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Effect of Pyrazinamide induced Hyperuricemia on Patient Compliance undergoing DOTS Therapy for Tuberculosis.

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ABSTRACT

Hyperuricemia, with or without arthralgia, is the main adverse effects of pyrazinamide, a first line anti-TB drug. Hyperuricemia may lead to non-compliance to therapy, monitoring of uric acid and symptoms of arthralgia are necessary for patient compliance. A prospective open study was conducted on patients diagnosed with TB and were initiated with intensive phase of anti-tubercular treatment. Blood was withdrawn at 0, 2, and at 8th week to estimate serum uric acid level. Arthralgia was assessed and recorded during the same period. Uric acid levels were increased by the end of 2nd week. The observed mean serum uric acid at 0th week was 5.1 mg/dl which increased to 6.8 mg/dl and 6.6 mg/dl at 2nd and 8th week, respectively. 48.72% patients showed 25-50% increase in the uric acid level. 41.02% patients showed an increase in serum uric acid level beyond normal range (>7 mg/dl) and increased uric acid levels in 41.02% patients from 2nd and 8th week was non-significant. Despite an increase in serum uric acid levels beyond the normal range, arthralgia was not seen in TB patients who were on DOTS. thus, it is concluded that thrice weekly regimen of pyrazinamide is safe and effective therapy for treatment of TB.

INTRODUCTION

Tuberculosis is a major health problem in developing countries. About 1/3rd of world's population is infected with *Mycobacterium tuberculosis*[1]. it is apprehended that unless urgent action is taken more than 15 million people worldwide[2], including more than 4 million in India will die from tuberculosis (TB) in the 1st decade of 21st century (WHO, 2000). As per ICMR (2001) estimate more than 40% adults in India are infected with TB; nearly 2 million people develop active disease every year and about 0.5 million die from it[3]. TB has been declared a public health emergency by WHO and if TB controls are not strengthened, the WHO estimates that by 2020 more than 70 million people will die from TB [4].

Revised National Tuberculosis Control Programme (RNTCP) was launched in 1993 with aims to achieve 85% cure rate of TB patient by the application of DOTS (Directly Observed Treatment, Short course chemotherapy). As per DOTS therapy the standard regimen for TB patient is 6-9 months therapy, which is divided into intensive phase and continuation phase, intensive phase involves the use of Rifampin, Isoniazid, Ethambutol and Pyrazinamide, for two months and continuation phase involves use of Isoniazid and Rifampin for 4 months[2]. Pyrazinamide is a first line anti-TB drug. It is bactericidal in action. Its inclusion in the intensive phase significantly improves sputum conversion rates[5].

One of the main adverse effects of pyrazinamide is hyperuricemia with or without arthralgia. Hyperuricemia during therapy with pyrazinamide is due to inhibition of uric acid excretion by pyrazinoic acid, the main metabolite of pyrazinamide[6]. When pyrazinamide was used in 2-3 gm/day doses, a higher incidence of hyperuricemia and arthralgia was reported[7-9]. The incidence of elevated serum concentration of uric acid for patients receiving rifampicin, isoniazid and pyrazinamide was 52.2% at 8 weeks while the incidence for patients receiving rifampicin and isoniazid was 5.4%. Arthralgia was reported in 6 patients compared to none on non pyrazinamide treatment

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regimen. If hyperuricemia accompanied by an acute gout arthritis occurs without hepatic damage causing liver dysfunction, pyrazinamide should excluded from treatment regimen[10,11].

Hyperuricemia is a side effect associated with or without arthralgia, articular pain and swelling[12]. As this may lead to non-compliance, monitoring of uric acid and symptoms is required. Thus, the present study is proposed to study the hyperuricemic effect of pyrazinamide in TB patients in India at St. Martha's Hospital, Bangalore and to document any symptoms of hyperuricemia like arthralgia or gout, when given in a dose of 1.5 gm/day thrice weekly. Uric acid levels of the patients with TB on intensive phase of DOTS therapy, were measured prior to pyrazinamide therapy and at 2nd and 8th week of after introduction and at completion of pyrazinamide therapy, respectively. Documentation of symptoms of hyperuricemia like arthralgia during the therapy.

