



Original Research Article

Serum uric acid estimation and arthralgia in patient receiving regimen containing pyrazinamide

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ABSTRACT

Aim: To demonstrate hyperuricemia and arthralgia in patient receiving ATT containing Pyrazinamide**Materials and Methods:** This study was carried out in tertiary health care center. 91 patients diagnosed to have Tuberculosis- both Pulmonary and Extra pulmonary was taken for study.**Results:** Total number of patients estimated for Uric acid is 91, (male-55, female-36). In this study hyperuricemia was found in 33 males (out of 55) and 25 females (out of 36) arthralgia male 9 positive (out of 55) and female 10 (out of 36).**Conclusion:** Pyrazinamide therapy is associated with hyperuricemia and arthralgia. Hyperuricemia and arthralgia are not synonymous.© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

Pyrazinamide was normally reserve regimen drug used for the treatment of patient who has failed as p[primary chemotherapy. Today Pyrazinamide is at the forefront of the chemotherapeutic armamentarium along with Rifampicin and INH as one of the pillars of SCC. A not infrequent reaction to Pyrazinamide is hyperuricemia and arthralgia which is probably due to inhibition of renal excretion of uric acid. However the exact mechanism of arthralgia is yet to be established on firmer grounds. The current study was undertaken to determine the incidence of hyperuricemia and arthralgia in regimens containing Pyrazinamide.¹⁻⁶

2. Materials and Methods

This study was carried out in patients attending the tertiary health care center. 91 patients diagnosed to have Tuberculosis both Pulmonary and extra Pulmonary were taken up for the study. This included sputum positive and

sputum negative Pulmonary Tuberculosis patients. Patients with Pleural effusion and Tuberculosis lymphadenopathy were also part of the study. S. Uric acid levels were estimated for all patients by Phosphotungstate method before treatment and at the end of 2 months.

2.1. Procedure for estimating serum uric acid by phosphotungstate method

PRINCIPLE: Uric acid in alkaline medium reduces phosphotungstic acid into Tungsten blue, a blue coloured complex which is measured calorimetrically.

2.2. Preparation of standard solution

50ML of distilled water is taken and 0.5ml of stock uric acid standard is added and mixed well. All other reagents are ready for use 3ml is taken from this and to this 1ml of sodium carbonate and 1ml of phosphotungstate are added. After waiting for 15 minutes, reading is noted on the colorimeter.^{7,8}

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2.3. Deproteinization of the sample: Step A

1ml of serum is taken in a centrifuge tube; 8ml of distilled water is added followed by 0.5ml of 2/3N sulphuric acid and 0.5ml of 10% W/v sodium tungstate wait for ten minutes. Then it is centrifuged for ten minutes till white precipitate completely separates.

2.4. Colour development: Step B

3ml of the above supernatant liquid is taken and to this 1ml of 14% W/v sodium carbonate and 1ml of phosphotungstate are added, mixed well and kept for 15 minutes in dark. The reading is then taken calorimetrically.

Calculation of serum Uric Acid in mg/100ml

$$\text{Normal Value} = \frac{O.D \text{ Test} - O.D \text{ Blank}}{O.D \text{ Std} - O.D \text{ Blank}} \times 10$$

Men = 2.5 – 7 mg/100ml

Women = 1.5 – 6 mg/100ml

1. Serum should be free from any hemolysis
2. Use clean and dry glassware.
3. Bring all the solution to Room temperature before use.
4. Prepare a blank and standard for each series of determinations.
5. Mark the test tubes properly as Blank (B), standard (S) and test (T) before proceeding for estimation.

3. Discussion

The incidence of hyperuricemia and arthralgia observed in the Pyrazinamide containing regimens was similar to those observed by other workers. The overall incidence of arthralgia in the various studies varies from nil (Zierski and Bek 1980) to as high as 67% has been reported by Iyer and Sreenivasan 1978. Tolerance of Pyrazinamide in SCC for Pulmonary tuberculosis in children (upto 15 years). This prospective study from Dept. of Paediatrics, Hospital Infantil la paz, Madrid, Spain (1985-95). Studies showed increased S. Uric acid in 92.2% of children (total of 114 children) and significant fell again one month after Pyrazinamide stopped. There was no sign of arthralgia.^{9–12}

Year	Worker	Hyperuricemia	Arthralgia
1981	Sharma et al	43%	16%
1978	Iyer and Sreenivasan	70%	67%
1961	Velu et al	58%	24%
1983	Tuberculosis Research Centre	69%	24%
1981	Malhotra et al	72%	10%
1980	TB Association of India	70%	13%
1981	Singapore / BMRC	49%	1%
1980	Ziierki and Bek	60%	0%

4. Conclusion

The addition of Pyrazinamide in chemotherapy for Pulmonary Tuberculosis in children was found to be safe.

Renal excretion of uric acid is suppressed by Pyrazinamide being less than 40% at first hours. The excretion of uric acid increases thereafter and returns to pre-treatment value at 24 hours. The serum concentration shows little or no change suggesting that the serum is probably saturated at this concentration and any further uric acid must be deposited in the joints or eliminated by uricolysis. The sustained level of uric acid increases at 24 hours after drug administration despite the urinary excretion returning to the pre-treatment levels may be due to the dynamic equilibrium between the deposited uric acid and the Serum uric acid by mobilising uric acid from tissues and this could be responsible for the lack of association between arthralgia and serum uric acid concentration.

