RELATIVE POTENCY OF SPIRONOLACTONE, TRIAMTERENE AND POTASSIUM CHLORIDE IN THIAZIDE-INDUCED HYPOKALAEMIA

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- 1 The influence of spironolactone 50 mg and 100 mg daily, triamterene 100 mg and 200 mg daily, potassium chloride 32 mmol and 64 mmol daily and placebo on plasma potassium and other variables was examined in a random crossover study of nine hypertensive patients taking bendrofluzide 10 mg daily.
- 2 Spironolactone and triamterene had significant and parallel dose-response curves for plasma potassium, with a relative potency for triamterene:spironolactone of 0.25:1, significantly lower than the accepted 0.5:1 ratio. These drugs also lowered serum sodium, bicarbonate and body weight, and increased serum urea and creatinine.
- 3 Potassium chloride increased plasma potassium above placebo values, but the dose-response was not significant and was not parallel with those of the potassium-sparing drugs. Seven of nine patients remained hypokalaemic despite treatment with 64 mmol potassium chloride daily.
- 4 The relative expense, convenience and toxicity of the potassium-sparing drugs should be assessed at equivalent doses, namely spironolactone 50 mg:triamterene 200 mg:amiloride 20 mg. Potassium chloride does not correct moderate diuretic-induced hypokalaemia even at doses of 64 mmol daily.

Introduction

Diuretic treatment of uncomplicated hypertension does not usually cause depletion of whole body potassium (Kassirer & Harrington, 1977), but hypokalaemia is common and unpredictable (Beevers *et al.*, 1971; Manner *et al.*, 1972; Ramsay *et al.*, 1977). In uncomplicated patients minor falls in plasma potassium probably need no treatment, and in recent years most reviewers have recommended treatment only when the plasma potassium concentration falls below 3.0 mmol/l. However, some patients do need reliable prophylaxis against diuretic-induced hypokalaemia, for example those taking digoxin or drugs which prolong the Q-T interval (e.g. prenylamine, phenothiazines or tricyclic antidepressants); those with arrhythmias, severe ischaemic heart disease or chronic liver disease; and elderly patients taking a poor diet. The choice of drug for the treatment or prophylaxis of hypokalaemia lies among the potassium-sparing drugs, spironolactone, amiloride and triamterene, and potassium chloride supplements. It depends on the relative efficacy, safety, convenience and expense of these drugs, and on their ancillary

properties such as additive diuretic or hypotensive effect. If these properties are to be compared fairly accurate knowledge of their relative potency is essential. The relative potency of amiloride and spironolactone has been defined (Ramsay *et al.*, 1980), but the potencies of potassium chloride and triamterene relative to spironolactone in correcting thiazide-induced hypokalaemia have not been established accurately, and that was the aim of this study.

Methods

Patients

We studied nine patients with essential hypertension (three men, six women; mean age 57, range 44-65 years). All were on long-term diuretic treatment, and eight were taking other antihypertensive drugs which were held constant throughout the study (β -adrenoceptor blockers in eight, and hydralazine, methyl-dopa, clonidine and debrisoquine each in one

patient). No patient had renal impairment (serum creatinine $> 130 \mu\text{mol/l}$) and none was taking digoxin or drugs known to prolong the Q-T interval. Diuretic treatment was altered to bendrofluazide 10 mg daily, potassium chloride or potassium-sparing drugs were stopped, and the plasma potassium was measured 4 weeks later. Patients entered the study if their plasma potassium was less than 3.5 mmol/l. They gave informed consent to the study which had been approved by the hospital ethics committee.

Protocol

There were eight treatment periods each of 4 weeks with no interval between the treatments. The eight treatments, added to bendrofluazide 10 mg daily, were:

1	Placebo (run-in)		
	Potassium chloride	32 mmol daily	} (8 mmol tablets)
	Potassium chloride	64 mmol daily	
2-7	Triamterene	100 mg daily	} (50 mg capsules)
	Triamterene	200 mg daily	
	Spironolactone	50 mg daily	} (25 mg tablets)
	Spironolactone	100 mg daily	
8	Placebo (run-out)		

All treatments were prescribed twice daily, in open fashion, with reliance on blind objective measurements to avoid bias. The six active treatments (2-7) were given in random order. The two placebo periods (1, 8) were compared to assess the constancy of the variables measured, over the 32 week study period.

At the end of each treatment phase venous blood was drawn without stasis to measure plasma potassium by flame photometry and other biochemical variables by routine automated methods. Blood pressure (Hawkesley random-zero sphygmomanometer; right arm; phase 5 diastolic; mean of three lying, three standing measurements); body weight; compliance (tablet counts); and side effects (by general enquiry) were also measured.

