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Original Research Article

Pyrazinamide Induced Hyperuricemia and Role of Allopurinol

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Abstract:

Introduction: Tuberculosis is contagious and airborne disease. It is a disease of poverty affecting mostly young adults in their most productive years .95% of TB related deaths occur in developing world. Thus, the prevalence of TB was halved. India is the highest TB burden country accounting for 1/5 of the global incidence. where the global annual incidence for TB is to be 9.4 million cases, nearly 2,000,000 cases are reported from India. India ranks 17th among the 22 high burden country in terms of TB incidence rate, Pyrazinamide is a synthetic pyrazine analog of nicotinamide. It has a strong bactericidal activity against mycobacterium tuberculosis and has become an important component of short-term multiple drug therapy of tuberculosis. Hepatotoxicity is the commonest dose related adverse effect. Hyperuricemia is another important adverse effect reported with drug. Pyrazinamide inhibits renal excretion of urates frequently resulting in hyperuricemia. The effect is usually asymptomatic but acute gout has occurred in some patients.

Methodology: This observational study was conducted in Indraprastha Apollo hospital Sarita Vihar New Delhi in the department of Respiratory Medicine Critical Care and Sleep Medicine prospectively from May 2010 to December 2012. A total of 100 newly diagnosed cases of pulmonary Koch's disease, patient who were on pyrazinamide containing regimen of category 1 ATT (intensive phase), Patients who gave consent for the study were included in the study.

Results: In this study uric acid level was increased more in age group 26 to 35 years against the age group 41 to 60 years in our study. 36% patient developed hyperuricemia at the end of second week, 52% develop hyperuricemia at the end of the third week and 42% developed hyperuricemia at the end of 4th week of people.

Keywords: Tuberculosis, Pyrazinamide, Hyperuricemia, Allopurinol.

Introduction

Tuberculosis is contagious and airborne disease. It is a disease of poverty affecting mostly young adults in their most productive years .95% of TB related deaths occur in developing world. The prevalence off tuberculosis has been constantly dropping since 2005. the prevalence Dropped to 8.8 million in 2010 including 1.1 million cases among people with HIV The TV death rate fell by almost 80% between 1990 and 2010 with deaths falling from 216000 to fifty-five thousand respectively. Thus, the prevalence of TB was halved. India is the highest TB burden country accounting for 1/5 of the global incidence. where the global annual incidence for TB is to be 9.4 million cases, Nearly 2,000,000 cases are reported from India. India ranks 17th among the 22 high burden country in terms of TB incidence rate.[1,2]

Pyrazinamide is a synthetic pyrazine analog of nicotinamide. It has a strong bactericidal activity against mycobacterium tuberculosis and has become an important component of short-term multiple drug therapy of tuberculosis. Pyrazinamide is well absorbed from gut and is widely distributed throughout the body including the central nervous system lungs and liver after oral administration. The drug is mainly excreted through the renal route. The daily dose for adult is 15 to 30mg per kg body weight orally given a single dose or in two divided doses. Hepatotoxicity is the commonest dose related adverse effect. It is therefore recommended that all patients put on this drug should undergo liver function test before the initiation of therapy and thereafter at regular interval. [3,4,5]

Hyperuricemia is another important adverse effect reported with drug. Pyrazinamide inhibits renal excretion of urates frequently resulting in hyperuricemia. The effect is usually asymptomatic but acute gout has occurred in some patients. Non gouty polyarthralgia, which appears to be related to increased serum uric acid concentrations, reportedly occur in up to 40% of the patient receiving pyrazinamide. Uricosuric agents administered concurrently may reduce pyrazinamide-induced hyperuricemia. However, if hyperuricemia is severe or is accompanied by acute gouty arthritis pyrazinamide should be discontinued. The sustained action of allopurinol on the plasma level of uric acid has led to its use in the treatment of hyperuricemia and gout. It is usually simple to administer readily acceptable to the patient and highly effective. In early uncomplicated gout there is probably little to choose between allopurinol and uricosuric drugs such as probenecid or sulphinpyrazolone, but there are several conditions for which allopurinol is specially indicated either alone or in combination with uricosuric therapy. They include severe tophaceoust gout which is not controlled by uricosuric treatment intolerant to uricosuric drugs gout with a high level of urinary uric acid, uric acid kidney stone, gout with advanced renal failure and acute uric acid nephropathy.

