Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 324 – 328
Received 25 April 2021; Accepted 08 May 2021.

Incidence of Hyperuricemia and Gouty Arthritis in Patients Taking Pyrazinamide for the Treatment of Tuberculosis

Ganesh Chandra Mohapatra[1*], Mohammad Javed Khan[2], SmrutiRanjan Nayak[3]
[*1]Associate professor, Department of Pulmonary Medicine, IMS & SUM Hospital, Siksha O Anusandhan (deemed to be) University, Bhubaneswar, Odisha.
[2]Assistant Professor, Department of Respiratory Medicine, Rohilkhand Medical College Hospital, Bareilly, UP.
[3]Professor, Department of Community Medicine, Kalinga Institute of Medical Science, Bhubaneswar, Odisha.
[*] Corresponding Author
Dr.Ganesh Chandra Mohapatra, Department of Pulmonary Medicine, IMS & SUM Hospital, Siksha O Anusandhan (deemed to be) University, Bhubaneswar-751003, Odisha.
Email- ganesh.ptr@gmail.com

ABSTRACT

Background and objectives: Pyrazinamide is an indispensable drug in the initial two months (intensive phase) of treatment for tuberculosis. World Health Organization recommends direct observed therapy shortcourse (DOTS) containing Pyrazinamide, Rifampicin, Isoniazid and Ethambutol in fixed dose combination tablets towards the treatment of tuberculosis in its intensive phase. Hyperuricemia (serum uric acid level more than 7mg/dl) is the main side effect of pyrazinamide therapy that may cause gouty arthritis. The aim and objective of this study was to determine the incidence of hyperuricemia and gouty arthritis due to pyrazinamide therapy through DOTS.

Methods: 196 tuberculosis patients, both pulmonary and extrapulmonary were taken for this study with proper inclusion and exclusion criteria. Tuberculosis was diagnosed on the basis of clinical, bacteriological, radiological and other relevant investigations. All the patients were started with pyrazinamide containing DOTS regimen while serum uric acid estimation was done at start, end of 2nd, 4th, 6th and 8th weeks of treatment for each. Every patient was instructed to report for any joint pain developed during this period.

Result: Overall incidence of hyperuricemia found was 28.57% with slight female preponderance, mostly seen in patients with age 60 years and above and during 6-8 weeks of treatment. The Incidence of gouty arthritis among the hyperuricemic subjects was 32%. All patients developing arthritis were relieved symptomatically with nonsteroidal anti-inflammatory drugs without discontinuation of DOTS.

Conclusion: The incidence of Pyrazinamide induced hyperuricemia was not high as it was previously. DOTS should be continued with symptomatic treatment for gouty arthritis.

Keywords:
Direct Observed Therapy Shortcourse (DOTS), Fixed dose combination (FDC), Gout Hyperuricemia, National Tuberculosis Elimination Program (NTEP)

1.Introduction

Tuberculosis (TB) is an infectious disease, remains a major global public health challenge. In 2019, 10 million people fell ill with TB worldwide. Eight countries account for two thirds of the total, with India leading the count with 28% of total world burden. Globally, TB incidence is falling at about 2% per year and between 2015 and 2019 the cumulative reduction was 9% [1]. India follows all the WHO recommended TB control strategies by a national program called National Tuberculosis Elimination Program (NTEP) in which Direct Observed Therapy Shortcourse (DOTS) is the most important component for the treatment of tuberculosis disease. The DOTS treatment strategy has two phases e.g. Initial two months of intensive phase with four anti-TB drugs (ATD), Rifampicin + Pyrazinamide + Isoniazid + Ethambutol followed by four months of continuation phase with three anti-TB drugs, Rifampicin + Isoniazid + Ethambutol for newly diagnosed TB patients [2]. Each individual anti-TB drug is assembled into one tablet in proper strength as per the body weight which is known as fixed dose combination (FDC) tablet

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 324 – 328
Received 25 April 2021; Accepted 08 May 2021.

and the number of tablets required to treat each patient is determined by individual body weight as per the DOTS guidelines. In most cases of tuberculosis the total duration of treatment is defined as six months. Anti-tubercular drugs can combat the infection either due to the active principle itself or their metabolites [3]. These drugs have been shown to induce various adverse drug reactions (ADR) or side effects, which may lead to nonadherence to the treatment with risk of treatment failure [4, 5]. So, this is an important clinical concern. The most common side effect of pyrazinamide therapy is to raise the serum uric acid level (hyperuricemia) in patients. Pyrazinamide causes hyperuricemia through its metabolic conversion to Pyrazinoic acid which causes inhibition of renal tubular secretion of uric acid from the blood. Hyperuricemia is normally defined as serum uric acid level greater than 7.0 mg/dL, the approximate level at which urate is supersaturated in plasma [6]. As a result, high serum uric acid levels can exceed the solubility threshold and precipitate in the form of sodium urate crystals, which may be deposited in the joint space to cause gouty arthritis [7].