Statistical analysis

For all variables except blood pressure the placebo values at the beginning and end of the study remained constant, and the mean of the two placebo values was used in the analysis. The statistical methods were Student's *t*-test for paired observations and product moment correlation.

Results

Plasma potassium

In the two placebo periods 28 weeks apart, during which the patients were taking bendrofluazide 10 mg daily alone, the plasma potassium concentration did not alter significantly (mean 3.11 mmol/l ν 2.97 mmol/l; s.d. of differences 0.20 mmol/l). The plasma potassium during placebo treatment ranged from 2.7-3.5 mmol/l between individual patients. The responses to the active treatments are shown in Table 1, and their dose-response curves in Figure 1. Potassium chloride, triamterene and spironolactone were all active in raising the plasma potassium significantly above placebo values (Table 1). The dose-response relations were significant for spironolactone (100 mg $>$ 50 mg, $P < 0.025$) and triamterene (200 mg $>$ 100 mg, $P < 0.01$), but not for potassium chloride (64 mmol ν 32 mmol, $P > 0.1$). The dose-responses for triamterene and spironolactone were convincingly parallel, but the range of responses for the two drugs did not overlap (Figure 1). As the log dose-response for spironolactone is known to be linear below this dose range (Ramsay *et al.*, 1980) extrapolation can be justified. The best estimate of the relative potency of triamterene:spironolactone was 0.25:1, and it was significantly less than 0.5:1, because spironolactone 100 mg $>$ triamterene 200 mg ($P < 0.025$) and spironolactone 50 mg $>$ triamterene 100 mg ($P < 0.02$).

Table 1 Mean (and s.e. mean) plasma potassium concentration in nine patients given two dose levels of spironolactone (S), triamterene (T), potassium chloride (K) and placebo in addition to bendrofluazide 10 mg daily, and the significance of differences between means.

Treatment	Plasma potassium (mmol/l)	Levels of significance					
		S100	S50	T200	K64	K32	T100
Placebo	3.04 (0.08)	****	***	***	*	**	NS
T100 mg	3.23 (0.09)	****	**	***	NS	NS	—
K32 mmol	3.24 (0.07)	****	*	**	NS	—	—
K64 mmol	3.32 (0.11)	***	NS	NS	—	—	—
T200 mg	3.58 (0.14)	*	NS	—	—	—	—
S50 mg	3.59 (0.16)	*	—	—	—	—	—
S100 mg	3.99 (0.11)	—	—	—	—	—	—

* $P < 0.025$; ** $P < 0.02$; *** $P < 0.01$; **** $P < 0.001$

Figure 1 Mean (and s.e. mean) results for plasma potassium concentration in 9 hypertensive patients taking bendrofluazide 10 mg daily plus placebo; potassium chloride (2 doses); triamterene (2 doses); and spironolactone (2 doses); each for 4 weeks. The significance of the differences between treatments is shown in Table 1.

The dose-response for potassium chloride was not significant, and it was not parallel with those of spironolactone or triamterene (Figure 1). Its potency relative to the potassium-sparing drugs could not therefore be estimated.

Spironolactone was significantly superior to potassium chloride at ratios of 50 mg:32 mmol, and 100 mg:64 mmol (Table 1). By extrapolation the dose of potassium chloride needed to match the effect of spironolactone 50 mg on plasma potassium would be

Figure 2 Correlation between plasma potassium responses (changes from placebo) to spironolactone and triamterene in 9 patients. Each point is the mean of two values at a ratio spironolactone 50 mg:triamterene 100 mg. $r = +0.82$, $P < 0.01$.

Figure 3 Relations between plasma potassium responses to spironolactone and potassium chloride (ratio 50 mg:32 mmol) in 9 patients, plotted as in Figure 2. $r = +0.12$, N.S.

approximately 512 mmol daily. The response to triamterene, calculated as the change in plasma potassium from placebo values, correlated highly with the response to spironolactone ($r = +0.82$, $P < 0.01$, $n = 9$, Figure 2). The response to potassium chloride did not correlate with that to spironolactone ($r = +0.12$, Figure 3).

Other biochemical variables (Table 2)

Potassium chloride, triamterene and spironolactone all reduced the serum bicarbonate significantly from placebo values. Triamterene and spironolactone caused significant reductions in serum sodium and significant increases in blood urea and creatinine compared to placebo. Potassium chloride but not the potassium-sparing drugs increased serum chloride levels significantly.

Body weight (Table 2)

Body weight was reduced significantly by triamterene and spironolactone, but did not alter during potassium chloride treatment.

