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Amiloride disposition in geriatric patients: importance of renal function

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1 The absorption and disposition of the potassium sparing diuretic amiloride were determined in nine elderly patients aged 71 to 87 years and in eight young (25 to 38 years) subjects following oral administration of 5 mg amiloride HCl daily to steady-state.
2 The maximum and steady-state plasma amiloride concentrations were significantly ($P < 0.05$ and $P < 0.001$) higher in the elderly patients. The renal clearance of amiloride was lower in the elderly than in young subjects (102 ± 36 ml min^{-1} *vs* 300 ± 64 ml min^{-1}, $P < 0.001$) as was the urinary excretion of amiloride (36 ± 13 *vs* 62 ± 18% of the dose, $P < 0.01$).
3 The steady-state plasma amiloride concentration correlated significantly ($r^2 = 0.61$, $P < 0.001$) with amiloride renal clearance and with creatinine clearance ($r^2 = 0.59$, $P < 0.001$). There was a very strong positive correlation between renal amiloride clearance and creatinine clearance ($r^2 = 0.76$, $P < 0.001$). The slope of the regression line was 2.5 indicating substantial proximal tubular secretion of amiloride.
4 Sodium and potassium excretion, along with urine volume were significantly ($P < 0.05$) lower in the elderly (by 39, 45 and 34% respectively).
5 The disposition of amiloride was highly dependent on renal function, with higher plasma amiloride concentrations in the elderly reflecting diminished renal function. The dose of amiloride should be titrated to individual response, and the lower potassium excretion in the elderly patients suggests that the dose of amiloride could be reduced in this group of patients.

Keywords amiloride geriatric patients disposition renal clearance kidney function

Introduction

The potassium sparing diuretics amiloride and triamterene still play an important role in attenuating the potassium-wasting effects of thiazide and more potent loop diuretics. Whilst the disposition of triamterene has been investigated in some detail (Mutschler *et al.*, 1983), the disposition of amiloride, the more commonly used of the two agents, has not been thoroughly studied (Smith & Smith, 1973; Weiss *et al.*, 1969). One reason for the paucity of documentation has been the lack of a sufficiently sensitive assay to measure the low concentrations in plasma resulting from clinical doses (5–10 mg daily) of amiloride.

The disposition of many drugs in the elderly (usually 60 to 75 years) has been reviewed

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(Greenblatt *et al.*, 1982; Ho & Triggs, 1984; Ouslander, 1981). Drug disposition in geriatric patients (> 75 years) has not been as thoroughly addressed. Amiloride is now commonly used in the elderly and geriatric patient population and although considered relatively safe in these patients, it is not without its adverse effects, especially hyponatraemia, hyperkalaemia (MacFarlane & Kennedy, 1972; Sunderam & Mankikar, 1983; Whiting *et al.*, 1979) and renal failure (Lynn *et al.*, 1985). Sabanathan & colleagues (1987) found a greater area under the plasma concentration-time curve of amiloride in elderly compared with young subjects. The effect of renal function on amiloride's disposition was not directly assessed and they concluded that further investigations on the effects of ageing on amiloride pharmacokinetics were warranted.

The aim of our study was to investigate the disposition of amiloride in geriatric patients receiving the drug for therapy, and to examine the importance of renal function on its pharmacokinetics.

Methods

Patients

The study was approved by the Human Ethics Committee of the Royal Adelaide Hospital. All patients agreed to participate in the study after being fully informed of the purpose and risks involved.