MATERIALS AND METHODS

Ethical committee clearance was obtained from Institutional Ethical Review Board, St. Martha's hospital.

Duration of study

Subjects were recruited for 6 months.

Source of data

Data was obtained from prospective series of patients who were started with anti-tubercular treatment after adequate diagnosis of TB at St. Martha's Hospital. Informed consent was taken from the patients.

Study Design

Prospective observational single patient group study where all patients are treated with the same drug through the study period

Study criteria

Inclusion criteria

- All in-patients diagnosed with TB admitted to medicine department, and started on intensive phase anti-tubercular treatment as St. Martha's Hospital, Bangalore.
- The TB patients who are prescribed pyrazinamide.

Exclusion criteria

- Patients with hepatic or renal dysfunction and gouty arthritis
- Patients who are hypersensitive to pyrazinamide.
- Patients who is not willing to give informed consent.

Method of Data Collection

- Patients who were diagnosed with TB (both pulmonary as well as extra pulmonary) and who were prescribed pyrazinamide in their regimen were selected for the study.
- Informed consent was obtained and detailed history was taken for all the patients enrolled in the study.
- Blood was withdrawn to check the uric acid levels at week '0', along with SGOT, SGPT and Liver enzymes.
- Pyrazinamide therapy was started
- Blood was withdrawn for determining uric acid levels at week 2, after introduction and at week 8, during completion of pyrazinamide therapy, respectively.
- Patients were observed and asked for any symptoms of arthralgia with the help of questionnaire[14].

Methodology for the assessment of uric acid level

Abnormal serum uric acid level was estimated by enzymatic colorimetric method. Unhemolyzed serum is mixed with uric acid reagent, incubated for 5 mins at 37°c. uric acid is converted by uricase into allontion and hydrogen peroxide, which in presence of peroxidase, oxidizes the chromogen (4-aminophenazone/3-hydroxy, 2,4,6-tribromo benzoic acid) to a red colored compound Quinoneimine. The intensity of Quinoneimine formed is

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proportional to the uric acid concentration in the sample. Absorbance of standard and each test was measured at 505 nm or 505/670 nm on bichromatic analyzers against reagent blank[15].

RESULTS

During the 6 months study, 39 consecutive TB patients receiving pyrazinamide in medicine department of St. Martha's hospital were enrolled as per the inclusion criteria. Out of total TB patients, 66.66% were male and 33.33% were female patients. The age of patients enrolled in the study ranged from 15-75 years with the mean of 35.38 year. Majority of the patients, 74.37% of patients belonged to the age group of 15-45 years and remaining 25.63% belonged to the age group of 46-75 years. the weight of patients ranged from 25-85 kg, majority of the patients 79.50% belonged to the weight range of 36-65 kg and 10.25% belonged to the weight range of 56-85 kg. Patients are also divided on the basis of type of TB. Pulmonary Koch's was found to be the most common type of TB which was seen in 46.16% patients. Other forms of TB included are cervical lymphadenopathy, granulomatous ascending colon TB, TB meningitis, miliary Koch's, cutaneous TB, abdominal Koch's and pleural effusion, which were in the percentage of 20.52%, 2.56%, 5.13%, 7.69%, 2.56%, 12.56% and 12.82% respectively.

