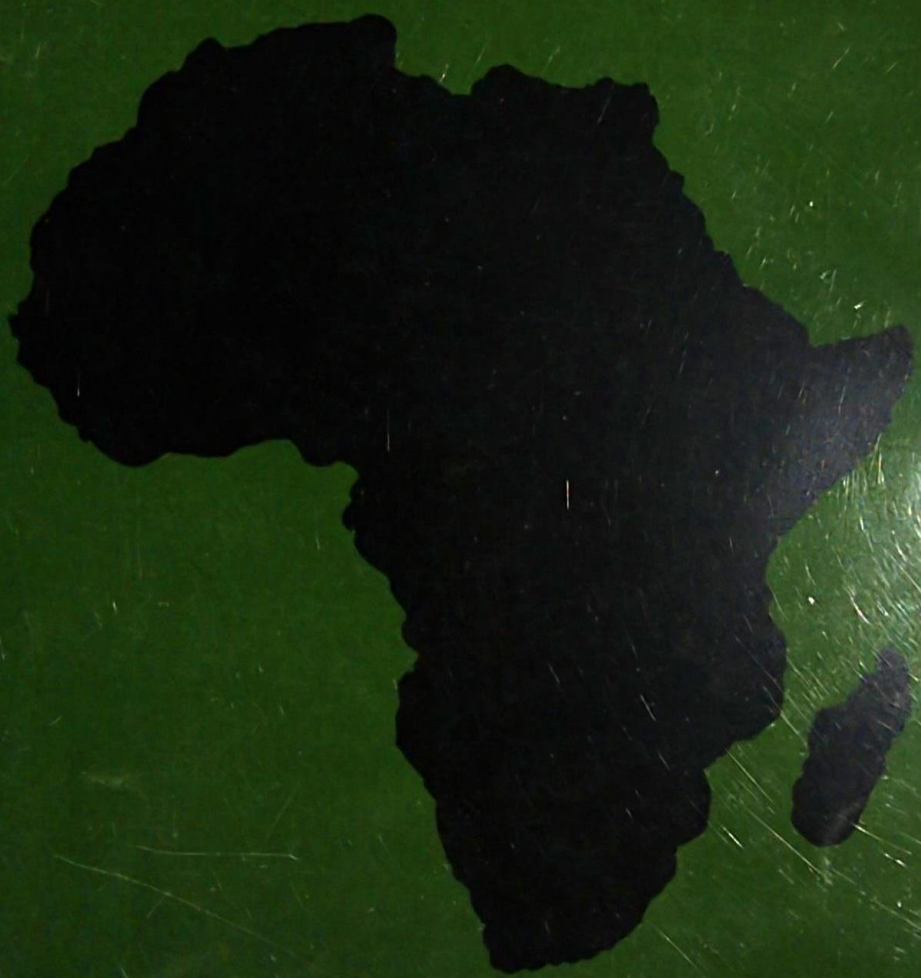
AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 29, NUMBERS 3 & 4, SEPT. & DEC. 2000



EDITOR:
B. O. OSOTIMEHIN

ASSISTANT EDITOR:
A. O. UWAIFO

ISSN 1116 — 4077

Afr. J. Med med. Sci. (2000) 29, 297 - 300

Effect of drug-induced hyperuricaemia on renal function in Nigerians with pulmonary tuberculosis

**SA Adebisi, **PO Oluboyo and *AB Okesina
*Department of Chemical Pathology & Immunology, **Department of Medicine
University of Ilorin, Ilorin, Nigeria.

