SPIRONOLACTONE IN THIAZIDE-INDUCED HYPOKALAEMIA: VARIABLE RESPONSE BETWEEN PATIENTS

L.E. RAMSAY & J. HETTIARACHCHI

Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow.

- 1 The influence of spironolactone 25, 50, 100 and 200 mg daily, and placebo, on plasma potassium and other variables was examined in a random crossover study of 15 hypertensive patients taking bendroflumazide 10 mg daily.
- 2 Spironolactone produced significant dose-related increases in plasma potassium and aldosterone, and reductions in plasma sodium and bicarbonate.
- 3 In 14 compliant patients plasma concentrations of the major metabolite canrenone were related linearly to the dose of spironolactone, and there was less than twofold variation between patients. The plasma canrenone concentration correlated negatively with body weight ($r = -0.77$, $P < 0.001$).
- 4 The plasma potassium response to spironolactone varied sevenfold between compliant patients. The response correlated negatively with placebo plasma potassium ($r = -0.62$, $P < 0.02$), positively with plasma canrenone ($r = +0.55$, $P < 0.05$), but was unrelated to plasma aldosterone ($r = -0.22$). In one patient relative resistance to spironolactone was attributed to exaggerated secondary hyperaldosteronism induced by the drug.
- 5 The variability in response to spironolactone between patients is such that fixed dose thiazide-spiro-nolactone combination tablets are unlikely to prevent hypokalaemia reliably.

Introduction

Spironolactone is often prescribed in fixed-dose combination with a thiazide diuretic, e.g. with hydroflumethiazide (Aldactide, Searle). The main purpose is prevention of thiazide-induced hypokalaemia, although it may also have an added diuretic or antihypertensive effect (George, Breckenridge & Dollery, 1973; Ibsen, 1974). The use of such combinations to prevent hypokalaemia presupposes a reasonable uniformity of response to spironolactone in different patients, when in fact considerable variability might be expected on both pharmacokinetic and pharmacodynamic grounds. Modern formulations of micronized spironolactone have satisfactory bioavailability (Clarke, Ramsay, Shelton, Tidd, Murray & Palmer, 1977), but the drug undergoes extensive and complex metabolism (Sadée, Dagcioglu & Schroder, 1973; Karim, Zagarella, Hribar & Dooley, 1976). The major unconjugated metabolite canrenone is responsible for approximately 70% of the renal antimineralocorticoid activity of spironolactone at steady state (Ramsay, Asbury, Shelton & Harrison, 1977). Plasma canrenone concentrations vary fourfold in healthy men (Clarke *et al.*, 1977) and fifteenfold in patients with heart failure and chronic liver disease (Sadée, Schroder, v. Leitner & Present address: University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF.

Dagcioglu, 1974) for a given dose of spironolactone. Pharmacodynamic variability might stem from the mode of action of the drug. Spironolactone and canrenone are specific mineralocorticoid antagonists (Kagawa, 1960), and as such their response may be influenced by the concentration of endogenous mineralocorticoids, particularly aldosterone, at tissue receptors. Spironolactone treatment itself alters aldosterone secretion in complex fashion. Through natriuresis and volume depletion it stimulates renin and angiotensin II, leading to secondary hyperaldosteronism (Nicholls, Espiner, Hughes & Rogers, 1976; Abshagen, Sporn, Schoneshofer, L'Age, Rennekamp & Oelkers, 1976; Ogilvie, Piafsky & Ruedy, 1977) but on the other hand it partially inhibits aldosterone biosynthesis by a direct effect on the adrenal gland (Erbler, 1974a, b; Abshagen *et al.*, 1976). The net effect of these opposing influences is elevation of the plasma aldosterone concentrations, but to levels lower than expected from simultaneous plasma concentrations of angiotensin II and potassium, two major stimuli to aldosterone secretion (Ramsay, Hettiarachchi, Fraser & Morton, 1980). We studied the response to spironolactone in thiazide treated hypertensive patients to examine the variability between patients and to relate this, if possible, to plasma canrenone and aldosterone concentrations.