1. **Percentage increase at 2nd week after introduction of pyrazinamide therapy is categorized into three divisions:**

    a. **Increase in serum uric acid level (0-25%):** 0-25% increase in serum uric acid level was observed in 33.34% patients. Out of which 76.92% were male and 23.08% were female patients. Mean age was 36.72 years, majority of the patients 76.93% belonged to the age group of 15-45 years, and 23.07% patients belonged to age group of 46-75 years. The mean weight was 37.69 kg, majority of patients 61.54% belonged to the weight range of 36-55 kg, and remaining 7.69% and 30.77% belonged to 25-35 kg and 56-85 kg respectively.

    b. **Increase in serum uric acid level (25%-50%):** Majority of the patients 48.72% showed 25-50% increased uric acid levels, out of which 57.89% male and 42.11% female. Mean age was 32.63 years, most of the patients 78.94% belonged to the age group of 15-45 years, 15.79% and 21.04% belonged to 25-35 and 46-65 years respectively. The mean weight was 48.42 kg, majority of patients 78.95% belonged to the weight range of 36-55 kg, and remaining 15.79% and 5.26% belonged to 25-35 kg and 65-75 kg.

    c. **Increase in serum uric acid level (>50%):** More than 50% increase was observed in 17.94%, out of which 71.42% were male and 28.57% were female patients. All the patients with mean age of 40 years (15-65) and mean weight of 50 kg (36-65), showed more than 50% increase in uric acid level.

2. **Increase in serum uric acid level beyond the normal range(>7 mg/dl) at 2nd week:** Of the total subjects, 41.02% showed an increase in serum uric acid level beyond normal range (>7 mg/dl) out of which 75% were male and 25% female patients. Mean age was 30.62 years, majority of the patients 93.75% belonged to the age group of 15-45 years, 6.25% belonged to 56-65 years. The mean weight was 50.62 kg, elevation in serum uric acid level above normal range occurred in all weight range from 25-85 kg. Majority of patients 75% belonged to the weight range of 36-65 kg, and remaining weight range between 25-35 kg and 66-85 kg showed 12.5% each (see table 1).

3. **Increase in serum uric acid level beyond the normal range(>7 mg/dl) at 8th week:** Of the total subjects, 33.33% showed an increase in serum uric acid level beyond normal range, out of which 76.93% were male and 23.08% female patients. Mean age was 30 years, majority of the patients 92.31% belonged to the age group of 15-45 years, 7.69% belonged to 56-65 year. The mean weight was 49.23 kg, elevation in serum uric acid level above normal range occurred in all weight range from 25-85 kg. Majority of patients 60.55% belonged to the weight range of 36-65 kg, 15.38% and 23.07% belonged to 25-35 kg and 56-85 kg respectively (see table 1). [13].

4. **Patients who continued to show increase in serum uric acid level from 2nd to 8th week:** The increase in serum uric acid level was observed in 41.02%, The level of increase in serum uric acid was not statistically significant, out of which 68.75% were male and 31.25% were female patients. Mean age was 41.25 years, no significant difference amount three different age groups but slight increase 37.05% occurrence was found in age group of 26-55 years, 31.25% belonged to both 15-25 and 56-65 age groups. The mean weight was 49.37 kg, majority of occurrence 87.5% in the weight range of 36-65 kg, whereas 6.25% each in 25-35 kg and 66-75 kg respectively (see table 2).

5. **Patients who showed decline in serum uric acid level from 2nd to 8th week:** The decline in serum uric acid level was observed in 58.97%, out of which 65.22% were male and 34.78% were female patients. Mean age was 30.86 years, majority of the patients 91.32% belonged to the age group of 15-45 years and

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8.70% belonged to 46-65 year. The mean weight was 50.43 kg, majority of occurrence 73.93% was found in the weight range of 36-65 kg, and 13.04% in of 66-75 kg weight range (see table 3).

