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# A comparison of the potassium and magnesium-sparing properties of amiloride and spironolactone in diuretic-treated normal subjects

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1 The relative potencies of amiloride (5 and 20 mg) and spironolactone (25 and 100 mg) for plasma and erythrocyte electrolytes were investigated in a double-blind, randomised, balanced, crossover study in 12 normal men treated concomitantly with hydrochlorothiazide 100 mg daily for 1 week.

2 Participants satisfied an *a priori* requirement for a fall in plasma potassium concentration of at least 0.5 mmol $l^{-1}$ after 7 days of treatment with hydrochlorothiazide alone.

3 After hydrochlorothiazide alone, plasma potassium and sodium concentrations fell ($P < 0.001$). There were associated reductions in erythrocyte sodium ($P < 0.01$). Plasma magnesium concentration did not change, although erythrocyte magnesium decreased ($P < 0.001$).

4 Both amiloride and spironolactone attenuated the thiazide-induced fall in plasma potassium (relative potency, amiloride:spironolactone 10:1, 95% confidence interval 6.3–16.2:1). Amiloride but not spironolactone was associated with a dose-related increase in plasma magnesium; a relative potency estimation was precluded. There was little evidence of influences of amiloride or spironolactone on erythrocyte electrolytes.

5 On a weight basis, amiloride is ten times more potent than spironolactone as a potassium-sparing agent in diuretic-treated subjects but neither agent had major effects on erythrocyte potassium. The drugs may have divergent actions on magnesium handling; hydrochlorothiazide alone had no influence on plasma magnesium.

**Keywords** amiloride diuretics hydrochlorothiazide magnesium potassium relative potency spironolactone

## Introduction

The anti-kaliuretic effects of amiloride and spironolactone have led to their widespread use as potassium-sparing agents in combination with thiazide and loop diuretics. However, estimates of their relative potency have been inconsistent (Bull & Laragh, 1968; George *et al.*, 1973; Kohvakko *et al.*, 1979; McInnes, 1982; Ramsay *et al.*, 1980). An early report in a small number of patients with different illnesses suggested a relative potency for correcting thiazide-induced hypokalaemia (amiloride:spironolactone) of 5:1 (Bull & Laragh, 1968). Later studies in larger numbers of hypertensive patients indicated a relative potency between 2.8:1 (Ramsay *et al.*, 1986) and 10:1 (George *et al.*, 1973; Kohvakko *et al.*, 1979). A single dose study in normal subjects estimated a relative potency of 36:1 in attenuating urine potassium loss (McInnes, 1982).

Within individuals plasma potassium concentrations vary considerably with time (Morgan, 1981; Morgan & Davidson, 1980). In previous comparisons of amiloride and spironolactone, plasma potassium was measured at a single time point after dosing. Failure to take into account intra-individual variability in plasma potassium concentration may partly explain discrepancies in relative potency estimations.

Treatment with thiazide diuretics may also be associated with falls in plasma magnesium concentrations (Cocco *et al.*, 1987; Hollifield, 1989; Laerum, 1984). Diuretics cause a consistent increase in urine magnesium

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excretion (Beerman & Groschinsky-Grind, 1977; Parfitt, 1969; Swales, 1982; Wacker, 1961) and some authors have suggested that amiloride and spironolactone have magnesium-sparing properties (Mountokalakis *et al.*, 1975; Ryan *et al.*, 1981). Although many of the above studies had shortcomings, there is evidence that magnesium may have a role in potassium balance (Whang, 1968).

Potassium and magnesium are largely intracellular cations. It has been speculated that diuretics may deplete potassium and magnesium stores (Dyckner & Wester, 1978; Lim & Jacob, 1972) and potassium-sparing diuretics have been reported to correct these changes (Dyckner *et al.*, 1986, 1988). However, the relative effects of amiloride and spironolactone have not been defined clearly.

The main aim of this study was to make an accurate quantitative comparison of the influences of amiloride and spironolactone on thiazide-induced disturbance of potassium and magnesium handling. In an effort to improve precision, plasma and intracellular electrolyte concentrations were measured repeatedly after drug administration.

## Methods

### *Subjects*

In order to identify 12 healthy male subjects with a thiazide induced reduction in plasma potassium concentration exceeding a predetermined limit, 16 volunteers (mean age 33 years, range 24–44) were screened. The 12 subjects who entered the study proper had a mean age of 33 years, range 25–43.