Methods

Patients

We studied 15 hypertensive patients (6 men; 14 essential hypertension, 1 chronic pyelonephritis; mean age 50, range 27–63 years) who had taken a diuretic for an average of 30 months. Six were taking diuretic alone, eight one additional drug (methyldopa 3, clonidine 2, propranolol 2, oxprenolol 1), and one two additional drugs (methyldopa plus propranolol). None had renal impairment (serum creatinine $> 130 \mu\text{mol/l}$), liver dysfunction or heart failure. Where necessary diuretic treatment was altered to bendrofluazide 10 mg daily, and potassium supplements or potassium-sparing drugs were stopped, four weeks before entry. Antihypertensive treatment was then held constant. The mean ($\pm$ s.d.) blood pressure at entry to the study was $167 \pm 22/99 \pm 9$ mm Hg recumbent and there were no significant changes during the study (Ramsay *et al.*, 1980). The patients gave informed consent, and the protocol was approved by the hospital ethical committee.

Protocol

During a larger study comparing amiloride, spironolactone and potassium chloride (Ramsay *et al.*, 1980) the patients received in random order five treatments, each of 4 weeks, against a background of bendrofluazide 10 mg daily. The treatments were placebo (2×25 mg placebo spironolactone tablets); spironolactone 25, 50, 100 mg (25 mg tablets) and 200 mg (100 mg tablets) daily, all taken as a single daily dose after breakfast. Ten patients had a second four week placebo period at the end of the study, and results from this phase were used to assess the constancy of plasma potassium in individual patients over the period of study. On the last day of each four week treatment phase patients were seen approximately 7 h after the morning dose of tablets. Compliance was assessed by tablet counts, which were $> 90\%$ in all except patient 12. This lady was clearly non-compliant on the only occasion when she actually returned her tablets for counting. Side-effects were sought by general enquiry. Venous blood was drawn without venous stasis or forearm exercise after 5 min recumbent.

Measurements

Plasma potassium and sodium were measured by flame photometry, aldosterone by the method of Fraser, Guest & Young (1973), and other electrolytes by routine automated methods. Canrenone concentration was measured by a fluorimetric method (Gochman & Gantt, 1962) with a coefficient of variation averaging 12%. The statistical methods used

were Student's *t*-test for paired samples and product-moment correlations.

Results

Constancy of plasma potassium

Ten patients had two placebo periods, during which they received 10 mg bendrofluazide alone, separated by an average of 17 weeks (range 4–38 weeks). The mean plasma potassium concentration did not alter (3.15 mmol/l v. 3.12 mmol/l) and there was a high correlation between the two values for each patient ($r = +0.88$, $P < 0.001$, Figure 1). The difference between the two values increased with the interval between the measurements ($r = +0.64$, $P < 0.05$).

Figure 1 Reproducibility of plasma potassium concentration (mmol/l) in 10 patients who had placebo added to bendrofluazide 10 mg daily on two occasions separated by an average of 17 weeks. Solid line = line of equality, broken line = calculated regression. $r = +0.88$, $P < 0.001$.

Plasma electrolytes and aldosterone

The results for 14 patients, excluding patient 12 who was non-compliant (see below), are shown in Table 1. Compared to placebo treatment (i.e. bendrofluazide alone) addition of spironolactone resulted in elevation of plasma potassium and aldosterone concentrations, and reductions in plasma sodium, serum bicarbonate and body weight. With the exception of body weight these changes were all highly significant and related to the dose of spironolactone.

Plasma canrenone

Patient 12, who was judged non-compliant by tablet counting, had canrenone concentrations more than

Table 1 Mean (and s.d.) results in 14 compliant hypertensive patients taking bendrofluazide 10 mg daily plus placebo and spironolactone at four doses.

	Placebo	Spironolactone			
		25 mg	50 mg	100 mg	200 mg
Plasma potassium (mmol/l)	3.00 (0.43)	3.37** (0.44)	3.52** (0.48)	3.83** (0.43)	3.91** (0.35)
Plasma sodium (mmol/l)	140 (2)	139 (3)	138* (3)	137** (4)	136** (3)
Serum bicarbonate (mmol/l)	30.8 (2.3)	29.7* (1.9)	28.7** (1.9)	28.2** (2.2)	27.7** (2.3)
Log plasma aldosterone (pmol/l)	1.08 (0.23)	1.20 (0.39)	1.50** (0.15)	1.54** (0.12)	1.63** (0.25)
Body weight (kg)	68.5 (8.6)	68.3 (8.5)	68.7 (8.9)	68.5 (8.5)	67.8* (8.5)

* $P < 0.05$, ** $P < 0.01$ v placebo values, Student's paired t -test.

three standard deviations below the mean for the other 14 patients at each dose level. In the 14 compliant patients plasma canrenone concentration was linearly related to the dose of spironolactone (Figure 2), with a two- and threefold difference between patients at each dose level. Using the mean of the four canrenone concentrations for each patient, the difference between patients fell to less than twofold. The mean plasma canrenone concentration was negatively related to body weight ($r = -0.77$, $P < 0.005$, Figure 3), but not to age or serum creatinine, albumin or bilirubin.