Materials and Methods

This observational study was conducted in Indraprastha Apollo Hospital Sarita Vihar New Delhi in the Department of Respiratory Medicine Critical Care and Sleep Medicine prospectively from May 2010 to December 2012. A total of 100 patient diagnosed with pulmonary tuberculosis who present to the department of Respiratory Medicine Critical Care and Sleep Medicine Were recruited on voluntary basis. Newly diagnosed cases of pulmonary Koch's disease, patient who were on pyrazinamide-containing regimen of category 1 ATT (intensive phase), Patients who gave consent for the study were included in the study. Patient with diagnosis other than pulmonary Koch's disease, patient suffering with renal disease, gout or any kind of arthropathies for excluded from the study. all patients were investigated before starting the category 1 ATT as advocated by the revised national tuberculosis program of India to rule out any other disease like renal hepatica cardiac etc. Baseline serum uric acid of Android patients were assessed at enrollment. Serum uric acid level were reassessed after completion of week 1, 2,3 and 4 of category 1 ATT. Analysis was done using with SPSS version 17.

Results

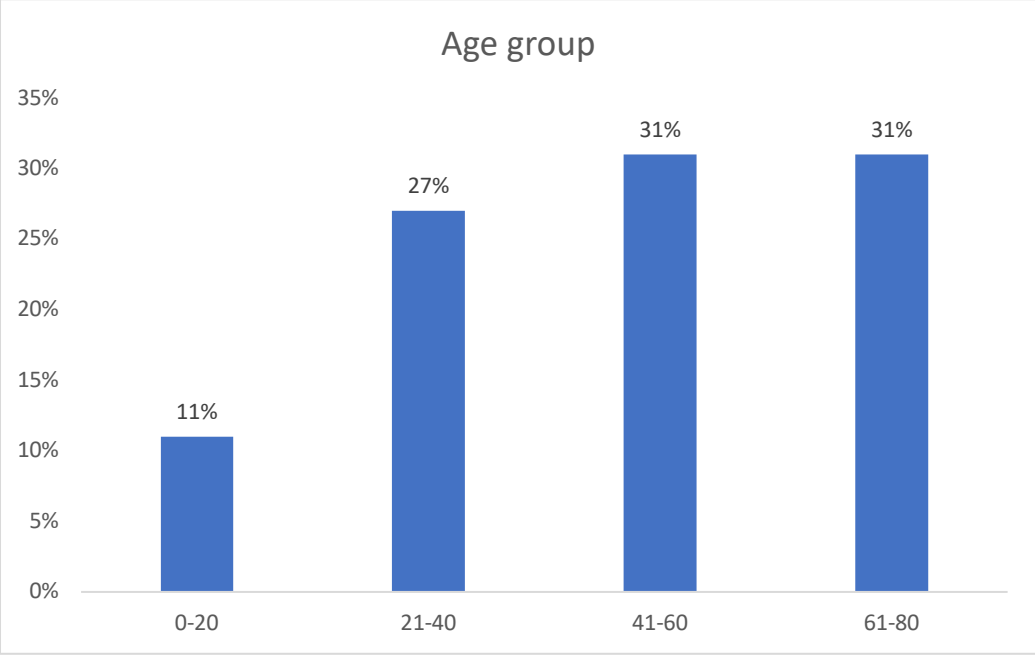

Figure 1: Age distribution of the study group

Figure 1 shows that age was analysed in age group of 0 to 20 years, 21 to 40 years, 41 to 60 years and 61 to 80 years, was observed that most of the cases were in the age group of 41 to 60 years and 61 to 80 years (31%). 27 cases that is 27% per in the age group of 21 year and only 11 cases that is 11% were in the age group of 0 to 20 years.