Summary

Some anti-tuberculosis chemotherapeutic agents have been established as causing hyperuricaemia. Hyperuricaemia in turn causes renal damage. This study therefore aims at establishing the effect of anti-tuberculosis drugs-induced hyperuricaemia on renal function of the patients. Fifty patients with newly diagnosed pulmonary tuberculosis with mean age of 36.8 years (SD 13.69) consisting of 14 females and 17 males were longitudinally studied each for 6 months to determine the effect of drug-induced hyperuricaemia on their renal function. The Biochemical indices determined included serum urate level, serum creatinine level, and creatinine clearance of newly diagnosed patient with tuberculosis, before and during treatment with anti-tuberculosis therapy. Serum urate level revealed that 16 (51.6%) and 15 (48.4%) of the patients were hyperuricaemic at the end of the first and second months of anti-tuberculosis therapy. There was no significant difference in the mean serum creatinine level of the control group 96 µmol/L when compared with both the pre-treat value 89µmol/L ($P > 0.25$) as well as the value at the end of the sixth month of treatment 91 µmol/L ($P > 0.40$). However, there was a statistically significant difference in the mean creatinine clearance of the control group 102 ml/min/1.73m² when compared with the patient's mean pre-treatment value (89 ml/min/1.73m²) $P < 0.05$. Also the mean creatinine clearance increased to (103 ml/min/1.73m²) by the end of the 6th month of treatment, a value that is statistically significant when compared with the pre-treatment value of (89 ml/min/1.73m²) $P < 0.05$. We submit as follows; that pulmonary tuberculosis as a disease with significant impairment of renal function; despite the associated drug-induced hyperuricaemia recorded during the treatment, renal function steadily improved with the treatment of pulmonary tuberculosis to the extent that comparable values with control was obtained at the end of treatment. We conclude therefore that drug-induced hyperuricaemia associated with treatment of pulmonary tuberculosis has no detectable negative effect on renal function of the patient

Keywords: *Hyperuricaemia, drug induced, renal function, tuberculosis*

Résumé

Certain agents chimiotherapeutiques anti-tuberculeux ont ete établis comme cause d'hyperuricaemie. L'hyperuricaemie oi en tour abime les reins. Le but de cette etude est d'etablir l'effet des medicaments anti-tuberculeux enduit hyperuricaemie sur la fonition renale des malades. Cinquante patients ayant la tuberculose pulmomaire nouvellement diagnostique, d'age moyen de 36,8 aus (SD 13.69) constitue de 14 femmes et de 17 hommes ont ete etudie longitudinallement, chacem pendant 6 moix, pour determiner l'effet des medicaments induis d'hyperuricaemie sur leur fonition remale. Les indices biochimiques determines incluaient le niveau du serum urate, niveau de serum creatimine, *et al* disparition de la creatinine chez les patients nonvellement diagnostiques de la tuberculose, avant et au conrs du traitement de therapic anti-tuberculeux. Le niveau du serum urate a revele que 16 (51,5%) et 15 (48, 4%) des patients etaient hyperuricaemique a la fin du premier et second mois de traitement anti-tuberculeux. Fe n'yavait pas de difference significative sur le niveau moyen du serum creatinine du groupe de control 96: mol/L lorsque compare avec la valeur pre-traitement 89: mol/L ($P < 0,25$) ainsi que la valeur a la fin des six mois de traitement 91: mol/L ($P > 0,40$). Cependant, il yavait une difference statistique significative du nivean moyen de dispation du senum creatinine du groupe de controle 102 ml/min/1,73 m^2 lorsque compare avec la valeur moyenne (89 ml/min/1,73 m^2) $P < 0,05$. Nous sonmettons par la suite, que la tuberculose pulmonaire comme moladie abimant la fonition renale; malgre l'association de medicament induis d'hyperiricaemie relevec au courant du traitement, la fonition renale improvait progressivement avec le traitement de la tuberculose jusqu'a le que des valeurs comparables a ceux du controle etaient obtemues a la fin du traitement. Nous coniluous alors que le medicament induit associe au traitement de la tuberculose pulmonaire n'a aucum effet nigatif detectable sur la fonction renale du patient.