Joint involved	No. of cases
Knee JT	13
Ankle JT	2
Multiple JT	4

In the present study the incidence of hyperuricemia and arthralgia with pyrazinamide therapy was 63.7% (58 out of 91) and 20.8% (19 out of 91) respectively. The onset of arthralgia was within 15 days of starting therapy in the majority of cases. However none of the patient had to be discontinuing treatment because of arthralgia. In this study all of the arthralgic patients were hyperuricemic. However 1/3 rd of hyperuricemics had arthralgia indicating that hyperuricemia and arthralgia were not synonymous. In other words hyperuricemia associated with Pyrazinamide was mostly asymptomatic. It was also noticed that there was a statistically significant reduction in the incidence of hyperuricemia with advancing age.

Further work on this association is indicated there was no correlation between the degree of hyperuricemia and severity of arthralgia symptoms. There was no incidence of acute Gout in our study. There was no relationship between the dosage of Pyrazinamide and development of hyperuricemia and arthralgia. Hyperuricemia and arthralgia had no statistically significant association with sex. Multiple joint involvements were seen in 4 cases. There was no involvement of small joint in our study. In contrast in gout involvement of small joints like toes is usual and simultaneous involvement of 2 or more joints is uncommon. There is only circumstantial evidence to implicate hyperuricemia in Pyrazinamide arthropathy. As pointed out of Horse fall et al on account of difference in the types of joints involved between Pyrazinamide arthropathy and Gout it is possible that different mechanisms may be operative in the two diseases. The reduction of arthralgia was purely a subjective phenomenon. No leading questions

Table 1: Age distribution of regimen containing pyrazinamide and also hyperuricemia and arthralgia

Age of pt	Total no of pts	Regimen		Hyperuricemia		Arthralgia	
		Hrez (50)	Hre(41)	Positive	Negative	Positive	Negative
12-20	14	6	8	12	2	3	11
21-30	19	12	7	17	2	6	13
31-40	18	11	7	14	4	4	14
41-50	16	9	7	8	8	4	12
51-60	16	8	8	5	1	1	15
>60	8	5	3	2	6	1	7

Youngest patient was 12 and the oldest patient was 70yrs

Total number of patients- 91

were asked and any spontaneous complaint was noted followed by examination of the affected joint. This could depend on various factors like patient's willingness to be forthcoming with his problems, awareness of the patient.

Table 2: Percentage of hyperuricemia and arthralgia for all 91 patients receiving pyrazinamide

Regimen	Hyperuricemia		Arthralgia	
	Positive	Negative	Positive	Negative
HREZ (50pts)	32(64%)	18(36%)	10(20%)	40(80%)
HRZ (41pts)	26(63.4%)	15(36.6%)	9(21.9%)	32(78.1%)
Total (91pts)	58 (63.7%)	33(36.3%)	19(20.8%)	72(79.2%)

Total number of patients -91 in this hyperuricemia positive -58 (63.7%)
arthralgia positive-19(20.8%)

Table 3: Sex distribution of regimen containing pyrazinamide

Regimen	Sex	
	Male	Female
HREZ	30	20
HRZ	25	16

Total patients-91 male-55 female- 36

Table 4: Sex distribution of hyperuricemia and arthralgia due to pyrazinamide

Sex	Hyperuricemia		Arthralgia	
	Positive	Negative	Positive	Negative
Male (55pts)	33(61%)	22(39%)	9(17%)	46(83%)
Female (36pts)	25(69%)	11(39%)	10(27%)	26(73%)

In contrast to the weight bearing joints like knee it which was involved in our study. Finally as far as the incidence of arthralgia is concerned it is unlikely that subjective error in the diagnosis of arthralgia would entirely account for the large geographical variation observed. Whether this is due to genetic, nutritional or some other factor remains to be determined. The susceptibility to arthralgia might depend on factors like concentration of urate binding proteins in individuals.

5. Result of the study

As shown in the above table 61 % of male and 69 % of female were hyperuricemic. There was no statistically significant association between incidence of hyperuricemia, sex and Pyrazinamide therapy.

17 % of male, 27 % of female had arthralgia, again no statistically significant association was found.

6. Conclusions

From the study we have arrived at the following conclusions.

1. Pyrazinamide therapy is associated with hyperuricemia
In our study out of 91 which 58 (63.7%) were hyperuricemia
2. Hyperuricemia and arthralgia are not synonymous
In our study out of 91 patients 19 (20.8%) only arthralgic not only hyperuricemic patients also normouricemic present with arthralgia. Age, sex and those of drug not related to arthralgia
3. Pyrazinamide induced hyperuricemia is not related to sex or dosage but is related to age which is statistically significant.
In our study compared to older age group. Younger age is more susceptible to hyperuricemia . age 12-40 (84%)
age 41-70 (35%).

7. Source of Funding

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8. Conflict of Interest

The authors declare they have no conflict of interest.

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