The aim and objective of this study was to determine the incidence of hyperuricemia due to Pyrazinamide therapy through DOTS and the incidence of gouty arthritis among the hyperuricemic subjects.

2. Materials and Methods-

This prospective observational study was done by taking 196 number of TB patients as study sample from both pulmonary and extra pulmonary TB patients attending the Respiratory Medicine department of Trichy SRM Medical College Hospital and Research Center, Trichy, Tamilnadu, India, over a period of one year (Feb 20 to Jan 21). Each case of TB was diagnosed as per case definition under NTEP guidelines. The common investigations done for pulmonary TB as per NTEP guidelines are, sputum for AFB and Cartridge based nucleic acid amplification test (CBNAAT), Broncho alveolar lavage for CBNAAT in case of patients having unproductive cough, chest X-ray and clinical diagnosis. Extra pulmonary TB cases were diagnosed by appropriate investigations as per specific organ involvement e.g. pleural fluid analysis, Adenosine deaminase (ADA) estimation, CBNAAT in fluid or tissue samples, Radiology (x-ray, USG, CT, MRI) and histopathology of involved organs. Most of the extra pulmonary TB patients in our study were being referred by other specialty department of this hospital or other outside hospitals with a diagnosis of TB for treatment purpose.

Inclusion criteria-

1. Newly diagnosed patients of Tuberculosis, both pulmonary and extra pulmonary TB.
2. Patients aged 15 years and above.

Exclusion criteria-

1. Patients with history of prior anti-tubercular drug (ATD) treatment.
2. Patients with history of prior arthropathy of any cause.
3. Patients with history of any renal diseases/insufficiency or liver diseases.
4. Patients with abnormal renal function test or liver function test at baseline.
5. Patients with history of taking any other medications that may be a cause of hyperuricemia.

Pyrazinamide containing FDC tablet was administered to each TB patient in proper dosage as per NTEP-DOTS guidelines. Serum estimation for uric acid was done in each patient at 0, 2nd, 4th, 6th and 8th weeks of starting the treatment. Each patient was instructed to report for developing any joint pain during the treatment. Study parameters were age-sex distribution of TB patients, estimation of pulmonary and extra pulmonary tuberculosis, and treatment duration for developing

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 324 – 328
Received 25 April 2021; Accepted 08 May 2021.

hyperuricemia. All parameters were analyzed critically and statistically to determine the incidence of hyperuricemia and gouty arthritis in the study group of patients.

3. Result-

Out of total 196 patients, 123 (62.76%) were males and 73 (37.24%) were females. As per the age distribution of patients (Table-1), 39 patients were between 15-29 years, 52 patients between 30-44 years, 59 patients between 45-59 years and 46 patients with 60 years and above. Pulmonary TB was present in 143 (73%) patients, and extra pulmonary TB in 53 (27%) patients. The most common type of extra pulmonary TB were pleural effusion and TB lymph node. Others were with involvement of abdomen, spine, urinary bladder eyes, and meninges. Hyperuricemia was encountered in 56 (28.57%) patients out of which 33 were males and 23 were females. The incidence of hyperuricemia noted slight more in female patients (31.5%) than the male patients (26.82%). The maximum incidence of hyperuricemia was found in age group of 60 years and above and during 6-8 weeks of starting of the treatment. The average serum uric acid concentration before pyrazinamide containing FDC treatment was 5.1 +/- 1.4 mg/dL, while after treatment was 9.84 +/- 2.34 mg/dL, which was significantly higher than pretreatment level ($p<0.05$). Among the hyperuricemic subjects gouty arthritis with pain was found in 18 (32%) numbers. Joints mainly affected were Toes and ankle (50%), Knee (22.22%), Wrist and fingers (16.67%), Elbow (11.11%). All of them were relieved symptomatically with non-steroidal anti-inflammatory drugs (NSAID) treatment for 5-7 days. None of the hyperurecemic patients required discontinuation of DOTS during the course (intensive phase) of treatment for tuberculosis.

