

## ADVERSE EFFECTS OF PYRAZINAMIDE IN PAKISTANI PATIENTS

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**Abstract:** The effect of Pyrazinamide on Liver and Kidney function tests as well as on Serum and Urinary Uric Acid levels was studied in Patients with Pulmonary Tuberculosis. A rise in Serum total and direct bilirubin, SGOT and SGPT was observed. No significant rise was observed in alkaline phosphatase concentration. One out of fifteen patients developed Jaundice.

A rise in Serum Uric Acid, Serum Creatinine concentration during drug therapy was associated with a fall in Urinary Excretion of Uric Acid and Creatinine.

### Introduction

Pyrazinamide is a bactericidal drug for M. Tuberculosis, particularly when growth of organism is inhibited by an acid environment, for example, within macrophages.<sup>1</sup> The metabolism of pyrazinamide leads to the production of pyrazionic acid, which is converted to 5-Hydroxy pyrazionic acid in the presence of enzyme xanthine oxidase.<sup>2</sup> It is mainly eliminated by metabolism: about 30% being excreted in the urine as pyrazionic acid and about 40% as unchanged pyrazinamide. Arthralgia is relatively frequent reaction to pyrazinamide. Its mechanism of onset is uncertain, but it may be caused by inhibition of renal tubular secretion of uric acid by pyrazionic acid,<sup>3</sup> <sup>4</sup> the primary metabolite of pyrazinamide in man.<sup>2</sup>

All anti-tuberculosis drugs can cause hepatitis. In the past pyrazinamide acquired a reputation for being particularly hepatotoxic. This may result when large pyrazinamide doses are used<sup>5</sup> (40-50 mg/kg daily). Secondly, it was not realized that transient, asymptomatic increase in serum hepatic enzyme concentration were common during early weeks of tuberculosis chemotherapy and that these could almost always be expected to return to normal without interrupting or changing the regimen and were not clinically important.<sup>6</sup> In the case of pyrazinamide, there is evidence that the risk of drug induced hepatitis is dependent on dosage.<sup>7</sup>

Several studies demonstrated that hepatic toxicity was not a problem when pyrazinamide was given daily in dosages of 20 to 30 mg/kg body weight in combination with streptomycin,<sup>8</sup> or with streptomycin and para-amminosalicylic acid<sup>9</sup> and intermittently with streptomycin and Isoniazid.<sup>10</sup>

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Most of these studies were done in U.S, Europe or Africa. The present study was carried out to investigate changes in liver function tests, in Pakistani patients taking pyrazinamide without combination with isoniazid or rifampicin or streptomycin.

The present communication also describes the effect of pyrazinamide on Kidney function tests. Since the pyrazionic acid effect may be attributed to inhibit the renal tubular secretion of creatinine causing the serum creatinine to rise.

### **Material and Methods**

Fifteen subjects of both sexes were selected for the study from out-patient department of Chest Diseases of D.H.Q. Hospital, Abbottabad and T.B. Sanatorium, Dadar. The ages ranged from 15-60 years. All had clinical and radiological evidence of pulmonary tuberculosis and a positive A.F.B. Smear of Sputum. Those having history of hepatitis, gout, arthralgia, diabetes-mellitus or Kidney disease were excluded from the study.

All patients were given pyrazinamide (30 mg/kg daily) for a period of three months. Twenty-four hours' urine samples were collected for creatinine clearance. Serum and Urinary creatinine were determined by method of Hare,<sup>11</sup> Serum and Urinary uric acid levels by method of Henery,<sup>12</sup> Bilirubin by method of Malloy and Evelyn,<sup>13</sup> SGPT and SGOT by method of Reitman and Frankel<sup>14</sup> and alkaline phosphatase by Bessey and Lowery,<sup>15</sup> in all cases prior to administration of drugs. These were repeated monthly for a period of three months and then one month after withdrawal of pyrazinamide.