Introduction

Alterations in urate metabolism leading to hyperuricaemia is one of the important complications of drugs in use for the treatment of tuberculosis. Pyrazinamide, an important component of short course chemotherapy in the management of tuberculosis has been identified as the most potent chemical agent causing hyperuricaemia[1,2,3,4]. Pyrazinamide exerts its effect by suppressing normal tubular secretion of urate into the urine. This inhibition of tubular secretion also leads to reduction in renal elimination of urate by pyrazinamide as a result of reduction in the amount of urate delivered to the tubules.

Hyperuricaemia is a known cause of renal damage [6]. Both functional and structural damage to the kidney may result from hyperuricaemia [7]. However studies on effect of drug-induced hyperuricaemia is very rare in this environment. This fact informed our decision to study the effect of anti-tuberculous drug-induced hyperuricaemia on renal function 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 hospital were admitted to the study. Fifty age and sex matched healthy controls were also recruited from the General Medical Clinics of the Medical Out Patients. After a detailed medical history and thorough clinical examination was done to exclude those with evidence of renal impairment, urinalysis was carried out

Correspondence: Dr. P.O. Oluboyo, Department of Medicine, University of Ilorin, P.M.B. 1515, Ilorin, Nigeria.

Table 2: Clinical data of subjects

	SEX	AGE	PUR1	PUR2	PUR3	PUR4	PUR5	CC1	CC2	CC3	CC4	CC5
1	1	35	0.45	0.48	0.35	0.35	0.38	77.23	74.23	103.10	87.81	80.77
2	1	25	0.35	0.43	0.45	0.38	0.38	64.23	81.23	89.10	96.81	92.77
3	2	42	0.31	0.51	0.41	0.39	0.34	99.23	129.23	119.10	131.81	154.77
4	1	35	0.40	0.45	0.75	0.53	0.45	68.23	5.23	77.10	86.81	74.77
5	1	32	0.40	0.53	0.38	0.35	0.30	93.23	118.23	127.10	98.81	116.77
6	1	25	0.30	0.33	0.38	0.33	0.30	87.23	101.23	89.10	118.81	124.77
7	2	54	0.33	0.54	0.58	0.50	0.30	68.23	71.23	91.10	79.81	88.77
8	1	30	0.28	0.36	0.41	0.22	0.26	100.23	104.23	106.10	108.81	103.77
9	2	23	0.22	0.42	0.36	0.32	0.26	66.23	61.23	76.10	66.81	62.77
10	1	16	0.32	0.26	0.26	0.26	0.30	80.23	70.23	94.10	95.81	108.77
11	2	32	0.23	0.33	0.35	0.30	0.25	117.23	122.23	137.10	139.81	121.77
12	2	26	0.15	0.30	0.35	0.25	0.20	97.23	95.23	110.10	113.81	99.77
13	2	17	0.40	0.63	0.78	0.60	0.41	97.23	105.23	111.10	92.81	106.77
14	2	40	0.23	0.30	0.40	0.35	0.30	108.23	104.23	98.10	97.81	95.77
15	1	35	0.23	0.35	0.40	0.28	0.25	82.23	97.23	103.10	107.81	103.77
16	1	20	0.40	0.53	0.70	0.35	0.40	73.23	76.23	83.10	74.81	95.77
17	1	48	0.23	0.28	0.35	0.15	0.25	106.23	106.23	122.10	106.81	111.77
18	2	23	0.53	0.56	0.80	0.29	0.28	105.23	104.23	109.10	104.81	106.77
19	1	39	0.23	0.48	0.40	0.35	0.30	73.23	68.23	80.10	77.81	79.77
20	2	75	0.23	0.35	0.40	0.30	0.29	98.23	97.23	96.10	95.81	99.77
21	1	37	0.35	0.39	0.56	0.39	0.33	78.23	99.23	87.10	90.81	108.77
22	2	59	0.39	0.39	0.45	0.39	0.39	100.23	92.23	98.10	104.81	104.77
23	1	45	0.48	0.68	0.78	0.64	0.60	79.23	112.23	117.10	78.81	95.77
24	2	32	0.29	0.77	0.47	0.38	0.29	72.23	75.23	82.10	77.81	86.77
25	2	60	0.29	0.60	0.70	0.50	0.30	99.23	115.23	108.10	105.81	114.77
26	2	35	0.25	0.36	0.40	0.38	0.30	120.23	125.23	93.10	100.81	124.77
27	2	35	0.12	0.54	0.52	0.39	0.41	129.23	129.23	130.10	130.81	129.77
28	2	33	0.29	0.45	0.48	0.29	0.28	82.23	112.23	123.10	110.81	122.77
29	1	60	0.23	0.39	0.74	0.29	0.25	70.23	85.23	87.10	100.81	86.77
30	2	32	0.33	0.54	0.87	0.31	0.39	88.23	99.23	119.10	88.81	88.77
31	2	40	0.39	0.41	0.40	0.39	0.39	77.23	99.23	95.10	94.81	98.77

