Total exchangeable potassium in response to amiloride

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Summary

The use of amiloride is described in twenty-four hypertensive patients who became hypokalaemic as a result of thiazide diuretic therapy in spite of oral potassium supplements. Amiloride caused a significant rise in exchangeable potassium, exchangeable potassium/kg body weight, and plasma potassium, together with a significant fall in plasma total carbon dioxide, body weight, systolic and diastolic blood pressures.

These results suggest that amiloride has a useful role in this type of patient.

Introduction

Most studies of potassium changes in response to diuretics in hypertensive patients have failed to demonstrate a large total potassium deficit (Talso and Carballo, 1960; Graybiel and Sode, 1961; Gifford *et al.*, 1961; Anderson *et al.*, 1971; Wilkinson *et al.*, 1975; Leemhuis, van Damme and Stuyvenberg, 1976), and the need for potassium supplements has been questioned (Healy *et al.*, 1970; Wilkinson *et al.*, 1975).

Although an increased potassium loss has been shown in short-term experiments by studies of metabolic balance (Maronde, Milgram and Dickey, 1969), exchangeable potassium (Gifford *et al.*, 1961) and whole body potassium (Leemhuis *et al.*, 1976), the increased excretion appears not to persist, and the initial loss is partly reversed or compensated later on.

The plasma or serum potassium tends to remain lower than in the period before diuretics were administered (Beevers, Hamilton and Harpur, 1971), however, and it has been concluded that part of this effect, at least, is the result of redistribution of potassium between the intra- and extra-cellular body compartments (Leemhuis *et al.*, 1976). Talso and Carballo (1960) suggest that this may result from the hypochloraemic alkalosis that usually occurs during

diuretic treatment. This has not been confirmed by others.

Despite the frequent occurrence of hypokalaemia in patients taking thiazide diuretics for long periods, subjective symptoms are rare (Beevers *et al.*, 1971). In spite of this, it is felt desirable to minimize potassium depletion which may have serious consequences in the event of a potassium-losing state or the need for digitalis.

Triamterene has been found ineffective in reversing potassium depletion (McKenna *et al.*, 1971). Spironolactone has been shown to reduce the potassium loss to a considerable extent, but the use of this agent is limited by a high incidence of side effects, in particular gastric intolerance. Slow-release potassium chloride (Slow-K, Ciba) has been shown to be effective in replacing potassium loss resulting from prolonged thiazide diuretic administration (McKenna *et al.*, 1971). However, the number of patients studied was small and the authors have not found that slow-release potassium chloride in apparently adequate doses always prevents or reverses hypokalaemia and alkalosis (Antcliff *et al.*, 1971).

A solution of potassium chloride was demonstrated as not affecting total body potassium in patients treated with chlorthalidone (Leemhuis *et al.*, 1976).

The present authors have therefore investigated the ability of a 'potassium-sparing' diuretic, amiloride, to reverse the potassium deficit induced in hypertensive patients by long-term thiazide therapy in spite of oral potassium supplements.

Subjects and methods

Patients were selected on the basis of having developed and sustained a low level of plasma potassium, measured on at least two occasions whilst visiting the out-patient department for routine

blood pressure checks. The hypokalaemia developed in the course of long-term treatment with thiazide diuretics for hypertension alone, and the blood pressure was satisfactorily controlled throughout the period of assessment, with one exception (see Table 1). Furthermore, the low plasma potassium developed whilst the subjects were receiving at least 32 mmol potassium/day.

The potassium was in the form of slow release

potassium chloride (Slow-K, Ciba) in twenty-two cases; as potassium gluconate solution (Katorin, Boots) in one, and as effervescent tablets (Kloref, Cox-continental) in another. The thiazide diuretic was in most cases hydroflumethiazide 100 mg or 200 mg/day, but in two cases was hydrochlorothiazide and bendrofluazide respectively, and in a further two cases was chlorothiazide. Fourteen subjects received no other therapy but in two,

TABLE 1. Exchangeable potassium, plasma potassium, ratio K_e/kg , Tco_2 , Supine BP and the time at which they were measured after starting amiloride