The compliance and effect of therapy were evaluated clinically, radio- logically and bacteriologically during the subsequent visits. Random samples of 20 healthy individuals were collected and the values of serum bilirubin, SGOT, SGPT, Alkaline Phosphatase, Serum Uric acid and Creatinine, and also urinary creatinine and uric acid determined and used as standards.

### **Results**

The data of Serum total bilirubin SGOT, SGPT and alkaline phosphatase is summarized in Table I, in which various stages are grouped from I to V. Almost all the patients have their total bilirubin levels within normal ranges before drug therapy. The mean value was  $0.60 \pm 0.084$  mg/dl, which are almost identical to our mean total bilirubin of  $0.62 \pm 0.085$  mg/dl. During drug therapy there was a gradual rise in levels of total bilirubin. A significant difference was observed ( $P < 0.05$ ) between group I and IV for total bilirubin. In spite of a significant rise, the upper normal limit was hardly crossed over 1.69 mg/dl. However, in one case the level reached 2.68 mg/dl after one-month therapy and developed clinical Jaundice and the drug had to be withdrawn. No significant difference was observed between groups I and V.

Table 1. — Serum Bilirubin, Glutamate Oxaloacetate Transaminase (SGOT), Glutamate Pyruvate Transaminase (SGPT), and Phosphatase Levels before and after taking Pyrazinamide.

(Figures represent mean value)

Group	Serum Bilirubin Mg/dl	Serum Glutamate Oxaloacetate Transaminase (SGOT) U/L	Serum Glutamate Pyruvate Transaminase (SGPT) U/L	Serum Alkaline Phosphatase U/L
Pretreatment (I)	0.61 ± 0.08	19 ± 1.84	19 ± 1.37	22 ± 2.63
After 1 month (II)	0.93 ± 0.49	27 ± 3.66	26 ± 3.68	25 ± 2.67
After 2 month (III)	1.04 ± 0.16	36 ± 1.46	36 ± 3.08	26 ± 3.33
After 3 month (IV)	1.44 ± 0.18	41 ± 1.32	40 ± 2.25	28 ± 4.46
One Month after withdrawal (V)	0.64 ± 0.08	20 ± 0.89	20 ± 0.96	23 ± 2.07

The data of serum glutamate oxaloacetate (SGOT), Serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase, in various stages of treatment are shown in Table 1. The levels of SGOT, SGPT and alkaline phosphatase before drug therapy were within normal limits with a mean value of 19 ± 1.84 U/L for SGOT, 19 ± 1.37 U/L for SGPT and 22 ± 2.63 U/L for alkaline phosphatase. These values were almost identical to our normal values of 20 ± 1.95 U/L for SGOT, 19.50 U/L for SGPT and 21 ± 2.40 U/L for Alkaline phosphatase. During drug therapy it was observed that there was a gradual rise in the levels of both SGOT and SGPT and this was significant (P < 0.01) after three months of drug administration. No such change in alkaline phosphatase was observed. No significant change was found in SGOT and SGPT levels in pretreatment (I) and one month after withdrawal of drug (V), and these levels were identical to those of our normal levels.

In order to evaluate the effect of pyrazinamide on kidney, the estimation of creatinine clearance was determined in urine and serum. The values are presented in Table 2, according to groups. The mean level of Serum Creatinine before drug administration was 0.825 ± .042 mg/dl, and that of urine creatinine was 89.33 ± 2.126 mg/dl, which are identical to normal values, 0.838 ± 0.050 mg/dl for Serum Creatinine and 91 ± 1.912 mg/dl for urinary creatinine. Also, the mean value for creatinine clearance for pretreatment patients (101.53 ± 0.833 ml/min) was similar to normal subjects (101.50 ± 0.946 ml/min).

No significant change was found in serum creatinine and urine creatinine in pretreatment (group I) and one month after withdrawal of drug (group V). But, significant difference (P < 0.05) was observed in group I and IV. Also, there was a significant change (P < 0.01) between creatinine

Table 2— Creatinine Concentrations in Serum and Urine and Creatinine Clearance Test.

