PATTERN OF DRUG INDUCED HYPERURICAEMIA IN NIGERIANS WITH PULMONARY TUBERCULOSIS.

[1] Adebisi S.A., [1] Okesina A.B., [2] Oluboyo P.O.,
[1] Department of Chemical and Pathology and Immunology. [2] Department of Medicine Univeristy of Ilorin
P.M.B. 1515 Ilorin Nigeira

Thirty-one patients with newly diagnosed pulmonary tuberculosis were longitudinally studied between January 1997 and June 1998; each for 6 months to determine the pattern of drug induced hyperuricaemia. Biochemical indices determined were serum urate and 24 hours urinary output of urate, before and during treatment with antituberculosis therapy.

At the end of the 1st and 2nd months of therapy 16 (51.6%) and 15 (48.4%) of the patients respectively were hyperuricaemic. These were statistically significant when compared with the pretreatment data with P value of 0.001 and 0.002 respectively. At the end of the 6th months there was no significant difference in the incidence of hyperuricaemia observed as compared with the pretreatment level.

The pretreatment mean 24 hours urinary urate output was 4.83 mmol/24 hours, the corresponding values at the end of the 1st and second months of treatment was 3.38 mmol/24 hour and 3.74mmol/24 hours. These value are significantly lower than the pretreatment value with P value of P < 0.05 respectively. This however returns to the pretreatment range by the end of he 6th month of treatment with a value of 4.05 mmol/24 hours and P – value of 0.178.

We concluded therefore that while hyperuricaemia is a known cause of nephropathy, the pattern of drug induced hyperuricaemia that occurs in patients with pulmonary tuberculosis is self- limiting and should therefore not hinder us from optimizing the benefits of the drugs.

INTRODUCTION

In man, urate is the end product of catabolism of purine nucleoside, adenosine and guanosine. The elimination of urate from the body is mainly by renal excretion and to a lesser extent by intestinal uricolysis. Alterations in urate metabolism is one of the important complications of drugs used for the treatment of tuberculosis.

Three of the commonly used anti-tuberculous drugs: Ethambutol, Para-aminosalicylic acid (PAS) and Pyrazinamide have been shown to have effects on renal clearance of urate. Pyrazinamid is one of the first line drugs in the current antituberculosis drug regimen is used world wide, and it has remained the most powerful agent causing urate retention. Pyrazinamide exert its effects by suppresing normal tubular secretion of urate in the urine. By this action pyrazinamide becomes the most potent agent causing hyperuricaemia. This inhibition of tubular secreation also leads to reduction in renal elimination of urate by pyrazinamde.

The fact that hyperuricaemia causes renal damage is well established, this established fact informed our decision to examine the pattern of drug induced hyperuricaemia in patients with pulmonary tuberculosis.

MATERIALS AND METHODS

A total of 50 consecutive adults with newly diagnosed pulmonary tuberculosis from the chest clinic of the University of Ilorin Teaching Hospital were admitted to the study. After a detailed medical history and thorough clinical examination, to exclude people with evidence of renal impairment, urinalysis was carried out on every patient in order to define pretreatment renal function.

Patients that were included in the study were sputum positive on direction smear by Zheil Nelson stain for acid fast bacilli: a supportive chest x-ray was also mandatory. Individuals with any of the following conditions were excluded from the study; those with arthrits or findings suggestive of gout, those on uricosuric agent (like oestrogen, phenylbutazone or salicylate) those on hyperuricaemic drugs (like diuretics, salicylate, Nicotinic acid ethanol, L-Dopa and cytotoxic drugs), patients with myeloproliferative disease and those that have been previously treated for tuberculosis.

These patients had the six months, short course anit-tuberculous drug regime. This consist of isoniazid at 15mg/kg body weight, Rifampicin at 20mg/kg body weight. Ethambutol at 20mg/kg body weight and pyrazinamde at 25mg/kg body weight. Pyrazinamide and Ethambutol were used only for the first 2 months of the therapy.

Thirty one age and sex matched healthy controls were recruited (because of the 31% default among patients) also for the study. 5ml of blood was taken on the first day of visit before commencement of therapy. Subsequent samples were collected from the patients at the end of the 1st, 2nd, 4th and 6th months of therapy. Serum was separated from the blood sample and freezed at – 20°C unit assayed. Blood sample was taken from the control subjects for defining the reference range for the study.