Variability of response to spironolactone

During placebo treatment (i.e. bendrofluazide 10 mg alone) the degree of hypokalaemia differed consider-

Figure 2 Mean (vertical bars range) plasma canrenone concentrations related to the daily dose of spironolactone in 14 compliant patients. Results for one non-compliant patient shown by open circles. **Figure 3** Plasma canrenone concentration (mean of 4 spironolactone dose levels) related to body weight in 14 compliant patients. $r = -0.77$, $P < 0.005$.

ably between patients (2.4–3.7 mmol/l) and this could not be related to age, sex, body weight, serum creatinine, or treatment with antihypertensive drugs other than bendrofluazide. Plasma aldosterone concentrations were within normal for the laboratory (mean 12.5 ± 6.2 pmol/l; upper limit 18 pmol/l) and did not correlate with the plasma potassium ($r = -0.23$). The response to spironolactone for each patient was calculated as the mean of the four plasma potassium values during active treatments minus the placebo value. The response showed sevenfold variation between patients, from 0.18–1.22 mmol/l. Patients with the most marked hypokalaemia during placebo treatment had the largest response to spironolactone ($r = -0.62$, $P < 0.02$, Figure 4). This correlation did not simply reflect a common 'ceiling' plasma potassium response in all patients. For example, the patient with the smallest response had a

Figure 4 Correlation of plasma potassium response (mean of four spironolactone treatments—placebo value) with plasma potassium level during placebo phase in 14 compliant patients taking bendrofluazide 10 mg daily. $r = -0.62$, $P < 0.05$.

maximum potassium level of only 3.9 mmol/l starting from a placebo value of 3.2 mmol/l whereas the patient with the largest response attained a higher potassium concentration (4.4 mmol/l) despite a lower placebo value (2.8 mmol/l).

There was a weak, but significant, correlation between the mean log canrenone concentration for each patient and the plasma potassium response ($r = +0.55$, $P < 0.05$, Figure 5). There was no correlation between plasma aldosterone concentration and the plasma potassium response ($r = -0.22$). Inspection

Figure 5 Plasma potassium (K) response related to log plasma canrenone (mean for 4 spironolactone treatment periods in each patient) in 14 compliant patients. $r = +0.55$, $P < 0.05$.

of Figure 5 shows that one patient was relatively resistant to spironolactone, with an increment in plasma potassium of only 0.18 mmol/l despite a canrenone concentration of 1.33 log units. This patient also had the largest increment in plasma aldosterone during spironolactone treatment (49.5 pmol/l, compared to a mean increment of 17.8 pmol/l in the other patients). When the sensitivity of patients to canrenone, expressed as Δ plasma potassium per log unit canrenone, was plotted against increments in plasma aldosterone the relationship reached significance ($r = -0.53$, $P = 0.05$, Figure 6), but largely through the influence of this single patient.

Figure 6 Sensitivity of patients to canrenone (Δ plasma K/log unit canrenone) related to increment in plasma aldosterone concentration during spironolactone treatment. $r = -0.53$, $P = 0.05$, $n = 14$. Note the influence of one patient who had an exceptional degree of secondary aldosteronism.

Plasma canrenone and other variables

The log canrenone concentration did not correlate with changes in plasma sodium ($r = -0.01$) or serum bicarbonate ($r = -0.05$). Four patients had side-effects when treated with spironolactone 200 mg daily (nausea in 2, leg cramps in 1, headache in 1). Plasma canrenone concentrations in these patients ($43.5 \pm 7.7 \mu\text{g}/100 \text{ ml}$) were not significantly different from those for the 10 patients without side-effects ($51.5 \pm 13.0 \mu\text{g}/100 \text{ ml}$).