(Figures represent mean value)

Group	Serum Creatinine mg/dl	Urine Creatinine mg/dl	Creatinine Clearance ml/min
Pretreatment (I)	0.825 ± 0.042	89.33 ± 2.126	101.53 ± 0.833
After 1 Month (II)	0.88 ± 0.042	80 ± 1.799	88.00 ± 2.138
After 2 months (III)	0.975 ± 0.059	71.50 ± 1.950	74.15 ± 2.931
After 3 Months (IV)	1.094 ± 0.271	64.407 ± 1.697	64.73 ± 1.460
One Month after (V) Withdrawal	0.841 ± 0.36	89.87 ± 1.807	102.07 ± 1.099

clearance before drug administration and after three months of drug administration. The means of serum and urine concentration of Uric Acid in various stages are grouped in Table 3. No significant change, was found between pretreatment and one month after withdrawal of drug in serum uric acid levels, and urinary uric acid level. Moreover, these values were found to be similar to those of our normal mean values of 4.71 ± 0.185 mg/dl for uric acid and 1.20 ± 0.055 gm/day for urinary uric acid level. But during pyrazinamide therapy, there was a significant rise in serum uric acid levels (P < 0.05) and a significant decline (P < 0.05) in Urine Uric Acid levels.

Table 3. — Uric Acid Concentrations in Serum and Urine.

(Figures represent mean value)

Group	Serum Uric Acid mg/dl	Urine Uric Acid mg/day
Pretreatment (I)	4.75 ± 0.179	1.250 ± 0.057
After 1 month (II)	6.10 ± 0.314	1.12 ± 0.060
After 2 months (III)	7.10 ± 0.251	0.91 ± 0.040
After 3 months (IV)	7.30 ± 0.336	0.77 ± 0.077
One month after Withdrawal (V)	4.65 ± 0.181	1.25 ± 0.061

### Discussion

This study was primarily centered upon the effect of pyrazinamide therapy on liver and kidney function tests. A convincing evidence was obtained

showing a gradual and constant rise of serum bilirubin, SGOT and SGPT. This conclusion is in agreement with the finding of others.<sup>7</sup> However, these authors established that the hepatotoxic effects were due to pyrazinamide in combination with other anti-tuberculosis drugs, whereas our findings are without combination of other regimens. In studies in which the British Medical Research Council Tuberculosis and chest diseases unit has been involved of short course regimens containing all three drugs (Isoniazid, Rifampicin and Pyrazinamide) clinically evident, symptomatic hepatitis has been reported 0.2% in patents in East Africa, 0.7% in Hong Kong and 2.8% in Singapore.<sup>16</sup> Nevertheless, our finding showed the incidence of 6.6% (one out of 15 patients). This may be due to the variations in drug tolerance in different ethnic groups.<sup>17</sup>

In spite of significant rise in serum bilirubin, SGOT and SGPT, the normal upper limits were hardly crossed. This shows that pyrazinamide may cause a mild subclinical hepatic insult but it cannot be labelled as hepatotoxic. These findings are consistent with Hong Kong Study<sup>16</sup> which showed that frequency of hepatitis was no higher in pyrazinamide regimens.

Only creatinine clearance was estimated to expose and emphasize on the adverse effects of Pyrazinamide monotherapy on Kidneys. Experimental evidences suggest that such adverse effects invariably accompany the treatment and are manifested by an increase in serum creatinine and decrease elimination of urinary creatinine, with a decrease in creatinine clearance. This may be due to pyrazionic acid, the metabolic product of pyrazinamide, which suppresses the urinary excretion of creatinine by inhibiting its tubular excretion as it does in case of uric acid.<sup>34</sup> Such hypothesis, however, awaits experimental documentation.

We have already shown in our previous study that pyrazinamide increases serum uric acid and decreases excretion of urinary uric acid in combination with isoniazid and myambutol. In order to monitor the concentration of uric acid in serum and urine we employed pyrazinamide without combination with isoniazid and myambutol and initial results of our study revealed adverse effects of identical nature as were demonstrated in combination with isoniazid and myambutol. Thus one can speculate that pyrazinamide alone, through its metabolic product, pyrazionic acid, suppresses the urinary excretion of uric acid by inhibiting its tubular excretion.