Both the patients and the control subjects were also given one clean 2 litre plastic container for 24 hours urine collection. The volume was later recorded and an aliquot taken. Urate concentration both in the serum and in the urine was determined using the modified Caraway 1955 method. Prior to the assay, serum sample was allowed to thaw completely and to adjust to room temperature, while the urine sample was heated to 60°C to allow all urate precipitat to dissolve.

Statistical Analysis

Statistical analyses were carried out in an IBM compatible Personal Computer using EPI Info

*Corresponding Author

version 6.1. Which is a database and statistical software developed by the Centre for Disease Control, Atlanta, Georgia, United State of America. The percentages of those that developed hyperuricaemia was determined at the end of the 1st, 2nd, 4th and 6th month of therapy. The paired student t-test was used to determine the level of significance of mean urate values as compared with those of controls. The mean 24 hours urinary urate output at various stages of treatment was similarly assessed using paired student t-test.

RESULTS

The study which is longidinal lasted for 18 months One patient died, 4 requested for transfer letters while out of the remaining 45 patients, 31 (69%) completed the study while 14(31%) were lost to follow-up. 31 age and sex matched controls were also studied.
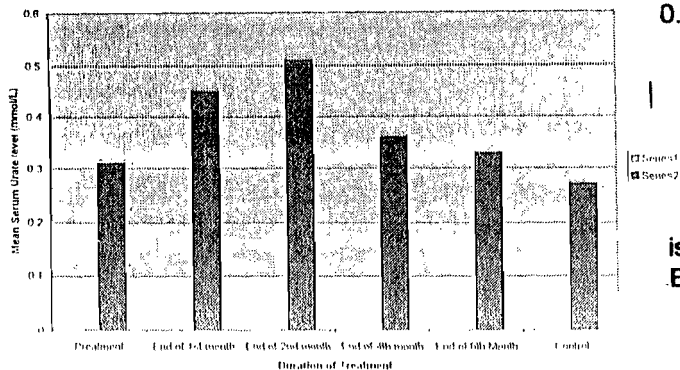
Serum Urate Level

Details of mean value of serum urate level and 24 hours urinary urate output of patients and controls is displayed in table 1. The table shows that the means serum urate level of controls subjects was 0.273 mmol/L (SD =0.777, range 0.119 – 0.427 mmol/4). The mean serum urate levels for the patients before the commencement of treatment, at the end of 1st month, end of 2nd month, end of 4th month and end of 6th month of treatment were: 0.311 mmol/L, 0.454 mmol/L, 0.510 mmol/L, 0.336 mmol/L and 0.330 mmol/L respectively.

VARIABLE	CONTROL	PATIENTS means (SEM)				
	Mean (SEM)	Pretreatment	End of first month	End of second month	End of fourth month	End of sixth month
Serum Urate mmol/L	0.27 (0.014)	0.31 (0.017)	0.45 (0.022)	0.51 (0.31)	0.36 0.019)	0.33 (0.014)
24 hours urinary urate excretion	3.40 (0.213)	4.83 (0.3349)	3.38 (0.326)	3.74 (0.402)	3.86 (0.407)	4.05 (0.467)

Table 1 Mean values of serum urate level of 24 hours urinary urate output.

Figure 1 shows that the mean serum urate level ncreases from pretreatment level with commencement of antituberculosis therapy and reaches its peak at the end of the second month. However, by the end of the 6th month it has fallen to the pre-treatment range. Using the mean serum urate level of the control population plus 2SD to define the upper limit for 95% of control subjects. Table II shows the percentage of patients with hyperuricaemia al various stages of treatment. Form the table it can be seen that 2(6.5%) subjects amongst the controls and 3(9.7%) amongst the patients before the commencement of treatment had hyperuricaemia.

There is no significant difference between these 2 percentage P > 0.89.

However, by the end of the 1st month of antituberculosis therapy, the number of patients with hyperuricaemia has increase to 16(51.6%). This percentage hyperuricaemia is statistically significant (P < 0.001) when compared with the controls. Also 15 (48.4%) patients were hyperuricaemic at the end of the second month of therapy. Again, this is statistical significant when compared with the control group (P < 0.02).

At the end of the 4th and 6th month of therapy the number of patients with hyperuricaemia had dropped to 5(16.15), and 2 (6.5%) respectively. These values are not significantly different from the control (P > 0.65 asd P > 0.89) respectively.

The changes in the percentage hyperuricaemia is graphically shown in figure 2. 24 hours Urinary Urate Excretion.