Nine patients with ischaemic heart disease were investigated. These patients were aged between 71 and 87 years and they weighed between 45 and 86 kg; five were females and four were males. The physical characteristics, renal function, medical histories and concomitant medication for these patients are listed in Table 1. These patients had been receiving amiloride 5 mg daily for more than 1 month to attenuate the potential potassium loss from their frusemide therapy. The data from these patients were compared with a group of eight young (25 to 38 years) subjects weighing between 65 and 99 kg, two of whom were females and the other six males. These subjects had received 5 mg amiloride daily for 6 days and were investigated on the seventh day. Details of these subjects have been recently described (Somogyi *et al.*, 1989). All subjects received 5 mg amiloride hydrochloride as one Midamor® tablet (Merck, Sharpe & Dohme, Australia Pty Ltd, Sydney, Australia) each morning after breakfast. The patients were confined to bed whilst the young subjects were seated throughout most of the first 12 h of the pharmacokinetic study.

Biological fluid collection

Venous blood (7 ml) was drawn from an indwelling catheter and stylet (Jelco®, Critikon Inc., Tampa, Fla.) placed in a forearm vein, into heparinised tubes, at the following times: 0 (just prior to the dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h and by separate venepuncture at 24 h (prior to the next dose). The blood was immediately centrifuged at 1600 *g* for 10 min and the resultant plasma stored at −20° C prior to analysis.

The subjects and patients emptied their bladders prior to the dose and all urine was subsequently collected over the 24 h dosing interval. The volume and pH were recorded and a 5 ml aliquot was stored at −20° C for analysis. All samples were assayed for amiloride within 4 months of collection.

Drug analyses

Amiloride was assayed in plasma and urine by a recently described high-performance liquid chromatography (h.p.l.c.) method employing ion-pair extraction and fluorescence detection (Somogyi *et al.*, 1988). This assay has a lower limit of detection of 0.2 ng ml^{-1} and shows precision and accuracy to within 10%. Urine and plasma concentrations of creatinine were measured by h.p.l.c. (Muirhead *et al.*, 1986). Sodium and potassium in urine were measured by flame photometry (EEL Model 150; EEL International Ltd, Bayswater, Australia). The conversion factor to S.I. units for amiloride concentrations is 4.35.

Pharmacokinetic and statistical analyses

Creatinine clearance was calculated as the rate of creatinine excretion in urine during the 24 h dosing interval divided by the steady-state plasma creatinine concentration. The ratio of the renal clearance of amiloride to the renal clearance of creatinine was also calculated.

Differences in the pharmacokinetic parameters (C_{min}, C_{max}, t_{max}, C_{av}, Ae, fe, CL_R) between the two groups were analysed for statistical significance by the non-parametric Mann-Whitney U test (Daniel, 1978). Correlations between pharmacokinetic parameters and physiological variables (e.g. age, renal function) were determined by linear regression analysis incorporating 95% confidence intervals. All data are tabulated as mean ± s.d.

Table 1 Description of patients' physical and biochemical characteristics.

Patient	*Age (years)*	*Sex*	*Weight (kg)*	S_{Cr}	$S_{Na}+$	S_K+	*Urea*	*Illnesses*	*Concurrent therapy*
1	83	F	69	0.08	139	3.7	4.9	Heart failure	Frusemide, digoxin, sorbide dinitrate, antacids
2	86	F	50	0.07	136	3.7	6.1	Pulmonary oedema, diabetes	Frusemide, tolbutamide
3	71	M	86	0.12	137	3.8	8.9	Gout, chronic airways disease	Frusemide, allopurinol, nifedipine, aspirin, pheniramine
4	75	F	52	0.08	136	3.1	6.7	Reflux oesophagitis	Frusemide, nitrates, theophylline
5	87	M	63	0.14	141	3.6	9.4	Vertebrobasilar insufficiency, diabetes	Frusemide, tolbutamide, diclofenac, aspirin, prochlorperazine
6	73	M	60	0.15	142	4.0	9.4	Left ventricular failure, diabetes	Frusemide, aspirin, tolbutamide, captopril
7	85	F	45	0.07	132	3.9	4.2	Heart failure	Frusemide
8	73	M	59	0.21	139	4.7	21.3	Duodenal ulcer, angina, diabetes	Frusemide, glibenclamide, ranitidine, nitrates
9	86	F	54	0.13	135	4.2	7.8	Angina, gastric ulcer	Frusemide, nitrates, ranitidine, digoxin, prochlorperazine
Young subjects (n = 8)	25–38	2F, 6M	65–99	0.07–0.1	138–144	3.3–4.0	3.9–7.1	Nil	Nil

S_{Cr}, $S_{Na}+$, S_K+, Urea = serum creatinine, sodium, potassium and urea in mmol l^{-1}.