Blood pressure (Table 3)

The blood pressure fell significantly between the two placebo treatments (i.e. between the run-in and run-out phases) and with this study design the fall could have been caused by a secular trend, by a carryover effect of the active treatments, or by both. Carryover effects would tend to lessen any differences between the treatments. The only treatment which had any discernible effect on blood pressure was spironolactone 100 mg daily, which was associated with lying systolic blood pressures significantly lower than those during both placebo periods (Table 3).

Table 2 Mean (and s.e. mean) results of serum biochemistry and body weight in nine patients having potassium chloride, triamterene or spironolactone added to bendroflumazide 10 mg daily.

Serum	Placebo (mean)	Potassium chloride		Triamterene		Spironolactone	
		32 mmol	64 mmol	100 mg	200 mg	50 mg	100 mg
Sodium (mmol/l)	138.8 (0.83)	137.8 (0.83)	139.1 (0.86)	136.8* (1.16)	137.8 (0.37)	137.1* (0.93)	136.5* (0.46)
Chloride (mmol/l)	95.4 (1.10)	97.0* (0.69)	97.4* (0.75)	96.3 (1.05)	96.0 (0.65)	96.3 (1.03)	96.1 (0.64)
Bicarbonate (mmol/l)	29.6 (0.56)	28.6** (0.50)	27.9* (0.56)	27.9 (0.48)	28.1* (0.61)	27.1* (1.14)	26.9* (0.58)
Urea (mmol/l)	5.23 (0.20)	5.46 (0.38)	5.73 (0.39)	5.99 (0.61)	7.01* (0.55)	7.08* (0.54)	7.25* (0.46)
Creatinine (μ mol/l)	93.4 (6.3)	96.4 (6.8)	96.3 (7.7)	104.4 (10.1)	114.3* (6.4)	104.7* (7.8)	106.4* (7.6)
Body weight (kg)	71.1 (3.6)	70.9 (3.6)	71.0 (3.6)	69.9* (3.6)	70.6 (4.2)	69.7* (3.9)	70.3** (4.3)

* $P < 0.05$; ** $P < 0.02$; * $P < 0.01$; ** $P < 0.001$ v placebo values.

Side-effects and compliance

One patient stopped spironolactone 100 mg daily because of severe leg cramps, and another stopped triamterene 200 mg daily because of severe migraine headaches. The other side-effects reported are shown in Table 3. Compliance, as assessed by tablet counts, was high throughout (97–99%) and was no different for placebo and active treatments.

Discussion

It matters little that one drug is more potent than another on a weight basis, but when the drugs have identical therapeutic indications an accurate estimate of relative potency is essential if their relative expense, convenience and toxicity are to be compared fairly. The three drugs compared in this study are all generally prescribed with thiazide or loop diuretics to prevent or treat hypokalaemia. They have been compared directly in few studies, all of which have been at single dose levels, and their relative potency has not been established accurately.

It has been suggested that triamterene 50 mg and spironolactone 25 mg are equivalent in effect (Cocke *et al.*, 1977; Holland *et al.*, 1977), i.e. that the relative potency of triamterene:spironolactone is 0.5:1, although the data of McKenna *et al.* (1971) do not support this and suggest a lower relative potency. The present study confirms that triamterene and spironolactone were active in raising plasma potassium, shows them to have significant and parallel dose-responses, and defines the relative potency of triamterene:spironolactone as 0.25:1. This estimate was significantly lower than the figure of 0.5:1 proposed

by Cocke *et al.* (1977) and Holland *et al.* (1977). Thus 200 mg triamterene was equivalent to 50 mg spironolactone and not to 100 mg spironolactone, and was indeed significantly inferior to 100 mg spironolactone.

The close correlation between the plasma potassium responses to triamterene and those to spironolactone is of interest and some practical importance. Spironolactone acts as a specific competitive antagonist of aldosterone, whereas triamterene and amiloride act directly on the membrane of the distal renal tubule, independently of aldosterone. Bull & Laragh (1968) suggested that the effects of spironolactone may therefore be less predictable because of its dependence on aldosterone. However, Ramsay *et al.* (1980) have shown that spironolactone is effective when aldosterone is not in excess, that its effect is no more dependent on aldosterone than is that of amiloride, and that the responses to spironolactone and amiloride correlate highly. As the response to triamterene also correlates closely with that to spironolactone, it seems that individual patients tend to respond similarly to all three potassium-sparing drugs. In the clinical setting there is unlikely to be much benefit from substituting one potassium-sparing drug for equivalent dosage of another.

Potassium chloride was active in raising the plasma potassium above placebo values, but the responses were very small in absolute terms, as shown before (Ramsay *et al.*, 1980). Thus a dose of 64 mmol daily, much higher than the average 18 mmol daily prescribed in ordinary practice (Ramsay & Ramsay, 1977), left the mean plasma potassium concentration still below normal (3.3 mmol/l), and only two of nine patients had values higher than 3.5 mmol/l. The relative potency potassium chloride:spironolactone

Table 3 Mean (and s.e. mean) results for blood pressure and side-effects in nine patients having potassium chloride, triamterene or spironolactone added to bendroflumazide 10 mg daily.