Subject	K_e (mmol)	Weight (kg)	Ratio (K_e/kg)	Plasma K (mmol)	Tco_2	Supine BP (mmHg)		Time (months)
						Syst.	Diastol.	
1	1840	65.20	28.22	3.1	28	140	80	0
	1955	64.15	30.48	3.8	29	120	70	5
2	2660	66.68	39.89	3.3	31	200	100	0
	2350	66.68	35.24	3.5	31	190	90	5
3	1965	66.68	29.47	3.2	29	170	90	0
	1904	64.86	29.36	3.2	27	160	90	6
4	2620	79.38	33.00	3.1	38	180	80	0
	3170	75.97	41.73	3.6	29	140	85	5
5	2385	69.62	34.26	3.3	34	140	80	0
	2690	68.71	39.15	4.0	32	120	80	6
6	1875	49.66	37.76	3.1	33	200	100	0
	1826	48.86	37.37	3.7	31	180	90	6
7	2700	72.34	37.32	3.0	27	150	90	0
	2275	70.76	32.15	5.0	27	130	80	4
8	2570	82.55	31.13	2.5	36	160	90	0
	3130	82.32	38.02	3.2	35	160	110	4
9	2800	82.32	34.01	3.2	34	130	90	0
	3200	80.29	39.86	3.3	28	140	90	6
10	2880	83.92	34.32	2.9	34	140	90	0
	3260	82.10	39.71	3.8	30	140	85	5
11	1440	75.97	18.95	3.8	28	210	130	0
	1465	75.51	19.40	4.3	28	170	100	3
12	1939	60.33	32.14	2.7	29	170	105	0
	2445	60.78	40.23	3.4	29	160	95	6
13	1530	58.51	26.15	2.8	29	140	90	0
	1870	55.10	33.94	3.8	27	140	95	9
14	2520	78.02	32.30	2.9	32	160	90	0
	2450	75.30	32.54	3.0	25	130	70	4
15	1985	65.77	30.18	3.9	33	140	80	0
	2360	65.77	35.88	3.8	32	140	80	5
16	2615	63.37	41.33	3.0	28	140	90	0
	1935	58.28	33.20	2.4	23	160	100	6
17	2120	64.52	32.86	3.4	27	180	110	0
	2530	63.50	39.84	3.6	28	145	90	6
18	2434	92.08	26.43	3.1	36	140	85	0
	3140	91.85	34.19	3.4	33	150	90	4
19	2210	72.58	30.45	3.1	33	140	100	0
	1840	70.07	26.26	3.6	27	160	100	2
20	2770	86.18	32.14	3.2	31	140	90	0
	3140	85.49	36.73	3.7	30	140	85	3
21	2290	78.69	29.10	3.7	32	150	95	0
	2495	78.23	31.89	3.4	32	140	80	5
22	1460	48.99	29.80	3.4	29	170	110	0
	1520	50.11	30.33	3.4	27	150	90	5
23	2680	81.19	33.01	3.1	33	140	85	0
	3448	82.55	41.77	4.3	28	110	75	2
24	2740	71.89	38.11	2.8	33	140	90	0
	2790	71.21	39.18	3.7	30	120	80	4

bethanidine was employed in addition and in seven, α -methyldopa was used; in one case both bethanidine and α -methyldopa were used.

The potassium supplement was stopped after the initial exchangeable potassium estimation, and the subjects then received between 10 and 20 mg amiloride/day in divided doses.

Twenty-four patients were studied on two occasions: before the onset of amiloride therapy and after a mean period of 4.8 months (range 2–9 months).

All of the patients were judged to be suffering from essential hypertension on the basis of clinical assessment, plasma electrolyte estimation before antihypertensive therapy, and other baseline investigations which were indicated clinically.

Subjects were not admitted to hospital, and took a normal diet for the total duration of the assessment.

Exchangeable potassium (K_e) was measured with ⁴²K; 60 μ Ci was injected intravenously and the excretion of ⁴²K measured in urine collected for the following 20 hr. Total exchangeable potassium was calculated from a urine sample collected after a further 1 hr as follows:

$$K_e = \frac{X - E}{C} \times m$$

C = concentration of tracer ⁴²K in urine sample

X = amount of tracer ⁴²K administered

E = amount of tracer ⁴²K lost in 20-hr urine

m = concentration of stable potassium in urine sample used for calculation.

Plasma potassium and total dioxide estimations were performed using a Technicon SMA 6/60 flame photometer.

The blood pressure was measured at each outpatient attendance using a standard mercury sphygmomanometer. Pressure was recorded in the supine position to the nearest 5 mmHg. The patient was weighed at each attendance.

Statistical analysis

The significance of the difference between sample means was estimated by Student's *t* test for the difference between the means of paired observations using a Hewlett-Pakard 9810A desk computer. Thus, each subject acted as his own control in this study.

Results

Total exchangeable potassium, plasma potassium, total CO₂ and weight and blood pressure were estimated at the beginning of the study and after a mean period receiving amiloride therapy of 4.8 months (Table 1). The mean alterations in each parameter are summarized in Table 2, together with statistical significance. Significant elevations of exchangeable potassium, plasma potassium and the ratio of exchangeable potassium to body weight are demonstrated together with a significant fall in total CO₂, weight and both systolic and diastolic blood pressures. The fall in systolic blood pressure level was statistically more significant than that of the diastolic pressure (Figs 1–5).

