INTRODUCTION

Tuberculosis is a common disease in a developing country like Pakistan and is also resurfacing again in the developed world. 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. Many drugs used in the treatment of tuberculosis are known to stress the kidneys and the liver. 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. 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 Hospital, Larkana from February 2000 to January 2003. 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 $5.07 \pm 0.57$ mg/dl and $0.87 \pm 0.11$ 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.

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. 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, i.e., week '0' were $5.07 \pm 0.57$ mg/dl and $0.87 \pm 0.11$ 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.

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RESULTS

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Pyrazinamide induced hyperuricemia in patients taking anti-tuberculous therapy

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 baseline 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 peritonitis in the case of urate. There does exist an active mechanism in peritoneal urate transport with a re-absorptive and, probably, a secretory component that resembles that of renal tubule urate transport.13

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-absorption, 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 after 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.

REFERENCES


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

<table>
<thead>
<tr>
<th>Paired samples test</th>
<th>Paired differences</th>
<th>95% confidence interval of the difference</th>
<th>Lower</th>
<th>Upper</th>
<th>t</th>
<th>df</th>
<th>sig. (s-tailed)</th>
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<tbody>
<tr>
<td>Pair 1 U0-U2</td>
<td>-4.811E-08</td>
<td>1.629E-08</td>
<td>-1108</td>
<td>-4.830E-08</td>
<td>-43931</td>
<td>-41.603</td>
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<tr>
<td>Pair 2 U2-U8</td>
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<td>4.145E-02</td>
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<td>1.535E-01</td>
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<td>4.356E-01</td>
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<tr>
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<tr>
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<td>5.802E-02</td>
<td>3.812E-02</td>
<td>-3.54E-03</td>
<td>-1.81E-02</td>
<td>-6.801</td>
<td>215</td>
</tr>
</tbody>
</table>

*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.