Table -1: Increase in uric acid level beyond the normal range (>7 mg/dl) at 2nd and 8th week

Sl. No.	Age In Years	Sex	Wt In Kg	Diagnosis	Serum uric acid level mg/dl		
					0 Time	2nd week	8th week
1.	39	M	44	Granulomatous ascending colon	6.6	7.9	7.6
2.	26	M	47	Right cervical TB lymphadenitis	6.9	7.6	7.3
3.	36	F	46	Rightt cervical TB lymphadenitis	3.0	8.0	4.5
4.	25	M	46	Pulmonary koch's	4.5	7.3	7.9
5.	22	M	54	Pulmonary koch's	8.7	12	8.9
6.	64	F	60	Pulmonary koch's	7.6	8.5	7.9
7.	33	M	71	Abdominal koch's	6.3	7.7	7.3
8.	45	M	47	Left sided pleural effusion-koch's	6.0	7.8	8.2
9.	18	M	45	Pulmonary koch's	7.7	9.0	9.3
10.	41	M	80	Right sided pleural effusion-koch's	6.6	7.8	7.3
11.	17	F	35	Pulmonary koch's	7.9	9.4	8.9
12.	42	M	60	Pulmonary koch's	6.2	7.8	6.8
13.	29	M	54	Right cervical lymphadenopathy	6.6	7.9	7.4
14.	21	M	62	Pulmonary koch's	4.6	7.4	6.2
15.	25	F	25	Right sided pleural effusion-koch's	5.8	7.3	7.6
16.	22	M	42	Left pleural fibrosis-koch's	6.9	7.8	7.3

Table - 2: Patients who continued to show increase in serum uric acid level from 2nd to 8th week

Sl. No.	Age In Years	Sex	Wt In Kg	Diagnosis	Serum uric acid level mg/dl		
					0 Time	2nd week	8th week
1.	40	F	67	Right cervical lymphadenopathy	5.4	6.3	6.8
2.	60	F	48	TB Meningitis	5.0	6.6	6.8
3.	60	F	36	Miliary koch's	2.5	4.8	5.0
4.	30	M	45	Pulmonary koch's	4.7	5.8	6.3
5.	25	M	46	Pulmonary koch's	4.5	7.3	7.9
6.	46	M	54	Pulmonary koch's	3.0	3.3	4.2
7.	25	F	46	Right cerivcal TB lymphadenitis	4.2	5.4	5.6
8.	66	M	52	Pulmonary koch's	4.8	5.8	6.3
9.	45	M	47	Left sided pleural	6.0	7.8	8.2
10.	18	M	45	Pulmonary koch's	7.7	9.0	9.3
11.	20	M	42	Left pleural fibrosis-koch's	4.3	6.2	6.8
12.	65	M	60	Pulmonary koch's	4.3	6.6	6.9
13.	60	M	48	Pulmonary koch's	4.8	6.4	6.6
14.	52	M	61	Miliary koch's	4.6	5.9	6.2
15.	25	F	25	Right sided pleural effusion	5.8	7.3	7.6
16.	52	M	61	Miliary koch's	4.6	5.9	6.3

Table-3: Patients who showed decline in serum uric acid level from 2nd to 8th week

Sl. No.	Age In Years	Sex	Wt In Kg	Diagnosis	Serum uric acid level mg/dl		
					0 Time	2nd week	8th week
1.	39	M	44	Ascending colon TB	6.6	7.9	7.6
2.	26	M	47	Right cervical TB lymphadenitis	6.9	7.6	7.3
3.	36	F	46	Right cervical TB lymphadenitis	3.0	8.0	4.5
4.	15	F	35	Cutaneous TB (Lupus vulgaris)	5.0	6.8	6.6
5.	22	M	54	Pulmonary koch's	8.7	12	8.9
6.	64	F	60	Pulmonary koch's	7.6	8.5	7.9
7.	24	M	58	Right cervical lymphadenopathy	3.7	5.4	5.3
8.	33	M	71	Abdominal koch's	6.3	7.7	7.3
9.	41	M	80	Right sided pleural effusion-koch's	6.6	7.8	7.3
10.	19	F	38	Pulmonary koch's	3.8	5.4	5.2
11.	17	F	35	Pulmonary koch's	7.9	9.4	8.9
12.	36	F	46	Right cervical TB lymphadenitis	4.5	6.2	6.0
13.	30	M	45	Pulmonary koch's	4.7	6.6	6.2
14.	15	F	35	TB Meningitis	5.0	6.8	6.6
15.	25	F	36	Pulmonary koch's	3.5	5.2	4.6
16.	42	M	60	Pulmonary koch's	6.2	7.8	6.8
17.	27	M	62	Right cervical lymphadenopathy	4.3	6.1	5.4
18.	29	M	54	Right cervical lymphadenopathy	6.6	7.9	7.4
19.	21	M	62	Pulmonary koch's	4.6	7.4	6.2
20.	54	M	48	Pulmonary koch's	3.6	5.8	5.3
21.	41	M	71	Pulmonary koch's	4.8	6.8	6.6
22.	22	M	42	Left pleural fibrosis-koch's	6.9	7.8	7.3
23.	30	M	48	Pulmonary koch's	3.4	5.4	4.9