Discussion

Repeated measurements of serum or plasma potassium within individual patients show considerable variation, and it is not known whether this reflects

true biological variability, or error introduced during the collection and processing of the samples (Morgan, 1978). We took steps to eliminate this second source of error by measuring potassium in plasma rather than serum, and by standardising posture, time of day, venepuncture technique, and sample handling. A second placebo (bendrofluazide) treatment phase was included to assess the reproducibility of plasma potassium measurements within patients over the duration of the study. Although the error between estimates increased significantly with the interval between them, they were reproducible enough for our purpose (Figure 1). Any error in the plasma potassium measurements was reduced further by using the mean results from four treatment periods to calculate the spironolactone response for each patient, as these were in effect replicate measurements. The results confirmed the efficacy of spironolactone in correcting thiazide-induced hypokalaemia, but the response showed sevenfold variation between patients, from 0.18 to 1.22 mmol/l. A surprising finding was that the initial degree of hypokalaemia predicted the response to spironolactone, the largest responses occurring in patients with the lowest plasma potassium concentrations. Such a relationship might emerge spuriously if there was a large random error in the placebo values, or if all patients had a common 'ceiling' response, but these explanations could both be discounted. The initial degree of hypokalaemia predicted 38% ($r^2 \times 100$) of the variability in response to spironolactone.

Plasma concentrations of the major unconjugated metabolite canrenone were related linearly to the dose of spironolactone over the range 25–200 mg daily. Differences in canrenone concentration between patients were smaller than anticipated, with less than twofold variation using four replicate measurements for each patient. It would in fact be possible to use canrenone levels as a measure of compliance in patients taking spironolactone, as shown by the results in one patient who was noncompliant. In compliant patients most of the variance in plasma canrenone concentrations (60%) was related to body weight and, we presume, to differences in the apparent volume of distribution. The relationship between plasma canrenone and body weight is unlikely to be of great importance in the routine prescribing of spironolactone, although side-effects, which are dose related (Ramsay *et al.*, 1980), might be expected most frequently in patients of low body weight.

Despite the narrow spread of plasma canrenone concentrations there was a significant correlation between log canrenone and the plasma potassium response, although only 30% of the variability between patients could be explained on this basis. We found no evidence that the plasma aldosterone concentration was important in determining the degree

of hypokalaemia during bendrofluazide treatment or, in the majority of patients, in determining the response to spironolactone. However, one patient was relatively resistant to spironolactone, as shown by a small increment in plasma potassium in relation to the canrenone concentration, and this was apparently related to an unusually large increment in plasma aldosterone concentration. An exceptional degree of secondary hyperaldosteronism may blunt the response to spironolactone in occasional patients.

A case can be made for the use of a combined thiazide-spironolactone tablet when it is particularly important to avoid hypokalaemia, e.g. in patients taking digoxin, but our results suggest that such combinations are unlikely to be entirely satisfactory. The severity of hypokalaemia with a given dose of thiazide diuretic varies widely and unpredictably between patients, as shown in the placebo phase of the present study, and in a previous study (Ramsay, Boyle & Ramsay, 1977). To this must be added the large variation in response to spironolactone shown in this study. Larger responses to spironolactone in patients with more marked hypokalaemia, as shown here, would tend to favour the efficacy of a combined tablet, but the overall response is still unpredictable. Thus a combination of bendrofluazide 10 mg plus spironolactone 100 mg daily would have resulted in plasma levels ranging from 3.0–4.6 mmol/l in the patients that we studied. One cannot, therefore, dispense with plasma potassium measurements when using a combined tablet, and it will be necessary to adjust the individual drug components in some patients. In uncomplicated hypertension it is widely recommended that treatment of thiazide-induced hypokalaemia should be reserved for the small minority of patients with potassium concentrations below 3.0 mmol/l (Dustan, Tarazi & Bravo, 1974; Kosman, 1974; Lant, 1977; Ramsay & Ramsay, 1977). The dose of potassium chloride needed to correct this degree of hypokalaemia is unacceptably large (Ramsay *et al.*, 1980), and a single daily dose of a potassium-sparing drug is preferable on the grounds of convenience alone. However, even this will not be uniformly effective. If, for example, the aim was to elevate the plasma potassium concentration from < 3.0 mmol/l to an arbitrary value of 3.5 mmol/l, addition of spironolactone 100 mg daily failed in one third of our patients, and one patient remained hypokalaemic (3.2 mmol/l) despite 200 mg spironolactone daily.

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