Table 3: Analysis of variance for mean values of serum urate, creatinine and creatinine clearance respectively.

Source of variance	Degree of freedom	Sum of square	Means square	Variance ratio	F
		Serum urate			
Time	5	1.22255	0.24451	19.20	<0.001
Residual	180	2.29235	0.01274		
Total	185	3.51489			
		Serum creatinine			
Time	5	792.5	158.5	0.24	0.946
Residual	180	120556.5	669.8		
Total	185	121344.0			
		Creatinine clearance			
Time	5	42,549	851.0	2.11	0.066
Residual	180	72,587.2	403.3		
	185	76,842.0			

serum urate levels.

The mean serum creatinine level was 96 µmol/L and 89 µmol. L for the control group and the patients respectively before commencement of treatment. The difference between these two mean values is not statistically significant ($P > 0.05$). The mean creatinine level of 92 µmol/L; 93 µmol/L 92 µmol/L; 934 µmol/L 92 µmol/L and 91 µmol/L at the end of the 1st, 2nd, 4th and 6th months of chemotherapy with corresponding P-values of 0.491 0.60; 0.50 and 0.40 when compared with the pretreatment value did not demonstrate any statistically significant difference.

The mean creatinine clearance values was 102 ml/min/173m² and 89 ml/min/173m² for the control group and the patients before treatment respectively. These two mean values were significantly different when compared with a *P*-value of 0.013. The mean creatinine clearance value at the end of the 1st month of chemotherapy (97 ml/min/173m²) was not significantly different from the pre-treatment value ($P = 0.085$). However, at the end of the 2nd, 4th and 6th months

on every patient in order to define their pre-treatment renal function.

Inclusion criteria were: patients with positive sputum on direct smear by Ziehl Neelson stain for acid fast bacilli, also a supportive chest x-ray was mandatory for inclusion. Exclusion criteria include presence of any of the following: (i) Arthritis or findings suggestive of gout, (ii) those on uricosuric agent like Oestrogen, phenylbutazone, salicylate or sufinpyrazxone (iii) those on hyperuricaemic drugs like diuretics, salicylate, Nicotinic acid, Ethanol, L-Dopa and cytotoxic drugs . (iv) patients with myeloproliferative disease (v) those that have been previously treated for tuberculosis.

The selected patients were subsequently placed on 6 months' short course anti-tuberculosis therapy consisting of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide with the last two drugs being used only for the first two months of therapy. Informed consent was obtained from the patients as well as the healthy controls, and the study was approved by the Ethical and Research Committee of the University of Ilorin Teaching Hospital.

Blood samples were taken from the patients before the commencement of chemotherapy and at the end of the 1st, 2nd, 4th and 6th month of therapy for the determination of serum urate and creatinine. Twenty four - hour urine collection was also carried out before treatment and at the end of the 1st, 2nd, 4th and 6th month of treatment for the determination of the creatinine clearance. Urate level was determined using the modified Caraway method. [8] Creatinine was determined using the Rebery-Folin method based on Jaffe's reaction [8] .