### *Design*

Potential subjects underwent a screening period in which they received hydrochlorothiazide 100 mg daily for 7 days. Only those subjects in whom plasma potassium fell by 0.5 mmol $l^{-1}$ or more during this period were eligible for inclusion in the study proper—a double-blind, randomised, balanced crossover comparison of amiloride (5 mg and 20 mg) and spironolactone (25 mg and 100 mg) each in combination with hydrochlorothiazide 100 mg. Each study phase lasted 8 days followed by a 2 week drug free interval. A similar period separated the screening period and the study proper.

### *Drugs*

Hydrochlorothiazide 100 mg alone (during screening period)
Hydrochlorothiazide 100 mg + amiloride 5 mg orally
Hydrochlorothiazide 100 mg + amiloride 20 mg orally
Hydrochlorothiazide 100 mg + spironolactone 25 mg orally
Hydrochlorothiazide 100 mg + spironolactone 100 mg orally

Drugs were taken once daily at 09.00 h.

### *Procedure*

In the screening period, subjects were studied the day before drug administration (day 0) and on day 7. In the study proper, subjects were studied on days 0 and 8 of each period. Blood samples were taken with minimal venous stasis and no forearm exercise to minimise sampling error in estimation of plasma potassium (Bergstrom, 1973). Alcohol was restricted from 40 h before treatment commenced until blood sampling was completed. Diet was constant within each individual for the last 64 h of each treatment phase. The subjects were ambulant throughout but vigorous exercise was avoided.

### *Measurements*

*Electrolytes* Venous blood samples for estimation of plasma potassium, magnesium and sodium concentrations were taken at 09.00 h and hourly until 17.00 h. Plasma was separated immediately and stored at −20° C until analysis.

Erythrocytes for measurement of potassium, magnesium and sodium concentrations were obtained at 09.00 h and every 2 h until 17.00 h. After removal of plasma, the cells were washed in isosmotic choline chloride, lysed with distilled water and aliquots were transferred to polythene bags which were heated to a constant weight at 37° C for 24 h. These were then stored at room temperature until extraction. For the extraction process, 1 M nitric acid was added to the aliquots which were stored for 1 month at 40° C. Values were expressed as mg $kg^{-1}$ (dry solids).

Samples were analysed in subject batches. Potassium and sodium were analysed by flame photometry using lithium as internal standard. Magnesium was assayed by atomic absorption spectrophotometry.

*Plasma aldosterone* Venous blood samples were taken at 09.00 h on days 0 and 7 in each phase of the study proper for estimation of plasma aldosterone concentrations by a specific radioimmunoassay method (Fraser *et al.*, 1973).

*Plasma canrenone and amiloride* On day 7 of each phase of the study proper, plasma concentration of canrenone, a major metabolite of spironolactone (Karim, 1986) and amiloride were measured hourly from 09.00 to 17.00 h. Assay was by specific h.p.l.c. methods (Dahlof *et al.*, 1979; Forrest *et al.*, 1988).

### *Statistical analysis*

Results were compared by analysis of variance for repeated measures. The between treatment variation was partitioned to test the difference between spironolactone and amiloride, the average slope of the two dose-response relationships and the difference between the slopes. Providing the average slope was significant at the 5% level and there was no significant difference between the slopes, the potency of amiloride relative to spironolactone was calculated with 95% confidence intervals (CI).

## Results

Results are presented for 16 subjects in the screening period and 12 subjects in the study period.

*Screening period*

*Plasma and erythrocyte electrolytes* Plasma potassium concentrations at each time point are shown in Figure 1; marked variability during the study days is evident. Mean (s.d.) results for plasma and erythrocyte potassium, magnesium and sodium during the screening period are given in Table 1. All subjects showed falls in plasma and erythrocyte potassium, erythrocyte magnesium and plasma sodium concentrations. Plasma magnesium and erythrocyte sodium concentrations were unchanged. Other than for plasma potassium responses, there were no differences between responders and non-responders.