	Placebo		Potassium chloride		Triamterene		Spironolactone	
	First	Second	32 mmol	64 mmol	100 mg	200 mg	50 mg	100 mg
<i>Blood pressure (mm Hg)</i>								
Lying systolic	147.3 (3.6)	134.2* (3.0)	140.5 (3.8)	141.0 (7.0)	136.1 (2.8)	137.8 (6.1)	141.3 (4.8)	123.6** (4.4)
Lying diastolic	93.1 (2.2)	88.7* (1.9)	90.9 (3.3)	90.9 (3.6)	91.3 (2.2)	87.9 (3.4)	91.7 (3.4)	83.1 (2.2)
Standing systolic	138.6 (4.0)	120.7* (3.6)	133.0 (3.5)	128.9 (6.2)	121.6 (4.4)	122.8 (7.0)	123.6 (5.8)	116.9 (4.6)
Standing diastolic	94.5 (5.0)	83.4* (4.0)	89.7 (3.4)	89.0 (3.6)	85.9 (4.4)	84.4 (5.5)	85.1 (3.6)	81.9 (3.9)
Side-effects (number of patients) [†]	0	0	1	0	3	4	1	3

* $P < 0.05$ v first placebo period.** $P < 0.001$ v first placebo, $P < 0.05$ v second placebo.

† Side-effects were: potassium chloride—dizziness (1); triamterene—nausea (3), dizziness (1), depression (1), migraine (1), cramps (1); spironolactone—cramps (1), skin rash (1), blurred vision (1).

could not be calculated because the dose-response for potassium chloride was non-significant, and non-parallel with that of spironolactone. Spironolactone 100 mg was highly significantly superior to potassium chloride 64 mmol, as in previous studies (Ibsen, 1974; Ramsay *et al.*, 1980), and it appears from Figure 1 that a massive dose of potassium chloride would be needed to match the effect of spironolactone 50 mg. The response to potassium chloride showed no correlation with that to spironolactone.

The effects of the three drugs on variables other than plasma potassium (Tables 2 and 3) have been described before, but one or two of them deserve emphasis. The two potassium-sparing drugs caused a significant decline in renal function as shown by rises in blood urea and creatinine, and, although the number of patients was small, they frequently caused subjective side-effects. We cannot draw firm conclusions about changes in blood pressure because the study design was unsuitable for the purpose, and the sample size was small. However, there was some evidence that spironolactone 100 daily had a hypotensive effect additive to that of bendrofluazide.

Current views on the equivalent doses of potassium chloride and the three potassium-sparing drugs need revision in the light of this study and that of Ramsay *et al.* (1980). Considering the volume of prescriptions for these drugs (Christopher, 1980) this will have considerable therapeutic and economic consequences. Unacceptably large doses of potassium chloride are quite incapable of correcting moderate or severe diuretic-induced hypokalaemia. Their reputation for safety, tolerability and low expense stems entirely from the widespread routine pre-

scribing of doses which are too low to have any useful effect, and these desirable qualities do not constitute a logical reason for prescribing a drug which is ineffective. The potassium-sparing drugs are effective and more convenient than potassium chloride, but their properties have been compared at dose levels which we have shown to be non-equivalent. For example, at the ratios accepted until now (spironolactone 50 mg: amiloride 10 mg: triamterene 100 mg) spironolactone was considered the most expensive and triamterene the least expensive in the United Kingdom (British National Formulary, 1981). At the true equivalent doses (spironolactone 50 mg: amiloride 20 mg: triamterene 200 mg) triamterene is the most expensive and spironolactone the least. The relative convenience, toxicity and ancillary properties of the three drugs should also be judged at these dose levels.

These findings are relevant to the general policy for prevention or treatment of diuretic-induced hypokalaemia. Routine prophylaxis could perhaps be justified if an effective, cheap and non-toxic drug was available, and it seems likely that many prescribing doctors view potassium chloride in this way. However, it is apparent that the efficacy of potassium chloride is quite unsatisfactory, and routine prophylaxis would mean the widespread prescribing of a potassium-sparing drug. This would entail considerable expense, many subjective side-effects, some decline in renal function and some risk of hyperkalaemia. It would seem advisable to concentrate on avoiding diuretic-induced hypokalaemia, e.g. by using small doses of diuretics, and to use potassium-sparing drugs only when they are clearly necessary, for example, in patients treated with digoxin.

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(Received January 26, 1982,
accepted January 28, 1982)