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Effects on Body Elemental Composition of Prophylactic Diuretic Treatment of Urinary Lithiasis

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Summary. Whole body elemental composition was measured by in vivo neutron activation analysis before and after treatment of urinary stone-formers with bendrofluazide for 6 months. There was no significant change in whole body calcium, sodium, nitrogen or body weight. There were significant reductions in whole body potassium (6%), chlorine (7.3%) and phosphorus (1.5%).

Key words: Neutron activation analysis - stone formers - bendrofluazide.

One method used to reduce recurrence of urinary tract stone disease is to reduce urinary calcium by either thiazide diuretics (17) or sodium cellulose phosphate (10). Our understanding of the mechanisms by which these drugs are effective is incomplete, and it is possible that they disturb the homeostasis of calcium to such an extent that patients also risk developing heterotopic calcification.

We have therefore examined the effect of a course of bendrofluazide given with potassium supplements on body elemental composition, as measured by total body in vivo neutron activation analysis.

PATIENTS

Eleven "idiopathic" stone formers (9 male, 2 female) were studied (Table 1). All gave their informed consent. No patient showed evidence of hyperparathyroidism as judged by estimations of serum calcium, phosphate and alkaline phosphatase, and calculated values of maximum tubular phosphate reabsorption per litre glomerular filtrate, phosphate excretion index, or urinary calcium/creatinine ratio. There was no evidence of renal impairment, since all gave normal values for serum creatinine and creatinine clearance, and all serum electrolytes were normal. Six patients had hypercalciuria as measured by atomic absorption spectrophotometry on a 24 h urine collection when on a free diet. The majority of stones available for analysis consisted of calcium phosphate, and there was one mixed calcium phosphate and oxalate stone. This accorded with the usual constitution of urinary tract stones in the Glasgow area (14). In five cases the stone had either been passed and discarded by the patient or was still in situ, the diagnosis then being made by X-ray.

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METHODS

Whole body potassium was measured by whole body counting, using its natural radioactivity. The whole body contents of calcium, phosphorus, nitrogen, sodium and chlorine were measured by in vivo neutron activation analysis. The equipment used and its performance are described in detail elsewhere (2, 6, 16). Briefly, the patient is irradiated with neutrons while lying on a bed which passes between two sealed-tube neutron generators. He is then transferred to a scanning bed, shadow-shield whole body counter with which

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Table 1.

Patient no.	Sex	Ht m	Wt kg	Age a	Duration of treatment months	Urinary calcium mmol/24 h* before	after	Stone formation	Stone analysis
1	M	1.76	82.8	40	6.7	-	-	single	Ca. Mg. phosphate
2	M	1.68	79.7	64	7.6	5.9	4.1	recurrent	Ca. phosphate
3	M	1.58	66.4	56	5.0	6.0	3.0	single	Ca. phosphate, oxalate
4	M	1.74	80.6	52	5.9	16.5	8.4	single	Ca. Mg. phosphate
5	M	1.77	73.2	56	6.7	12.3	9.7	recurrent	radiograph only
6	M	1.74	78.5	66	5.3	16.3	9.2	single	N.A.
7	M	1.58	77.0	49	5.0	5.0	-	single	N.A.
8	M	1.68	56.0	54	6.2	-	6.0	recurrent	radiograph only
9	M	1.74	85.8	48	5.0	11.3	6.2	recurrent	Ca. phosphate
10	F	1.50	53.6	44	4.9	10.4	9.2	recurrent	N.A.
11	F	1.50	54.0	48	4.9	15.3	9.3	recurrent	Ca. Mg. phosphate, oxalate
	mean	1.66	71.6	52.4	5.7	11.0	7.4		
	S.D.	0.10	12.1	7.9	0.9	4.9	2.6		

*normal range 3-6 mmol/24 h
N.A. Stone not available for analysis

the radioactivity induced by the neutrons is measured.

After initial measurements of whole body elemental composition, and urinary calcium, patients were given bendrofluazide 5 mg daily and Slow K (Ciba) 600 mg t.d.s. for periods ranging from 4.9 to 7.6 months (mean 5.7 mo). Whole body composition and urinary calcium measurements were repeated at the end of treatment, except that in a few cases a satisfactory urine sample was not obtained. The months in which measurements were made were distributed throughout the year to avoid bias in the results due to seasonal variations in calcium metabolism (9) and stone formation (12).

RESULTS

The efficiency of a thiazide diuretic in lowering urinary calcium has been confirmed (Table 1, $P < 0.01$, paired t-test). In addition during the period of treatment no patient produced a new stone and none complained of any side effect of therapy. There were no significant changes in serum electrolytes during treatment, and in particular serum potassium remained within the normal range.

The results of whole body elemental measurements before and after treatment are given in Table 2. Predicted values for each element according to the patient's height, weight, age and sex are also given. We have not yet studied normal subjects, and have therefore derived the predicted values from equations based on data from normal subjects studied elsewhere for potassium (1), calcium (4), sodium (5) and nitrogen (3); and for chlorine from normal values for extracellular fluid volume (13) multiplied by mean serum chloride concentration. We have found a constant phosphorus/calcium ratio in other studies (2), and from this ratio have derived expected phosphorus values. Before treatment the mean body potassium was higher than expected by 8.3% ($P < 0.05$, paired t-test), but for other elements the results were insignificantly different from predicted values. While the mean sodium was significantly lower than predicted, we have a similar finding in other groups of patients, suggesting that there is a small systematic difference between our measurements of sodium and those made by Ellis et al. (5) from which the predicted amounts were derived.