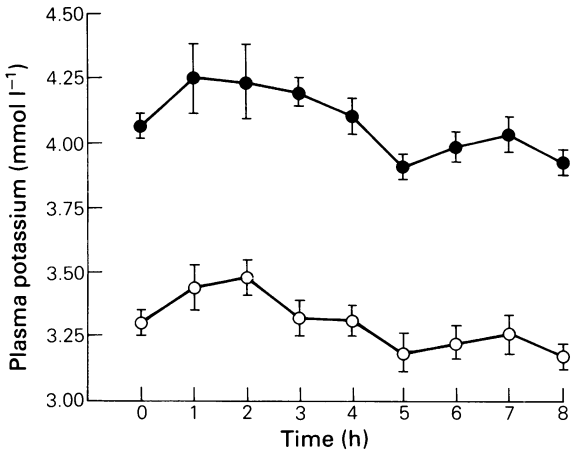


**Figure 1** Mean (vertical bars, s.e. mean) results for plasma potassium in 12 responders at baseline (•) and after 7 days of treatment with hydrochlorothiazide 100 mg (○).

*Study period*

*Plasma electrolytes* Mean results for plasma potassium, sodium and magnesium at baseline and after each treatment phase are shown in Table 2. Results given are the means of the mean of the nine concentrations (09.00–17.00 h) for each of the 12 subjects. For all three variables the differences between the four treatments were statistically significant. For potassium and sodium there were significant differences between amiloride and spironolactone. Repeated measurements 0–8 h after the final administration of each drug produced significant, parallel log dose-response relationships for amiloride and spironolactone, positive with respect to plasma potassium and negative with respect to plasma sodium. The relative potency estimates, amiloride:spironolactone, on a weight basis, were 10:1 for plasma potassium (95% CI, 6.3–16.2) and 10:1 for plasma sodium (95% CI, 6.1–23.6). There was also a highly significant difference between the two compounds in their effect on plasma magnesium. Amiloride was associated with a dose-related increase but spironolactone had no effect. Dose-response relationships for amiloride and spironolactone were non-parallel rendering a relative potency estimate invalid.

*Erythrocyte electrolytes* Mean results for erythrocyte potassium, sodium and magnesium are shown in Table

**Table 1** Mean (s.d.) results for plasma (mmol $l^{-1}$) and erythrocyte (mg $kg^{-1}$ dry solids) potassium, magnesium and sodium concentrations in 16 normal subjects (R = responders, NR = non-responders) before and after 7 days of treatment with hydrochlorothiazide 100 mg (HCTZ). Each value is derived from the mean of nine concentrations for each subject on each study day

| | *Potassium* | | *Magnesium* | | *Sodium* | |
|---|---|---|---|---|---|---|
| | *R* | *NR* | *R* | *NR* | *R* | *NR* |
| *Plasma* | | | | | | |
| Before HCTZ | 4.07 (0.13) | 4.00 (0.14) | 0.802 (0.050) | 0.817 (0.050) | 139.5 (1.0) | 139.7 (1.0) |
| After HCTZ | 3.39 (0.19) | 3.55 (0.88) | 0.806 (0.053) | 0.847 (0.044) | 137.2 (1.2) | 137.2 (1.0) |
| *Erythrocyte* | | | | | | |
| Before HCTZ | 251.2 (13.4) | 251.3 (13.8) | 5.75 (0.98) | 5.37 (0.92) | 24.0 (4.9) | 24.6 (6.8) |
| After HCTZ | 240.6 (13.3) | 241.9 (16.0) | 5.47 (0.82) | 4.96 (0.60) | 26.0 (5.3) | 23.7 (5.3) |

**Table 2** Mean results for plasma (mmol $l^{-1}$) and erythrocyte (mg $kg^{-1}$ dry solids) potassium, sodium and magnesium concentrations and plasma aldosterone concentrations (pmol $l^{-1}$) in 12 normal subjects at baseline and after treatment with hydrochlorothiazide in combination with amiloride (A) 5 mg, A 20 mg, spironolactone (S) 25 mg and S 100 mg. Also shown are results of statistical tests