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DISCUSSION

The issue of patient's tolerance of anti-tuberculosis drugs is extremely important for the treatment outcomes and as a consequence for tuberculosis control in general[4]. There is much debate therefore concerning the frequency and severity of adverse symptoms in patients with tuberculosis chemotherapy[2]. It has been suggested that only a minority of patients successfully complete their full course of anti-TB chemotherapy without significant side effects[12]. The main adverse effects of anti-TB drugs usually occur during the first two to three weeks of treatment. The timely strict monitoring for and management of notified adverse effects are therefore essential[16]. If these side effects are not recognized in time and managed properly they can lead to treatment interruption or can even be life threatening. Proper monitoring has to be carried out during the whole treatment course, including patient education, clinical examination, laboratory tests, etc[5].

Despite the development of potent regimen, the treatment for tuberculosis continues to be a problem in patients who do not tolerate these drugs. The objective was to study the effect of pyrazinamide on serum uric acid levels in patients with tuberculosis on intensive phase of DOTS therapy and to document any symptoms of hyperuricemia like arthralgia or gout. Usual dosage of pyrazinamide for use in conjunction with other anti-tuberculosis agents for the treatment of active TB is 15-30 mg/kg (up to 3 g) once daily or 50-70 mg/kg twice weekly[17].

One of the main adverse effect of pyrazinamide is hyperuricemia with or without gout. Hyperuricemia during therapy with pyrazinamide due to inhibition of uric acid excretion by pyrazinoic acid the main metabolite of pyrazinamide, the occurrence of clinical gout in patients receiving chemotherapy for tuberculosis led us to investigate the possibility of an association between symptomatic hyperuricemia with pyrazinamide therapy[18]. As previously reported in literature that the serum uric acid was elevated in patients receiving pyrazinamide but not in patients being treated with other anti-TB drugs[19].

The reason which promoted us to take up the monitoring of serum uric acid level and symptoms on pyrazinamide therapy because, of its hyperuricemia associated with arthralgia, articular pain and swelling, which may lead to non-compliance to therapy[8]. Thus the present study was proposed to monitor hyperuricemic effect of pyrazinamide in TB patients in India at St. Martha's Hospital, Bangalore, when given in a dose of 1.5 g thrice weekly. Despite documenting an increase in serum uric acid with pyrazinamide including beyond the normal range, no subject was symptomatic with joint pains. All the patients completed two months intensive phase of DOTS therapy, indicating that pyrazinamide therapy does not cause arthralgia in TB patients on DOTS.

Hyperuricemia was documented to an extent of 25% to >50% increase over base line, but no patient was symptomatic with joint pain. Concomitant administration of rifampicin may have attributed to this effect[20]. Hence findings suggested that degree of hyperuricemia and its symptoms in patients treated with pyrazinamide could be reduced by giving pyrazinamide intermittently and along with rifampicin[21, 22, 23]. Thus, it is concluded that thrice weekly regimen of pyrazinamide is safe and effective therapy for treatment of TB.

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