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#### REFERENCES

1. Mitchison, D.A. Basic Mechanism of Chemotherapy. *Chest*. 1979; 76 (6 Suppl): 771.
2. Ellord, G.A. Absorption, metabolism and excretion of Pyrazinamide in man. *Tubercle*. 1969; 50 : 144.
3. Ellord, G.A. and Haslam, R.M. Observation on the reduction of renal elimination or urate in man caused by administration of Pyrazinamide, *Tubercle*. 1976; 57 : 97.
4. Yu, T.F., Burger, L., Stove, D.J., Wolf, J. and Gutman, A.B. Effect of Pyrazinamide and Pyrazionic acid on urate clearance and other discrete renal functions. *Proceedings of the experimental biology and Medicine*. 1957; 96 : 264.
5. McDermott, W., Ormond, L., Muschenheim, C., Deuchle, K. and McCune, R.M. Pyrazinamide-Isoniazid in Tuberculosis. *American Review of tuberculosis*. 1954; 69 : 319.
6. Bpron, D.N. and Bell, J.L. Serum enzyme changes in patients receiving antituberculosis therapy with Rifampicin or p-aminosalicylic acid, plus Isoniazid and Streptomycin. *Tubercle*. 1974; 55 : 115.
7. United States Public Health Service. Hepatic toxicity of Pyrazinamide used with Isoniazid in Tuberculosis Patients. A U.S. Public Health Service tuberculosis therapy trial. *American Review of Resp. diseases*. 1959; 80 : 371.
8. Velu, S., Dawson, J.J.Y., Devadatta, S., Fox, W., Kulkarni, K.G., Mohan, K., Rama Krishnam, C.V. and Stott, H. A controlled comparison of streptomycin plus pyrazinamide and streptomycin plus PAS in the retreatment of patients excreting Isoniazid-resistant organism.
9. East African/British Medical Research Councils. Streptomycin Plus PAS plus Pyrazinamide in retreatment of Pulmonary tuberculosis in East Africa. Second Report. *Tubercle*. 1973; 54 : 283.
10. Tuberculosis Chemotherapy Centre, Madras. A controlled comparison of a twice weekly and three once-weekly regimens in initial treatment of pulmonary tuberculosis. *Bulletin of World health organisation*. 1970; 43 : 143.
11. Hare, R.S. Endogenous creatinine in Serum and Urine. *Proc. Soc. Exp. Biol. Med*. 1950; 74 : 148.
12. Henery, R.J., Sobel, C. and Kim, J.A. Modified Carbonate-Phosphatungstate methods for the determination of Uric acid and Comparison with Spectrophotometric uricase methods. *Am. J. Clin. Pathol*. 1957; 28 : 645.
13. Malloy, H.T. and Evelyn, J.A. (1973). In Annino, J.S., Giese, R.M. *Clinical Chemistry*. 4th Ed., Little Brown and Co., Boston. 1976; 217-22.
14. Reitman, S. and Frankel, S. (1957). In Annino, J.S., and Giese, R.W. *Clinical Chemistry*. 4th Ed., Little Brown and Co., Boston. 1976; 258-261.
15. Bessey, O.A., Lowery, O.H. and Brock, M.J. (1946). In Annino, J.S and Giese, R.W. *Clinical Chemistry* 4th Ed., Little Brown and Co., Boston. 1976; 252-257.
16. Hong Kong Tuberculosis Treatment Services/British Medical Research Council. Adverse reactions to shortcourse regimens containing streptomycin, Isoniazid, Pyrazinamide and Rifampicin in Hong Kong. *Tubercle*. 1979; 57 : 81.
17. Ilyas Khan, M. Adverse reactions of antituberculosis drugs with special reference to Rifampicin and Pyrazinamide. *JPMA* 1987; 37 : 76.