| | *Baseline* | *A 5 mg* | *A 20 mg* | *S 25 mg* | *S 100 mg* | *Residual s.e. mean* | *P value between four treatments* | *P value between two compounds* |
|---|---|---|---|---|---|---|---|---|
| Plasma potassium | 3.92 | 3.55 | 3.83 | 3.46 | 3.68 | 0.040 | <0.001 | 0.005 |
| Plasma sodium | 140.2 | 136.1 | 134.6 | 136.6 | 135.5 | 0.286 | <0.001 | 0.002 |
| Plasma magnesium | 0.794 | 0.804 | 0.837 | 0.802 | 0.789 | 0.0078 | <0.001 | 0.003 |
| Erythrocyte potassium | 247.1 | 238.8 | 238.1 | 238.6 | 240.3 | 1.203 | 0.60 | 0.44 |
| Erythrocyte sodium | 22.1 | 21.9 | 21.5 | 23.4 | 21.7 | 0.292 | <0.001 | 0.008 |
| Erythrocyte magnesium | 5.07 | 5.10 | 5.12 | 5.13 | 5.17 | 0.042 | 0.74 | 0.40 |
| $Log_{10}$ plasma aldosterone | 1.064 | 1.449 | 1.680 | 1.364 | 1.554 | 0.040 | <0.001 | 0.013 |

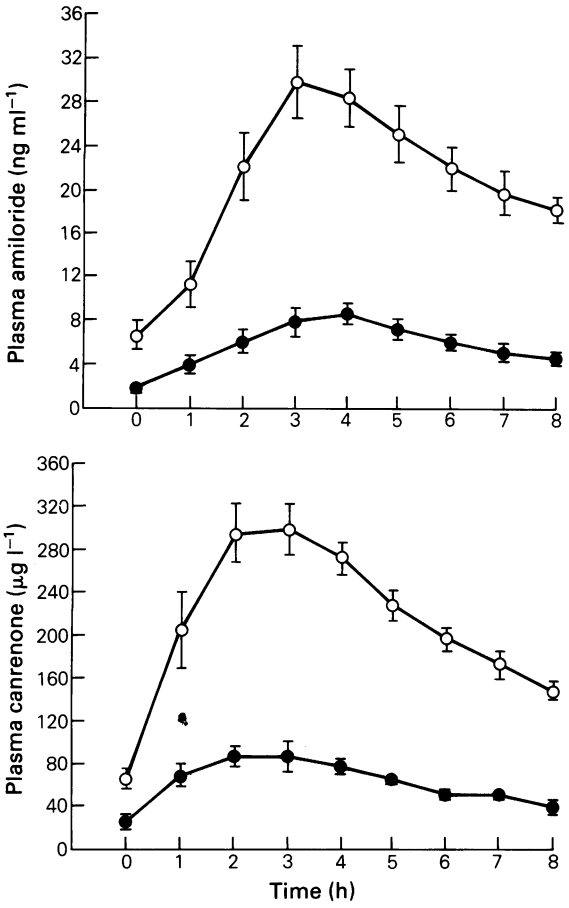


**Figure 2** Mean (vertical bars, s.e. mean) results for plasma a) amiloride and b) canrenone concentrations in 12 normal subjects after 7 days of treatment with hydrochlorothiazide 100 mg in combination with amiloride 5 mg (•), amiloride 20 mg (○), spironolactone 25 mg (•) and spironolactone 100 mg (○).

2. Coefficient of variation of the erythrocyte magnesium assay was 2.9%. Potassium and magnesium responses in the four treatment groups did not differ significantly. Erythrocyte sodium content showed a significant difference between the four treatment groups and between the two compounds but dose-response relationships were non-parallel, precluding an estimation of relative potency.

*Plasma aldosterone* Logarithmically transformed results for plasma aldosterone are also shown in Table 2. There was an increase from baseline on all treatments with significant differences between the four treatments and the two drugs.

*Plasma drug concentrations* Mean (s.d.) results for plasma amiloride and canrenone levels are given in Figure 2. The expected mean ratio of peak concentrations is 4:1. For amiloride the observed mean ratio was 3.59 which is not statistically different from that predicted but for canrenone the mean ratio was 3.10, significantly less than predicted ($P < 0.01$).

*Adverse effects* Nine of the 12 subjects reported an adverse effect on at least one of the four treatments. The most common adverse effect was lethargy/fatigue reported at the higher doses of both compounds. There were no significant differences between the two compounds. No subject had to be withdrawn because of adverse events.

