ORIGINAL ARTICLE

PYRAZINAMIDE INDUCED HYPERURICEMIA IN PATIENTS TAKING ANTI-TUBERCULOUS THERAPY

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ABSTRACT

Objective: To record the effect of pyrazinamide on uric acid in patients of tuberculosis.
Design: Descriptive and observational study.
Place and Duration of Study: Chandka Medical College Hospital, Larkana from February 2000 to January 2003.
Patients and Methods: All patients receiving anti-tuberculosis drugs with pyrazinamide were included. Serum uric acid levels were monitored at weeks 0, 2, 8 and 12 of therapy. Serum creatinine was done at weeks 0, 8 and 12.
Results: Results were reported on 216 patients. Mean uric acid and creatinine levels at the start of therapy, i.e., week '0' were 5.07 ±0.57 mg/dl and 0.87 ±0.11 mg/dl respectively. The results show significant increase in uric acid levels from week '0' to week '2', at the end of week '8', the levels remained elevated and there was no statistical significant difference from that at week '2'. The uric acid levels reduced at week '12' after pyrazinamide was stopped and the difference was significant. Despite that renal function steadily improved with the treatment of tuberculosis to the extent that comparable pre-treatment values were obtained at the end of treatment.
Conclusion: Anti-tuberculous therapy with pyrazinamide affects the uric acid levels early. This change is reversible after the withdrawal of the agent.

KEY WORDS: *Uric Acid. Pyrazinamide. Tuberculosis. Anti-tuberculous therapy. Adverse effects.*

INTRODUCTION

Tuberculosis is a common disease in a developing country like Pakistan and is also resurfacing again in the developed world.[1] Treatment is with standard therapy of three or four drugs in the initial eight weeks. This initial period may contain pyrazinamide as one of the agents.[2] Many drugs used in the treatment of tuberculosis are known to stress the kidneys and the liver.[3,4] Clearance of uric acid is of concern especially in certain circumstances where drugs, essential for the treatment, tend to stress the kidneys. The clearance of uric acid also varies in different conditions. It has been observed that tubular secretion of uric acid negatively correlated with body mass index.[5] Pyrazinamide (PZA) is a well-known modulator of urate transport via the proximal tubules and it is also an important component of anti-tuberculosis therapy (ATT). This study, therefore, aims at establishing the effect of PZA induced hyperuricemia in patients of tuberculosis.

PATIENTS AND METHODS

It was a prospective and observational study conducted at Chandka Medical College, Larkana during the period February 2000 to January 2003. All patients receiving standard four drug anti-tuberculosis therapy (Rifampicin, Pyrazinamide, Ethambutol and Isonazide) were included. All drugs were given in fixed dose combination according to the weight as recommended by WHO.[6,7] Serum uric acid levels were monitored at weeks 0, 2, 8 and 12 of ATT. Serum creatinine was noted at weeks 0, 8 and 12. PZA was withdrawn after 8 weeks of therapy. Patients with elevated creatinine and uric acid at week 0 were excluded. All biochemistry was done on automated analyser. Statistical analysis was done by independent Samples 't' test and paired samples 't' test as indicated.

RESULTS

Two hundred forty-seven patients were initially included in our study. We used approved and fixed dose combination of four drugs of proven bioequivalency.[8-10] Twenty-one patients were lost to follow up, 10 had elevated creatinine levels at week 0. The results of 216 patients, 116 (53.7%) males and 100 (46.3%) females are reported here. Mean age according to the gender was 39.9 years in males and 43.3 years in females. There was no significant difference in the age between the gender when estimated by independent-samples 't' test ($p = 0.14$; $t = 1.45$; $df = 214$; 95% CI -1.22 to 8.12). Mean uric acid and creatinine levels before the start of therapy at week '0' were 5.07 ±0.57 mg/dl and 0.87 ±0.11 mg/dl respectively. Details of levels at different weeks are given in Table I. Statistical analysis of mean values of uric acid and creatinine levels was done

Table I: Mean uric acid and creatinine levels during therapy.