FIG. 1. Total exchangeable potassium before and after amiloride (mean duration 4.8 months).

TABLE 2. Total exchangeable potassium (K_e), exchangeable potassium per kilogram body weight (K_e/kg), plasma potassium (mmol/l), total CO₂, body weight and supine systolic and diastolic blood pressure, before and after amiloride therapy. The mean values are shown, with s.e. mean, s.d., and the statistical significance by paired *t* test

	Before		After		<i>t</i>	<i>P</i>
	Mean	s.e. mean	Mean	s.e. mean		
K _e (mmol)	2292	97.3	2466	121	2.295	< 0.05
K _e /kg (mmol/kg)	32.17	0.94	34.93	1.1	2.79	< 0.02
Plasma K ⁺ (mmol/l)	3.15	0.07	3.62	0.1	4.27	< 0.001
Total CO ₂ (mmol/l)	31.5	0.62	29.1	0.55	4.48	< 0.001
Weight (kg)	75.51	2.26	70.35	2.28	3.818	< 0.001
Systolic blood pressure (mmHg)	157.1	4.7	145.6	4.0	3.25	< 0.01
Diastolic blood pressure (mmHg)	93.3	2.4	87.3	2.0	2.60	< 0.02

FIG. 2. Ratio of total exchangeable potassium (mmol) to body weight (kg) before and after amiloride therapy (mean duration 4.8 months). (Means and standard error of the mean are shown *P* values derived by student's paired *t* test.)

FIG. 3. Plasma potassium before and after amiloride therapy (mean 4.8 months).

FIG. 4. Plasma TCO₂ before and after amiloride.

FIG. 5. Weight (kg) before and after amiloride.

FIG. 6. Supine systolic and diastolic blood pressure of twenty-four patients before amiloride therapy and after a mean period of 4.8 months.

Discussion

Amiloride is an oral natriuretic and mild diuretic drug which appears to act primarily on the distal nephron.

It has a mild antihypertensive action in some patients (Bull and Laragh, 1968). It has been shown to elevate the plasma potassium when used alone (Surveyor and Saunders, 1968), or when it is substituted for oral potassium supplements in patients who have become hypokalaemic whilst taking thiazide diuretic along with potassium supplements (Antcliff *et al.*, 1971).

On the other hand, a tablet containing amiloride (5 mg) with hydrochlorothiazide (50 mg) (Moduretic, Merck, Sharp & Dohme), did not prevent hypokalaemia from resulting from its administration, nor restore to normal the plasma potassium level in patients already hypokalaemic (Antcliff *et al.*, 1972).

Although hypokalaemia and mild metabolic alkalosis are common in hypertensive patients treated for prolonged periods with thiazide diuretics, symptoms are quite rare (Beevers *et al.*, 1971), and the need to correct this has been questioned (Wilkinson *et al.*, 1975; Healy *et al.*, 1970). However, most clinicians are reluctant to allow patients who are already taking cardiac glycosides or who are in a group at increased risk of requiring them, to remain persistently hypokalaemic. The risk of a sudden potassium-losing state, such as diarrhoea or vomiting, has already been mentioned. It is therefore desirable to discover an agent which will effectively increase the plasma and whole body potassium if they become depleted.

Oral potassium was demonstrated, as a slow-release potassium chloride, in a group of seven patients with hypertension treated with chlorthalidone, to replace the depleted K_e and plasma potassium. However, twenty-four patients are presented, whose plasma potassium was diminished and in

whom a raised TCO₂ was recorded. These were measured on two separate occasions in spite of receiving at least 32 mmol K⁺/day and often much more.

These patients were drawn from a population of patients attending a Hypertension Clinic over a period of about 12 months, in whom significant hypokalaemia was quite common in spite of oral potassium supplements. As triamterene seems ineffective in replacing potassium, and spironolactone is often poorly tolerated, it seems important to assess the efficiency of amiloride in this situation. It has been demonstrated that amiloride in a dosage of 10–20 mg/day causes a significant rise of exchangeable potassium, plasma potassium and K_e/kg. There is also a significant fall in the TCO₂ and weight and blood pressure. In view of the number of patients using the thiazide diuretics, the routine use of this agent would be prohibitively expensive. In most patients, the degree of depression of the plasma potassium that has been recorded in this group does not occur and hence this form of treatment is probably not necessary. It has been demonstrated, however, that in patients who develop and maintain a significant hypokalaemia it is effective in at least partly replacing the exchangeable potassium and elevating the plasma potassium into normal range. It is believed, therefore, that amiloride has a useful part to play in this group of patients.

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