Fig 1. Pattern of Serum Urate level of patient at various level of Treatment

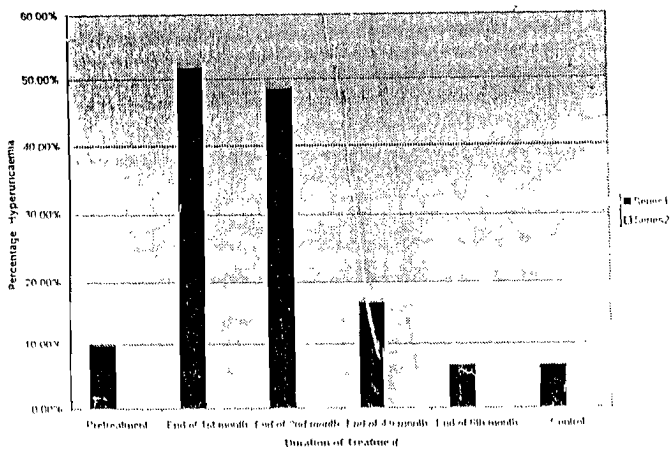Fig. 2. Percentage Hyperuricaemia Against the Duration of Treatment

Table 2 shows that the mean 24 hours urinary urate excrtion in the control group was 3.40 mmol/24 hours (SEM = 0.215), while the pretreatment value for the patients was 4.83 mmol/ 24hours (SEM = 0.350). Using student t-test for these two mean values (P > 0.005), there difference is statistically significant. Upon commencing anti-tuberculosis therapy the mean 24 hours urinary excretion reduced to 3.38 mmol/24 hours (SEM = 0.325) and 3.74 mmol/24 hours (SEM = 0.400) at the end of the 1st and 2nd months respectively. These mean values were significantly different from the pretreatment mean value with (P < 0.05 and P < 0.05) respectively. This however returns to the pretreatment range by the end of he 6th month with corresponding values of 4.05 mmol/24 hours (SEM = 0.475) and P – value of 0.178.

Duration of treatment	No of patients with value >0.427 mmol/L	n	% of patients with hyperuricaemia	P-value
Pretreament	3	31	9.7%	0.8946
End of 1st Month	16	31	51.6%	0.0001
End of 2nd month	15	31	48.4%	0.0002
End of 4th month	5	31	16.15%	0.655
End of 6th month	2	31	6.5%	0.8946
Control	2	31	6.5%	

Table II
Scrum Urate Level of patients compared with that ot controls

Figure 3 shows the relative proportions of the 24 hours urinary urate output.

Fig. 3. Pattern of Mean 24 Hours Urinary Urate Excretion in patient on Treatment
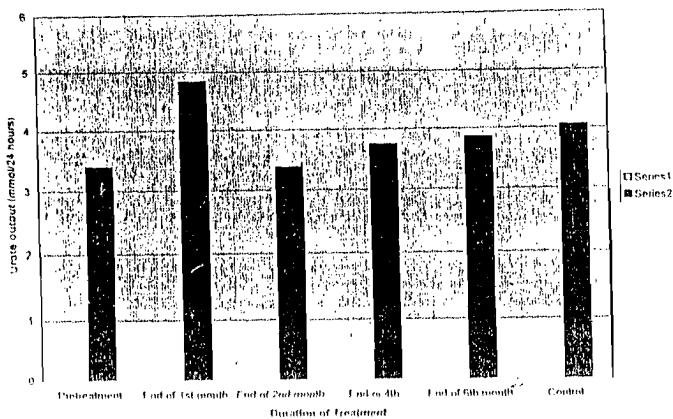
DISCUSSION

DeCock et al and many other workers revealed that the prevalence of tuberculosis is increasing in sub-saharan Africa. As Gizybowski put it that "in order to reduce the tuberculosis problem, we must reduce the risk of tuberculosis infection; this is best achieved by finding cases of tuberculosis and curing them permanently with approprite chemotherapy". The six-month short course regimen using isioniazid, rifampicin, pyrazinamide and ethmabutol (or streptomycin) is the common drug regime in use globally now. However, the problem of poor drug compliance remains a very difficult one to solve, in fact Houston et al in their review concluded that "very poor compliance is the rule rather than the exception in operational surveys of tuberculosis programmes". The present study recorded a 31% default rate, a value that is an agreement with the summation of Houston et al.