	Uric acid mg/dl		Creatinine mg/dl	
	Mean	SD	Mean	SD
Week 0	5.07	0.57	0.87	0.11
Week 2	9.68	1.52		
Week 8	9.64	1.43	0.97	0.25
Week 12	5.08	0.57	0.90	0.11

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by paired-samples 't' test and results are detailed in Table II. The results show significant increase in uric acid levels from week '0' to week '2', at the end of week '8' the levels remained elevated and there was no statistical significant difference from that at week '2'. The uric acid levels reduced at week '12' after PZA was stopped and the difference was significant. Similarly, the levels of creatinine were also raised during the therapy but were reduced when PZA was stopped.

The uric acid levels were increased in 138 (63.8%) of patients from their base line values, but symptoms of arthritis were produced in only 6 (4.3%) patients in which the uric acid levels were increased. No patient was withdrawn from ATT due to the high uric acid levels.

PZA also influences the transport of urate from peritoneum too. In a study conducted in stable patients of chronic ambulatory peritoneal dialysis administration of PZA showed decrease in clearance and mass transfer area coefficients of urate, urea and creatinine but dialysate-to-plasma concentration (D/P) ratios were only decreased significantly for urate. This supports the hypothesis that unrestricted diffusion is not the only transport mechanism in peritonium in the case of urate. There does exist an active mechanism in peritoneal urate transport with a re-absorptive and, probably, a secretive component that resembles that of renal tubule urate transport.[13]

Table II: Statistical analysis of uric acid and creatinine levels*.

Paired samples test

	Paired differences					t	df	sig. (s-tailed)
	Mean	Std. deviation	Std. error mean	95% confidence interval of the difference Lower	Upper			
Pair 1 U0-U2	-4.6116	1.6291	.1108	-4.8301	-43931	-41.603	215	.000
Pair 2 U2-U8	4.167E-02	.3244	2.207E-02	-1.84E	8.517E-02	1.888	215	.060
Pair 3 U8-U12	4.5620	1.5356	.1045	4.3561	4.7680	43.662	215	.000
Pair 4 U0-U12	-7.87E-03	4.295E-02	2.922E-02	-1.36E-02	-2.11E-03	-2.693	215	.008
Pair 5 C0-C8	-9.77E-02	.2298	1.563E-02	-.1285	-6.69E-02	-6.249	215	.000
Pair 6 C8-C12	7.176E-02	.2339	1.591E-02	4.040E-02	.1031	4.510	215	.000
Pair 7 C0-C12	-2.59E-02	5.602E-02	3.812E-02	-3.34E-03	-1.81E-02	-6.801	215	.000

*U0=Uric acid at week 0; U2=Uric acid at week 2; U8=Uric acid at week 8; U12=Uric acid at week 12;
C0=Creatinine at week 0; C2=Creatinine at week 2; C12=Creatinine at week 12.

Discussion

Urates are primarily produced in tissues containing xanthenes oxidase like liver and small intestine. At any time, the amount of the urate in body is due to the balance between the amount produced and amount excreted. Kidneys are the main organ for excretion of urates. There are four components in its renal homeostasis i.e. glomerular filtration, tubular re-absoption, secretion and postsecretory re-absorption. Approximately 8 to 12% of urate filtered by the glomeruli is excreted in the urine as uric acid. After filtration, 98 to 100% of the urate is re-absorbed; about half the re-absorbed urate is secreted back into the proximal tubule, and about 40% of that is again re-absorbed.

The present study shows that the PZA increases the levels of uric acid significantly during the course of the therapy. But fortunately it was also shown that the results returned back to normal once the drug was stopped. Similar findings have been reported from many countries.[11] The PZA effects handling of urate, urea and creatinine by the kidneys. It was reported from Nigeria that among patients taking ATT with PZA, 51.6% developed hyperuricemia that returned back to normal when PZA was withdrawn ater 8 weeks.[11]

Similar findings are reported in paediatric patients suffering from tuberculosis. Significant increase in uric acid mean concentrations after 1 month of therapy of ATT with PZA (from 3.7 ±0.7 mg/dl to 5.7 ±1.6 mg/dl, $p < 0.05$) were observed, which fell again to (4.0 ±1.1) 1 month after PZA was stopped. There were no signs of clinical gout or arthralgias. In no case was the treatment interrupted.[12]

Conclusion

Despite the drug-induced hyperuricaemia recorded during the treatment, renal function steadily improved with the treatment of tuberculosis to the extent that comparable pre-treatment values were obtained at the end of treatment. We, therefore, conclude that drug-induced hyperuricaemia associated with treatment of pulmonary tuberculosis has no detectable negative effect on renal function of the patient.

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