin in enhancing the urinary excretion of both uric acid (by about 25%) and pyrazinoic acid (by about 16%) (Raghupati Sarma *et al,* 1983[18]). This could lead to a lower deposition of uric acid in joints with consequent lowering of arthralgia in patients receiving this drug.

The joints most frequently affected during pyrazinamide arthralgia in South Indian patients are large weight-bearing joints nearly always the knees and frequently the ankles. In Hong Kong patients with arthralgia during pyrazinamide treatment, the large joints were also more frequently affected than the small ones; however, the joint most commonly affected (72%) were the shoulders (Horsfall *et al,* 1979[17]). In both studies, the involvement of small joints was infrequent and there was simultaneous involvement of two or more types of joints in about 60-70% of the patients. In contrast, in gout, which is another metabolic disorder caused by high levels of circulating uric acid, the joints most commonly affected are the small ones like the toes (76%). and simultaneous involvement of two or more joints (11%) is uncommon (Grahame and Scott, 1970[19]). There is only circumstantial evidence to implicate hyperuricaemia in arthralgia during pyrazinamide therapy and as pointed out by Horsfall and others (1979[17]), on account of the differences in the types of joints affected between pyrazinamide arthralgia and gout, it is possible that different mechanisms may be operative in the two disorders.

Studies carried out in certain other parts of India and in other countries show an interesting geographical variation in the incidence of pyrazinamide arthralgia. Thus, in South India the incidence is high, 67% of 45 patients from Trivandrum (lyer and Srinivasan, 1976[3]), and 61% of 376 patients in Bangalore (unpublished findings) had arthralgia. In Madras patients, Velu and others in two retreatment studies (1961[1], 1964[2]) with pyrazinamide-containing regimens have reported an incidence of 24% in 103 patients. In an earlier short-course regimen study undertaken at this Centre (Tuberculosis Research Centre, Madras. 1983[4]), the incidence was 24% of 338 rifampicin patients and 46% of 345 non-rifampicin patients; in the present report, 38% of 353 rifampicin patients and 66% of 179 non-rifampicin patients complained of arthralgia. In North India, the proportions have been reported to be 10% of 146 patients in Agra (Mehrotra *et al,* 1981[20]), 13% of 60 patients in Delhi (Tuberculosis Association of India, 1980[21]), and 16-19% of a total of 307 patients in Jaipur (Sharma *et al.* 1981[13], 1983[14]). In Hong Kong 7% of 174 patients (Hong Kong Tuberculosis Treatment Services/British Medical Research Council, 1976[16]), in Singapore 4% of 397 patients (Singapore Tuberculosis Service/British Medical Research Council, 1981[22]), in East Africa 1% of 693 patients (East African/British Medical Research Councils Study, 1981[23]) and in Poland none of 119 patients (Zierski and Bek, 1980[24]) complained of arthralgia during pyrazinamide therapy. In Britain, of a total of 334 patients (approximately a fifth of whom were probably of Indian subcontinent origin) who received pyrazinamide daily for two months, arthralgia occurred in only two patients, one of whom was probably of subcontinent origin (British Thoracic Association, 1981[25]). It is unlikely that subjective errors in the diagnosis of arthralgia could entirely account for the large geographical variation observed. Whether this variation is due to genetic, nutritional or some other factors remains to be determined.

Acknowledgements

The authors thank the medical and nursing staff and the social workers of the Centre for their enthusiastic cooperation, Professor Wallace Fox and Mr. P. R. Somasundaram for their helpful comments, Mr. K. Jayashankar for technical assistance, and Mr. A.S.A. Mahadevan and Miss S. Martyn for secretarial assistance.

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