Statistical analyses were carried out in an IBM-compatible Personal Computer using EPI Info version 6.1. A one-way ANOVA was done for mean values of serum urate, serum creatinine, and creatinine clearance; with further evaluation using the Student t-test. The percentages of those that developed hyperuricaemia was determined at the end of the 1st, 2nd, 4th and 6th months of therapy.

Results

The study lasted for 18 months, January 1997 to June 1998. Four patients requested for transfer before completing the study, one patient died during the first week of treatment. Of the remaining 45 patients, 31 (69%) completed the study while 14 (31%) were lost to follow-up. This was made up of 17 males and 14 females with mean age of 36.77 years (SD 13.69) and age range of 16-75 years. Only the corresponding 31 age and sex matched controls were involved in the analysis. Tables 1 and 2 shows the clinical data of the control group and the subjects respectively

The mean serum urate level of control subjects was 0.273 mmol/L (SD = 0.077). 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: 0.31 mmol/L, 0.45 mmol/L, 0.512 mmol/L, 0.34 mmol/L and 0.33 mmol/L respectively. Using the mean serum urate level of the control population plus 2SD to define the upper limit for 95% of control subjects, 3 (9.7%), 16(51.6%); 15 (48.4%); 5(16.1%) and 2(6.5%) of the patients developed hypericaemia before commencement of chemotherapy, at the end of the 1st , 2nd, 4th and 6th month respectively. Table 3 shows the one-way analysis of variance for serum urate, creatinine and creatinine clearance. With an F probability of <0.001 this shows that there existed a statistically significant difference in the mean

Table 1: Clincal data of control group

Sex	Age	Pur	CC
1	20	0.20	76.33
1	60	0.28	89.33
2	65	0.25	74.59
1	23	0.25	114.84
1	38	0.18	58.29
1	30	0.20	97.15
2	56	0.28	195.82
1	55	0.43	102.74
2	50	0.23	79.49
2	47	0.33	102.52
2	30	0.40	74.59
1	28	0.33	95.64
1	37	0.48	74.66
1	32	0.25	143.01
2	28	0.40	117.05
2	28	0.20	126.87
2	25	0.28	82.18
2	26	0.25	72.25
2	24	0.23	61.24
2	26	0.30	104.19
2	25	0.20	143.01
1	23	0.28	105.29
1	25	0.15	156.65
1	22	0.28	87.99
1	19	0.13	102.74
1	24	0.30	114.92
1	22	0.25	100.97
1	25	0.28	80.62
1	40	0.28	113.47
2	33	0.23	109.45
2	26	0.30	104.19

Keys for Tables 1 and 2

Sex: 1 = Male; 2 = Female

Pur = Serum urate

CC = Creatinine clearance

1 = Pre-treatment value

2 = End of first month

3 = End of second month

4 = End of fourth month

5 = End of sixth month

of anti-tuberculosis chemotherapy, the mean creatinine clearance values were 102 ml/min/173m², 99 ml/min/173m² and 103 ml/min/173m² respectively. These values were significantly higher than the pre-treatment creatinine clearance value with *P*-values of 0.003; 0.018 and 0.002 respectively. When the mean creatinine clearance at the end of 6 months of anti-tuberculosis therapy (103 ml/min/173m²) was compared with the control group value (102 ml/min/173m²) using Student t-test, it showed that there was no statistically significant difference between these two means $P > 0.05$.

Discussion

Hoston *et alv* [4] and Young [10] observed that the greatest burden of tuberculosis morbidity is borne by people in the reproductive age-group (15-52 years). Our study with a mean patient's age of 36.8 years (SD 13.69) is in agreement with these earlier findings. Tuberculosis infection therefore predominantly affects people upon whom the society depends both economically and socially. Zierski and Beki [11] reported that 56% of patients on pyrazinamide developed hyperuricaemia. Many other workers have since confirmed the hyperuricaemia at the end of the first month of anti-tuberculosis chemotherapy agreeing with the above-stated associated between anti-tuberculosis therapy and hyperuricaemia.