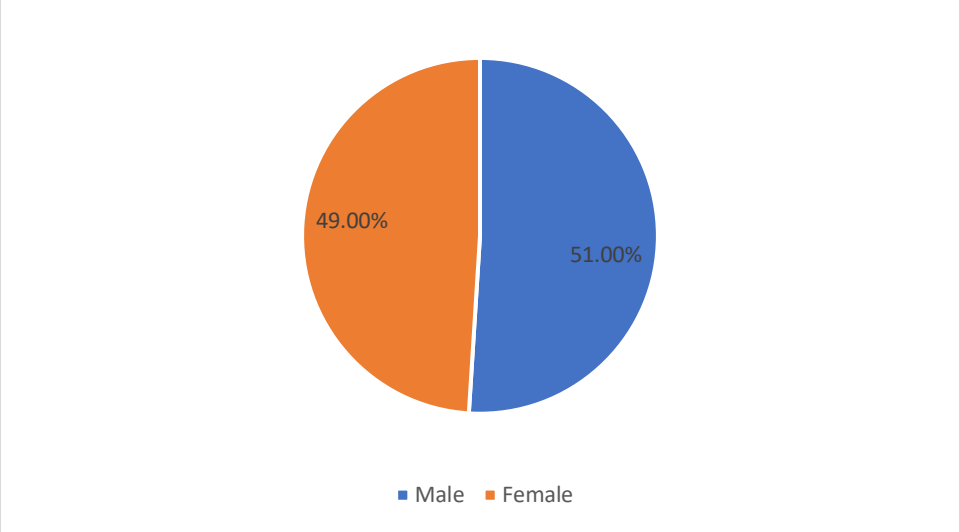

Figure 2: Sex distribution in the study group

The study consisted of 49% females and 51% males. The male female ratio was calculated to be 1.04. The sex distribution is depicted in the figure 2.

Table 1: Mean serum uric acid level over the observation

Serum uric acid	Mean and Standard deviation	P value
baseline	4.89 ± 1.18	0.000
first week	5.88± 1.60	0.000
second week	6.67± 2.11	0.000
third week	7.55± 2.71	0.000
4th week	7.34± 2.78	0.000

Table 1 shows mean serum uric acid level over the observation. The result shows that the mean serum uric acid level was observed to be within the normal limits of <=7.3 mg/dl during the first two weeks after the initiation of ATT. ANOVA reveals a significant difference in the distribution of the mean uric acid levels over the observation.

Table 2: Patients who require allopurinol among those who develop hyperuricemia

Allopurinol requirement among hyperuricemia	Number of patients	Percentage
no	16	16%
yes	36	36%
total	52	52%

In our study group out of total 52 patients who develop hyperuricemia till third week, only 36% patient required allopurinol because they were symptomatic because of race uric acid level. Remaining 16% patient were asymptomatic in spite of having eurythmia and so they did not require allopurinol.

Table 3: Sex distribution among study group as for allopurinol requirement

Sex	Allopurinol Requirement				P Value
	No		Yes		
	Number of Patients	Percentage	Number of Patients	Percentage	0.001
female	39	60.9%	10	27.8%	
male	25	39.1%	26	72.2%	
total	64	100%	36	100%	

In our study group out of the patient who required allopurinol dose 10 patient (27.8%)were female and 26(72.2%) patients were male.

Table 4: Smoking status among the study group As for allopurinol requirement smoker

Smoker	Allopurinol Requirement				P Value
	No		Yes		
	Number of Patients	Percentage	Number of Patients	Percentage	0.001
female	54	84.3%	19	52.8%	
male	10	15.7%	17	47.2%	
total	64	100%	36	100%	

In our study out of patients who required allopurinol, 19 (52.8%) patients were non-smoker and 17 (47.2%) patients were smoker.

Table 5: Alcohol drinker among the study group As for allopurinol requirement smoker

Alcoholic	Allopurinol Requirement				P Value
	No		Yes		
	Number of Patients	Percentage	Number of Patients	Percentage	0.149
female	51	79.7%	24	66.7%	
male	13	20.3%	12	33.3%	
total	64	100%	36	100%	

In Austria do you group among the patients who required allopurinol 12(33.3%) were alcoholic and 24 patients (66.7%) were non alcoholic.

Discussion

Tuberculosis is a common disease in developing country like India and is also resurfacing again in the developed world. In our strategy we have correlated patients smoking alcohol and dietary habit contribution in developing of hyperuricemia related symptoms and requirement of allopurinol. This study group 73% patient were non-smokers, and 27% patient were smokers and among those the patient who required allopurinol dose, 58 52.8% patients were non-smokers and 47.2% patient were smokers so smoking was considered as a risk factor for development of hyperuricemia related symptoms.

In our study groups 75% patient were nonalcoholic and 25% patients were alcohol drinker and among those the patient who required allopurinol dose, 33.3% were alcohol drinker and 66.7% patient were non-Alcoholics, so alcohol intake was also considered as a risk factor for the development of hyperuricemia related symptoms.

In our study 62% patient were non vegetarian and 38% patients were vegetarian by type and among those patients who required allopurinol dose 63.9% patient were non vegetarian by dye and 36.1% patient were vegetarian. So non vegetarian dietary intake was also considered as a risk factor for the development of hyperuricemia related symptoms.

A prospective and observational study was conducted by Zuberi et al6between 2000 2003. All patient received fixed dose combination comprising of standard four drug anti tuberculosis drugs namely, rifampicin, pyrazinamide, ethambutol and isoniazid as recommended by WHO [6,7]. Male comprised 51% of our study population while 49% were female the mean age in our study was 45.2 ± 19.04 years. The main uric acid level measured at enrollment was less than 7.3 MG per deal which was absorbed in 80% patient whereas the mean uric acid level before the start of therapy at week 0 was5.07± 57 MG per dl. Significant elevation of uric acid level causes not observed in up to 64% patient till the end of Week 2.