After treatment with bendrofluazide no significant changes were observed in whole body calcium, sodium and nitrogen nor in body weight. There were significant reductions in potassium ($P < 0.01$, paired t-test), chlorine ($P < 0.01$), and phosphorus ($P < 0.02$).

DISCUSSION

Prolonged drug therapy is always likely to produce side effects which may be of a subtle biochemical nature and therefore not readily noticed. Thus, treatment with a long course of a thiazide diuretic is potentially hazardous. Whole body

Table 2. Whole body elemental composition

Patient no.		Weight kg	Ca g	Ca/Ca_p	P g	P/P_p	N g	N/N_p	Na g	Na/Na_p	Cl g	Cl/Cl_p	K g	K/K_p
1	a	82.8	1192	1.051	665	0.979	1952	0.951	84.9	0.991	66.3	0.928	164	1.072
	b	85.8	1184		645		1880		81.0		67.2		152	
2	a	79.7	1035	1.041	532	0.902	1649	0.928	77.3	0.946	73.1	1.133	139	1.078
	b	78.9	1015		538		1594		67.8		57.5		113	
3	a	66.4	853	1.002	506	1.041	1574	0.865	69.0	0.954	53.3	1.018	143	1.342
	b	65.8	883		480		1622		68.1		47.1		126	
4	a	80.6	1241	1.153	688	0.973	2124	1.035	83.8	0.999	71.0	1.026	164	1.155
	b	80.6	1221		680		2083		83.7		63.9		150	
5	a	73.2	986	0.907	575	1.023	1824	1.014	78.6	0.962	77.1	1.122	141	1.022
	b	74.2	1027		576		1853		87.8		68.9		130	
6	a	78.5	1083	1.023	606	0.982	1758	1.091	79.5	0.954	70.0	1.023	124	0.918
	b	79.8	1072		598		1803		86.9		69.7		125	
7	a	77.0	1010	1.132	570	0.990	1629	0.918	79.6	1.034	60.5	1.076	139	1.159
	b	75.8	1063		551		1724		79.2		55.8		136	
8	a	56.0	722	0.781	414	1.006	1358	0.911	63.2	0.899	52.1	0.934	113	1.018
	b	55.3	719		405		1425		60.4		51.7		108	
9	a	85.8	1146	1.043	626	0.958	1932	0.973	79.5	0.922	69.1	0.972	158	1.060
	b	82.9	1150		621		1981		82.4		65.5		156	
10	a	53.6	720	1.020	381	0.928	1319	1.095	54.3	1.030	49.8	1.061	87	1.088
	b	50.5	676		382		1242		51.9		42.3		84	
11	a	54.0	671	0.946	352	0.920	1068	0.956	49.5	0.915	39.6	0.840	79	1.000
	b	52.6	632		348		1034		50.3		39.9		79	
Ratio of initial measurement to predicted value														
mean				1.009		0.973		0.976		0.964		1.012		1.083
S. E. M.				0.031		0.013		0.022		0.014		0.027		0.033
Ratio of 2nd/1st measurement														
mean		0.991		0.996		0.985		1.002		0.999		0.927		0.940
S. E. M.		0.008		0.011		0.005		0.012		0.020		0.022		0.017

a) before, b) after treatment

potassium is liable to be reduced initially, although homeostasis usually restores potassium over a longer period (8, 15). It is interesting that we have observed no change in mean total body sodium, in contrast to the fall in exchangeable sodium observed by Healey (7) using chlorthalidone over a shorter period (8-15 weeks). Either exchangeable sodium does not reflect total sodium in these circumstances, or, more likely, an initial loss of sodium is gradually corrected, this process being completed in less than 6 months. Loss of chlorine, which is identified with extracellular fluid, is also to be expected with diuretic treatment, as we have observed.

The small loss of total body phosphorus (1.5%) could be due to a reduction in renal tubular reabsorption of phosphate caused by bendrofluazide. While the level of calcium in urine is reduced by the action of the diuretic, we do not know what happens to calcium homeostasis in these circumstances. In particular, if there is no corresponding reduction in absorption of calcium, there may be a risk of heterotopic calcification. This is especially relevant to hypercalciuric stone formers, who have abnormally high absorption of dietary calcium (11). Also, these patients are liable to be given long courses of treatment, so any effects may be cumulative and consequently magnified.

The observed reduction in urinary calcium, if maintained throughout the period of treatment, represents a total reduction in calcium excretion of about 30 g for each patient. However, no

change in whole body calcium was observed, and the 95% confidence limits for this measurement were ± 20 g. The reduction in calcium excretion therefore seems unlikely to have resulted in a corresponding retention of calcium in the body to the same extent. Instead there may have been some compensatory reduction in calcium absorption.

We conclude that for 6 months at least, the body's defences are equal to the therapeutic reduction in calcium excretion by bendrofluazide.

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