Despite the finding of high incidence of hyperuricaemia during treatment, it is however noteworthy from our findings that no significant difference was found between the mean serum creatinine of the control group and that of patients throughout their period of treatment. However, there was a significant difference in the mean creatinine clearances of the control group (102 ml/min/173m²) and the patients in their pre-treatment (89 ml/min/173m²) state ($P < .05$). This shows that there was some impairment of renal function associated with the disease of pulmonary tuberculosis. Also the present study reveals that the creatinine clearance increases significantly when the mean creatinine clearance of the patients before treatment (89 ml/min/173m²) was compared with their end of 6-month therapy value (103 ml/min/173m²). The difference observed from the statistical analysis of the values of serum creatinine and creatinine clearance is consistent with the observation of Andrew et al [14]. They reported that serum creatinine may remain within the normal range at values for glomerular filtration rate as low as 20-30 mls/min/173m². This relative stability of serum creatinine despite changes in the creatinine clearance further confirm the established fact that serum creatinine is not as sensitive as creatinine clearance in monitoring changes in glomerular filtration rate.

We therefore conclude that the target population for pulmonary tuberculosis remains that of people in their most productive age. Also some degree of renal impairment is associated with pulmonary tuberculosis as a disease. Hyperuricaemia during anti-tuberculosis therapy is transient and reversible. Lastly, there was no evidence of functional damage to the kidney by the drug-induced hyperuricaemia, rather there was evidence of renal function improvement with treatment of the tuberculous disease.

References

1. Cullen JH, LeVine M and Fiore JM: Studies of Hyperuricaemia produced by pyrazinamide. Am. J Med 1957; 23: 587-595.
2. Weiner IM and Tinker JP: Pharmacology of pyrazinamide: Metabolic and renal function studies related to the mechanism of drug induced urate retention. J. Pharmacol Exper. Thera. 1972; 180: 411-433.
3. De Cock KM, Soro B, Coulibably IM and Lucas SB: Tuberculosis and HIV infection in Sub-Saharan Africa. JAMA 1992; 268: 1581-1587.
4. Steel TH: Urate secretion in man: the pyrazinamide suppression test. An Int med 1973; 79: 734-737.
5. Ellard GA and Haslam RM: Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. Tubercule 1976; 57:97-103.
6. Kjell MC and Campell DC: Hyperuricaemic acute renal failure. Arch Intern Med. 1979; 133:349-359.
7. Weinman EJ and Kinght TF: Uric acid and the kidney. In Suki WN, Eknoyan G (editor). The kidney in systematic disease. 2nd edition. New York, Medical Publication 1981; 285-305.
8. Omidosu JO and Babawale DT: Chemical Pathology Laboratory Manual. 2nd edition. Ilorin University Press, 1980.
9. Houston S, Pozniak A and Ray CS: Therapeutic review: Tuberculosis. Centr. Afr. J. Med. 1991; 37: 250-259.
10. Young DB: Tuberculosis: The return of an old nemesis: ODYSSEY 1995; 1:10-17.
11. Zierski M and Bek E: Side effects of drugs regimens used in short course chemotherapy for pulmonary tuberculosis. A controlled clinical study. Tubercle 1980; 61:14-49.
12. Combs DL and O'Brian RJ: USPHS tuberculosisshort course chemotherapy trial 21: Effectiveness, toxicity and acceptability. The report of final results. Ann intern Med. 1990; 12: 397-406.
13. Amajed SA, Pandya I, Alhalla SR, Alwakeel J and Alsharif N: Hyperuricaemia during treatment for active pulmonary Tuberculosis in a Multiracial population. Saudi Med. J. 1995; 16: 330-333.
14. Andrew SL., Ronal DP and Nicolas EM: Serum creatinine and renal function. Ann Rev. Med. 1988, 39: 465-490.