EFFECT OF PYRAZINAMIDE ON SERUM AND URINARY URIC ACID LEVELS

Pages with reference to book, From 76 To 78

Ronaq Zaman (Chest and Tuberculosis Department, Ayub Medical College, Abbottabad.)
Shaukat Ali Orakzai (Bjochemistry Department, Ayub Medical College, Abbottabad.)
Atique Yunus (Department of Physiology, Ayub Medical College, Abbottabad.)

Abstract

The effect of pyrazinamide on serum uric acid and urinary excretion of uric acid was studied in patients with pulmonary tuberculosis. A rise in serum uric acid concentration during drug therapy was associated with a fall in urinary excretion of uric acid. No significant difference was observed between two and three months of drug administration. one out of twenty patients developed arthralgia (JPMA 37: 76 , 1987).

INTRODUCTION

Pyrazinarnide, the synthetic pyrazine analogue of nicotinarnide, is a bactericidal for M. Tuberculosis, particularly when growth of organism is inhibited by an acid environment, for example within macrophages.[1] The metabolic product of pyrazinamide is pyrazinoic acid, which in the presence of xanthine oxidase is converted to 5-Hydroxy pyrazinoic acid[2,3]. The drug is absorbed from gastrointestinal tract and diffuses readily into body tissues and fluids including C.S.F. It is mainly eliminated by metabolism, about 30% being excreted in urine as pyrazinoic acid and only about 4% as unchanged pyrazinamide. Pyrazinoic acid is believed to inhibit the renal tubular secretion of uric acid causing the serum uric acid concentration to rise; this is much more marked during daily rather than intermittent administration of drug[4], but is usually symptomiess.

The potent antituberculosis activity of pyrazinamide has been well established as it plays unique and important role in modern short course chemotherapy. It has been shown that pyrazinamide, in combination with Isaniazid and Rifampcin has changed the attitude towards treatment of tuberculosis[5]. The present communication describes the effect of pyrazinamide on uric acid levels in serum and urine and its correlation with arthralgia in combination with Isaniazid and myambutal.

MATERIAL AND METHODS

Twenty subjects of both sexes were selected from out patient department of Chest diseases. Their ages ranged from 6-60 years. All had clinical and radiological evidence of pulmonary tuberculosis and a positive A.F.B. smear of sputum. Those having history of arthralgia, gout, hepatitis or diabetes mellitus were excluded from the study.

All patients were given Myambutal (15 mg/Kg), Isoniazid (5mg/kg) and Pyrazinamide (30 mg/Kg) for a period of three months (The drugs were supplied free of cost to ensure compliance). Serum and urinary uric acid levels were determined by the method of Henery[6] in all cases prior to the administration of drugs. They were repeated monthly for three months and then after one month of withdrawal of drugs.

RESULTS

The data of serum and urine uric acid levels is summarized in Table I,

TABLE – I
Uric Acid Concentration in Serum and Urine.

Group	Serum Urine Acid mg/dl		Urine Uric Acid Gm/day	
	Mean	± S.D.	Mean	± S.D.
Pretreatment(I)	6.35	0.76	0.97	0.18
After one month (II)	7.70	0.92	0.83	0.23
After two months (III)	8.70	0.80	0.71	0.17
After three months (IV)	8.90	0.28	0.53	0.07
One month after (V) withdrawal	6.06	0.56	0.97	0.17

in which various stages are grouped from I to V.

TABLE – II

Mean Values of Uric Acid in Serum and Urine plotted in descending Order. The Bars showing no significant difference at 95% confidence Limit.

Serum Uric Acid (Mg/dl)	8.70	8.90	7.70	6.35	6.06
Urine Uric Acid (Gm/day)	0.97	0.97	0.91	0.71	0.53

Table II shows the mean comparison of uric acid concentrations in serum and urine before administration of drugs, during drug administration and one month after withdrawal of drugs. No

significant change in serum urinary and uric acid levels was found in pretreatment period and after withdrawa of the drug. However, during pyrazinamide therapy, there was a rise in the serum uric acid ($P < 0.05$) and a decline ($P < 0.05$) in urinary uric acid levels.
Group I and V (drugs free) and II, III and IV (with drugs) were combined and regression equation (Table III)

TABLE – III

Regression Equation (y=a+bx) derived to show the Effect of increasing Uric Acid levels and Urinary excretion of Uric Acid when y (Urine Uric acid) is dependent variable and x (Serum Uric Acid) being independent Variable.

	Regression equation (Y = a+bx)	Corelation coefficient (r)
With pyrazinamide.	1.079 - (0.0438 x X)	-0.2008
Without pyrazinamide	- 0.082 + (0.169 x X)	+0.624

were derived to find the effect of pyrazinamide on serum uric acid level and urinary excretion of uric acid. The regression co.efficient for drug free group was (a = -0.082 and r=0 .624). The slope of regression curve was steeper (a=1.079) with a negative correlation (r .0.2008) when patient were receiving drugs.