## Discussion

The reduction in plasma potassium concentration after treatment with hydrochlorothiazide and the partial attenuation of this effect by amiloride and spironolactone are in keeping with general clinical experience (Morgan & Davidson, 1980). The relative potency (amiloride: spironolactine 10:1) is in agreement with previous work in hypertensive patients (George *et al.*, 1973) but considerably greater than the ratio (2.8:1) obtained in another study where the drugs were administered to subjects already hypokalaemic after thiazide treatment (Ramsay *et al.*, 1980). Even the lower confidence limit exceeded the best estimate in that study. The explanation for this difference is not clear. There is little evidence that responses in normal subjects differ from those in hypertensives or that the relative efficacy of amiloride and spironolactone depends on their use to prevent or correct hypokalaemia (Morgan, 1981). However, other differences in study design might be responsible for the disparate findings. Previous comparisons measured plasma potassium concentrations at only one time point during drug administration while we made frequent estimates to allow for within individual variability and differences in the time courses of action of the drugs. Since considerable changes in plasma potassium can occur with time within subjects (Morgan, 1981; Morgan & Davidson, 1980) and this variability may increase during treatment with potassium-sparing diuretics (Toner *et al.*, 1991), frequent potasssium measurements appear desirable in studies of this nature.

In agreement with results from other workers (Ramsay *et al.*, 1980), plasma aldosterone concentrations were well within the normal range at baseline and responded to both potassium-sparing agents in a dose-related manner. The effect of amiloride was more marked than that of spironolactone but hyperaldosteronism did not appear to offset potassium-sparing efficacy. There was little evidence to suggest any important differences between amiloride and spironolactone with respect to onset and duration of action within the 24 h period following each dose. Relative potency for plasma sodium was similar to that for plasma potassium suggesting that both compounds have a similar tendency to reduce plasma sodium at equivalent potassium sparing doses.

Hydrochlorothiazide reduced erythrocyte potassium concentration but neither potassium-sparing diuretic seemed to have an influence on that variable. This finding contrasts with reports which have suggested that amiloride and spironolactone maintain intracellular potassium concentration (Dyckner *et al.*, 1986, 1988). These studies had serious design flaws (McInnes, 1989) and the evidence that either drug has a major influence on intracellular potassium remains insubstantial. Erythrocyte sodium was little affected by any of the drugs.

There was no demonstrable change in plasma

magnesium concentrations during therapy with hydrochlorothiazide. Erythrocyte magnesium concentrations fell after hydrochlorothiazide therapy and it may be that efflux of magnesium from the intracellular pool maintains plasma levels (Lim & Jacob, 1972). The evidence that thiazide diuretics increase urine magnesium excretion is convincing (Beerman & Groschinsky-Grind, 1977; Parfitt, 1969; Swales, 1982; Wacker, 1961) and it is widely assumed that falls in plasma magnesium concentrations accompany these changes (Ahlstrand *et al.*, 1984; Hollifield, 1984; Seller *et al.*, 1965). However, the quality of the data supporting this view has been criticised elsewhere (Ramsay, 1986).

Amiloride induced a dose-related increase in plasma magnesium concentration but, in the absence of any reduction after hydrochlorothiazide, this effect is of uncertain clinical significance. Spironolactone appeared to have little effect, although plasma magnesium concentration tended to be lower at the higher dose. Neither drug had perceptible effects on erythrocyte magnesium concentration. It has been suggested that correction of magnesium deficiency is necessary for the maintenance of intracellular potassium status (Dyckner & Wester, 1979; Whang & Welt, 1963) and the results of a series of inadequate studies have been taken to support a magnesium-sparing effect of amiloride and spironolactone (Dyckner & Wester, 1984). The results of this study in normal subjects casts doubt on these conclusions and the relationship between magnesium and potassium deficiency.

The plasma concentration-time profiles for both agents indicate that measurable drug was present throughout the dosage interval. The fluctuations in plasma drug concentrations were not reflected in variability in plasma potassium concentrations. Plasma amiloride concentrations were dose-related but there was indication that the dose-concentration relationship for spironolactone was not directly proportional. In view of the lack of a close concentration-effect relationship, this finding is unlikely to be of major pharmacological significance.

This study indicates that, relative to spironolactone, amiloride may be a more potent potassium-sparing agent than has previously been suggested. However, our findings fail to support the notion that these drugs have major influences on intracellular cation concentrations. Amiloride and spironolactone had divergent effects on plasma magnesium but hydrochlorothiazide alone did not alter this variable.

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