Table 1. Age and sex distribution of TB patients:

Age Group (In yrs.)	Total No. of patients	Male	Female
15-29	39	23	16
30-44	52	33	19
45-59	59	38	21
60 & above	46	29	17
Total	196	123	73
Percentage	100	62.76	37.24

Table 2. Age and sex distribution of hyperuricemia:

Age group In years	No. of males Shown hyperuricemia	%	No. of females Shown hyperuricemia	%
15-29	4	17.39	4	25
30-44	9	27.27	5	26.31
45-49	11	28.94	7	33.33
60 and above	9	31.03	7	41.17
Total	33	26.82	23	31.50

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 324 – 328
Received 25 April 2021; Accepted 08 May 2021.

Table 3. Correlation between treatment duration and hyperuricemia.

Duration of treatment with pyrazinamide Through DOTS	No. of cases developed hyperuricemia	%
At start of treatment	0	0
At end of 2 weeks	9	16.07
At end of 4 weeks	12	21.43
At end of 6 weeks	16	28.57
At end of 8 weeks	19	33.93
Total	56	100

4. Discussion-

Pyrazinamide is a unique anti-tuberculosis drug that plays a key role in shortening the treatment duration for tuberculosis by killing non-replicating persisters Mycobacterium tuberculosis that other drugs cannot. Pyrazinamide is used during the first two months of intensive phase, as giving longer than 2 months does not appear to add any additional benefit [8]. In different studies Hyperuricemia has been reported as 43% to 100% in patients treated with pyrazinamide alone or in combination [9, 10]. Furthermore, gouty attacks have been associated with patients taking pyrazinamide [11]. In our study the incidence of hyperuricemia was not high and was limited to 28.57% only, with slight female preponderance. Patients with age 60 years and above were more susceptible to pyrazinamide induced hyperuricemia and few of them developed gouty arthritis which was relieved by NSAID treatment. Pyrazinamide induced hyperuricemia did not warrant discontinuation or stoppage of the drug and the treatment.

5. Conclusion-

Incidence of pyrazinamide induced hyperuricemia now a days is not high, probably due to better dose calculation and formulation as per fixed body weight in fixed dose combination in DOTS strategy while treating tuberculosis. Incidence of gouty arthritis is also very low in pyrazinamide induced hyperuricemic patients that needs only symptomatic treatment with mild NSAID agents with continuation of DOTS to treat tuberculosis.

Source of Support: Nil
Conflict of Interest: None

References

[1] WHO, Tuberculosis, Key facts, published on 14.10.2020. https://www.who.int/news-room/fact-sheets/detail/tuberculosis

[2] World Health Organization. Essential first-line anti-tuberculosis drugs. Treatment of Tuberculosis: Guidelines. 4th ed. Geneva: WHO; 2010. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK138747/. [Last accessed on 2017 Oct 15].

[3] Vieira DE, Gomes M. Adverse effects of tuberculosis treatment:

[4] Experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. J Bras Pneumol 2008; 34:1049-55.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 324 – 328
Received 25 April 2021; Accepted 08 May 2021.

[5] Kigozi G, Heunis C, Chikobvu P, Botha S, van Rensburg D. Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. Int J Infect Dis 2017; 54:95-102.

[6] Singh A, Prasad R, Balasubramanian V, Gupta N, Gupta P. Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. CEGH 2015; 3:S80-90.

[7] Harris A, Siegel L, Alloway J. Gout and hyperuricemia. Am Fam Phys. 1999; 59(4):925–934.

[8] Becker MA. Asymptomatic hyperuricemia. UpToDate. 2013 Apr; Available at: http://www.uptodate.com/contents/asymptomatic-hyperuricemia. Accessed May 2014.

[9] Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999; 3:S231–279.

[10] Gerdan G, Nurullah A, Ucan ES, et al. Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricemia. Singapore Med J. 2013; 54(6):e125–128.

[11] Sharma TN, Jain NK, Mathur BB, et al. Hyperuricemia and arthralgia during pyrazinamide therapy. Ind J Tub. 28(2).

[12] Scott JT. Drug-induced gout. BaillieresClinRheumatol. 1991; 5(1):39–60.