DISCUSSION

The present study is conducted with idea of exposing and emphasizing the adverse effect of pyrazinamide when administered in treatment of tuberculosis.
Experimental evidences suggest that such adverse effects invariably accompany the treat. ment and are manifested by an increase in the concentration of serum uric acid and decreased elimination of urinary uric acid. This may be due to pyrazinoic acid, the metabolic product of pyrazinamide, which suppresses the urinary excretion of uric acid by inhibiting its tubular excretion[7,8.]
The differences in concentration of uric acid in serum and urine between group I and II, and II and 111 are significant ($P<(0.05)$ whereas the differences in serum uric acid concentration for group III and IV are not significant ($P>0.05$), which indicates that serum probably becomes saturated at this concentration of uric acid after two months and that the retained uric acid must be deposited either in joints or tissues. At the same time there is a decline in urinary excretion of uric acid during drug therapy.
Analysis of variance was done for serum and urine uric acid levels between groups II, III and IV and

the differences in concentration, among groups were highly significant (P<0 .00 1).
The results are further supported by regression equation (Table III), which suggests that with the rise in serum uric acid concentration during drug therapy the urinary excretion of uric acid falls steeply.
It has been reported that 7% of patients on daily pyrazinamide developed arthralgia[9] .The incidence of arthralgia is also reported in patients with pyrazinamide administration in combination with streptomycin, Isoniazid, Rifampicin and in regimens including streptomycin, and Isoniazid[10,11] However in the present study only one patient (5%) developed arthralgia and the drug had to be withdrawn. This may be due to the variations in drug tolerance in different ethnic groups[12].
Concomitant administration of Rilampicin decreases the incidence of arthralgia caused by pyrazinamide[5], by exerting a uricosuric effect and also by causing a more rapid elimination of pyrazinoic acid, the inhibitor of uric acid excretion. It is possible that Rifampicin reduces the period of maximal suppression of uric acid excretion caused by pyrazinamide administration. The increased rate of uric acid elimination would in turn inhibit the rise in serum uric acid levels and this could lead to decreased tissue levels of uric acid with consequent lowering of incidence of arthralgia. In the present study concomitant administration of myambutal and INH caused decreased incidence of arthralgia following daily administration of pyrazinamide.

REFERENCES

1. Mitchison, D.A. Basic mechanism of Chemotherapy. Chest, 1979;76 (6 Suppi) : 771.
2. Ellord, GA. Absorption, metabolism and excretion of pyrazinamide in man. Tubercle, 1969; 50: 144.
3. Fanelli, G.M. and Weiner, LM. Pyxazinoate excretion in chimpanzee; relation to urate deposition and the actions of uricosuric drugs.J Clin. Investigat., 1973;52:1946.
4 Hong Kong Tuberculosis Treatment Services/ British Medical Research Council. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and Rifampicin in Hong Kong. Tubercie, 1976;57:81.
5. Sharma, G. R., Acharyulu, G.S., Kannapiran, M., Murthy, K., Gururnurthy, P. and Tripathy, S.P. Role of Rifampicin in arthialgia induced by pyrazinamide. Tubercie, 1983; 64:9 3.
6 Henery, R.J., Sobel, C. and Kim, J. A modified carbonate-phospototungstate methods for the determination of uric acid and comparison with the spectrophotometric uricase methods. Am. J. Clin. Pathol., 1957;28:645.
7. Yu, T.F., B urge, L., Stone, D.J., Wolf, J. and Gut-man, A.B. Effect of pyrazinamide and pyrazinoic acid on urate clearance and other discrete renal functions. Proc. Soc. Exp. Biol. Med., 1957 ; 96: 264.
8. Weiner, I.M. and Linker, J.P. Pharmacology of pyrazinamide; metabolic and renal functions studies related to mechanism of drug-induced urate retention. J. Pharmacol. Exp. Ther., 1972; 180: 411.
9. Hong Kong Tuberculosis Treatment Services! British Medical Research Council. Controlled trial of 6- and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong. Tubercle, 1975;56:81.
10. Tuberculosis Research Centre, Study of Chemotherapy regimens of 5 or 7 months duration and the role of Corticosteriods in treatment of sputum-positive patients with pulmonary tuberculosis in South India. Tubercie, 1982; 64:73.
11. Tripathy, S.P. Madras study of short-course chemotherapy in tuberculosis. Bull. Int. Union AgainstTubercul 1979;54:28.
12. Ilyas Khan, M. Adverse reactions of antituberculosis drugs with special reference to Rifampicin and Pyrazinamide.JPMA., 1984: 34:12.