In addition to poor compliance, the problem of side effects and biochemical derangements, mot'importantly hyperuricaemia has been well documented. The use of pyrazinamide in the treatment of pulmonary tuberculosis was first reported by Yeager et al in 1952. They noted the occurrence of pain and

restricted joint motion without redness, in one-fourth of the patients they treated. Also Zierski and Bek reported that 56% of patients on pyrazinamide developed hyperuricaemia. Our study with 51.6% of the patients developing hyperuricaemia is in agreement with above mentioned works on the prominence of hyperuricaemia, as a drug induced problem in patients with tuberculosis.

However, the pattern of hyperuriaemia as revealed by this study that 9.7%, 51.6%, 48.4%, 16.1% and 6.5% of the patients have hyperuricaemia before treatment at the end of the 1st, 2nd, 4th and 6th months of therapy respectively is very instructive: While it confirms the earlier finding that hyperuricaemia is derangement of high frequency, it however shows also that the serum urate level returns to normal by the end of the sixth month of therapy.

This study recorded significantly higher 24 hours urinary urate output by patients before treatment when compared with the control group. This could possibly result from the diseased state impairing the extrarenal pathway of urate excretion or enhancing tubular secretion of urate like nephrotic syndrome does to creatinine secretion. However, because of inhibition of tubular secretion of pyraziamide there was a significant reduction in the 24 hours urinary urate output. This finding is in agreement with the findings of Elland and Haslam. They also observed a significant decrease in the 24 hours urinary urate output n patients on pyrazinamide. The lower 24 hour urinary urate excretion at the end of the 6th month of therapy when compared to the pretreatment 24 hours urinary urate excretion has been attributed to activation of extrarenal routes by the hyperuricaemia associated with the treatment.

We therefore conclude that the drug induced hyperuricaemia seen in patients with pulmonary tuberculosis is transient and also helps in opening up the extrarenal pathway of urate excretion blockd by the disease itself before treatment. We however suggest that further studies be done to assess the effect (if any) of the transient hyperuricaemia on the renal function in patient with pulmonary tuberculosis on treatment.

REFERENCES

1. Cullen JH, LeVine M, Fiore JM: Studies of Hyperuricaemia produced by pyrazinamide. AMJ Med. 1957; 23: 587-595.
2. Kelly Wal: Effect of drugs on urate in man. Annu Rev. Pharmacol 1995: 15: 327-250.
3. Weiner IM, Tinker JP: Pharmacology of Pyrazinamide: Metabolic and renal function studies related to the mechanism of drug induced urate retention. J of Pharmacol and Exper. Therapeu 1972: 180: 411–433.
4. DeCock KM, Soro B, Coulibably IM, Lucas SB: Tuberculosis and HIV infection in Sub-Saharn Africa JAMA 1992: 268: 1581-1587.
5. Steel TH: Urate secretion in man: the pyrazinamde suppresion test. Ann Inter med 1973: 79: 734-737.
6. Ellard GA, Haslam RM: Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamde. Tubercule 1976: 57-97-103.
7. Kjell MC, Campell DC: Hyperuricaemic acute renale failure. Arch Intern Med. 1979: 133: 349-359.
8. Omidosu, J.O. Babawale DT: Chemical Pathology Laboratory Mannual 2nd edition. Ilorin University Press, 1980.
9. Houston, S. Pozniak A, Ray CS: Therapeutic review: Tuberculosis. The centr. Afr. J. Med. 1991: 37-250-259.
10. Taylor DA, Thomas SEP: the clinical pattern of Tuberculosis in Zimbabwe, 1994-81 The Centr. Afr. J. Med. 1983: 29: 193-196.
11. Grzybowski S: strategies for world-wide control tuberculosis. Chest 1979, 76 (Supp) S1-S8.
12. Onadeko BO, Sofowora EO: Comparative trial of Thiacetazone with isoniazid and para-aminosalicylic acid (PAS) with isoniazid in the treatment of pulmonary tuberculosis in Nigeria J. Trop Med Hyg. 1995: 78:210-205.
13. Combs DL, O'Brian RJ: USPHS tuberculosis short course chemotherapy trial 21: Effectiveness, toxicity and acceptability. The report of final results. Ann Intern Med. 1990: 112:397-407.
14. Yeager R.L. Munraf WGC, Dessam Fl: Pyrazinmide (aldinamide) in the treatment of pulmonary tuberculosis. AM Rev. Tubers 1952: 65:523.
15. Zierski, M, Bek E: Side effects of drugs regimes used in short course chemotherapy for pulmonary tuberculosis. A controlled clinical study. Tubercle 1980: 61:14-49.
16. Sorensen IB: the elimination of urate in man studied by means of C labbeled urate. Scand Jelin lab invest 1960: 12 supplementum 54.