We noted significant increase in the uric acid level in 52% patient at the end of week 3 and symptoms of arthritis in 36% of patient for which they required allopurinol.

However, this was in contrast to the observation by Zubariet al [6] who noted significant increase of uric acid level in 63.8% patient between week 0 to week 2 whereas, only 4.3% patient reported symptoms suggestive of arthritis. Another study from Nigeria reported that 51.6% of all the patients taking ATT with PZA, left hyperuricemia that returned back to normal PZA was withdrawn after eight week. [7]However, please add a withdrawal was not required in our study as patient became better after initiation of allopurinol. Similar findings have also being reported pediatric patients suffering from tuberculosis. Significant increase in mean uric acid concentration after one month of PZA containing ATT were observed, which reverted to the baseline after one month of stopping PZA. There were no sign of clinical gout in any case.[8] Another study conducted by Shah et al[10] from Pakistan, 119 patient received pirates in a white containing regimen and observed for development of hyperuricemia. It was noted that 13% developed hyperuricemia while in our study 36% patient develop hyperuricemia.

In this study uric acid level was increased more in age group 26 to 35 years against the age group 41 to 60 years in our study. In the set study only male patient develops hyperuricemia but in our study female preponderance was noted in the age group of 0 to 20 years and 21 to 40 years whereas male preponderance was noted in the age group of 41 to 60 years and 61 to 80 years. All these above differences seem to arise due to the baseline differences in the demographic distribution of the population rather than being a result of age and or sex related pharmacokinetics.

In the study conducted by Shah et al. there was no increase in uric acid level from baseline during the first two months of treatment but in our study 36% patient developed hyperuricemia at the end of second week, 52% develop hyperuricemia at the end of the third week and 42% developed hyperuricemia at the end of 4th week of people. Does the uric acid level gradually increased from second to third week and then decrease over the next one week similar results were reported by Adebesiet al who reported that hyperuricemia 13% patient received pyrazinamide-containing regimen.[9]

Khannaet al [10] conducted a prospective study with three groups. Group E received regimen containing ethambutol group Z containing pyrazinamide but no Ethambutol and group ZE received regimen containing ethambutol and pyrazinamide administered concomitantly. A rise in the serum uric acid level was observed in all the three groups the hyperuricemia was higher in the ZE group which was 91.34% compared to each group having 51.6% but not much higher compared to Z group which had 73.68%. Arthralgia occurred in 17.39% subjects of ZE group, 15.79% of the Z group and 3.22% of E group while none developed arthritis. Arthralgia was not severe enough to warrant the termination of the therapy which was similar to our findings.[11]

References

1. WHO Lowell facts. 2011-2012.
2. WHO global TV report 2010.
3. Gupta S, Gupta B, Kapoor B et al. J Indian Medical Association. 2007; 105: 341-2.
4. McEvory, GK. American Hospital formulary service-drug information 2002. Bethseda, MD: American Society of Health System Pharmacists, Inc. 2002; 507.
5. Scott JT, Hall AP, Grahame R, British Medical Journal, 1966, 2, 321.
6. Solanki GA, Zuberi FB, Shaikh S et al. Pyrazinamide induce hyperuricemia in patient taking antituberculosis therapy. JCPSP. 2004; 14(3): 136-138.
7. Mavromatidis K, Magoula I, Tsapas G. Urate homestatis in polycystic kidney disease: comparison with chronic glomerulonephritis kidney. Reh Fail. 2002; 24:447-59.
8. Blomberg B, Spinaci S, Fourie B et al. Fixed dose combination tablets for treatment of tuberculosis. Bull WHO. 2001; 79:61-8.
9. Sanchez-Albisua I, Vidal ML, Joya-Verde G, Del Castillo Fe, García-Hortelano Jo. Tolerance of pyrazinamide in short course chemotherapy for pulmonary tuberculosis in children. The Pediatric Infectious Disease Journal. 1997 Aug 1;16(8):760-3.
10. Khanna BK, Kumar J, Hyperuricemia effect of Pyrazinamide and Ethambutol administered concomitantly. Ind. J. Tub. 1998;38,21
11. Ghulam Akbar, Solangi, Shaikh Sikandar, and Shaikh Wazir Muhammad. Pyrazinamide induced hyperuricemia in patients taking antituberculous therapy. 2004; 136-138.