Table 2 Comparison of pharmacokinetic data for amiloride between young ($n = 8$) and elderly ($n = 9$) subjects (mean ± s.d.)

Parameter	*Elderly*	*Young*	*Statistical significance* (P)
t_{max} (h)	4.1 ± 1.8	4.0 ± 1.3	NS
C_{max} (ng ml^{-1})	18.2 ± 3.4	14.3 ± 3.1	< 0.05
C_{min} (ng ml^{-1})	7.7 ± 2.7	3.7 ± 1.1	< 0.001
$AUC_{ss}(\tau)$ (ng ml^{-1} h)	281.6 ± 43.5	174.3 ± 53.6	< 0.001
C_{av} (ng ml^{-1})	11.7 ± 1.8	7.3 ± 2.3	< 0.001
% dose in urine	36.4 ± 12.8	62.4 ± 17.7	< 0.01
Renal clearance (ml min^{-1})	102 ± 36	300 ± 64	< 0.001
Creatinine clearance (ml min^{-1})	41 ± 13	114 ± 12	< 0.001

NS: $P > 0.05$

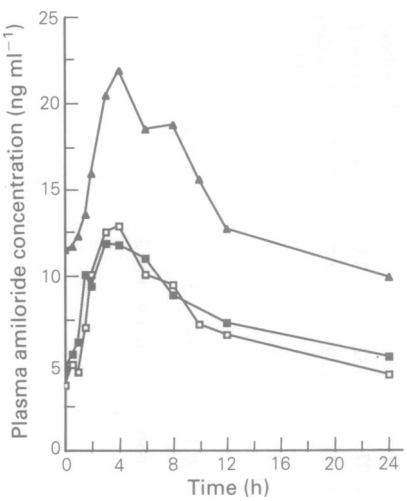

Figure 1 Plasma amiloride concentration-time profiles during a 24 h interdosing interval in two elderly patients, one with the highest concentrations (▲) and one with the lowest concentrations (■). The mean concentrations (□) in the young subjects ($n = 8$) are also shown.

Results

Figure 1 shows the ranges in the plasma amiloride concentrations in the elderly subjects compared with those in the young subjects and Table 2 lists the resultant mean pharmacokinetic parameters. The minimum and maximum plasma concentrations were significantly higher in the elderly, the former being almost double the value seen in the young subjects (7.7 ± 2.7 ng ml^{-1} versus 3.7 ± 1.1 ng ml^{-1}; $P < 0.001$). In the elderly, the average steady-state plasma concentration was significantly ($P < 0.001$) higher by an average of 62%, and by an average of 38% when corrected for variations in body weight. With regard to the urinary elimination of amiloride, the elderly excreted significantly ($P < 0.01$) less of the absorbed dose (36.4 ± 12.8% elderly *vs* 62.4 ± 17.7% young), the average percentage decrease being 42%.

Amiloride's renal clearance in the elderly was on average 34% of that in the young subjects.

Apart from differences in age, the elderly patients weighed significantly less ($P < 0.05$) than the young subjects (60 ± 12 kg *vs* 73 ± 11 kg). Their serum creatinines were not significantly different ($P > 0.05$), but creatinine clearance was significantly lower in the elderly (41 ± 13 ml min^{-1} *vs* 114 ± 12 ml min^{-1}; $P < 0.001$).

There was a highly significant negative correlation between the steady-state plasma amiloride concentration (C_{av}) and amiloride renal clearance ($r^2 = 0.61$; $P < 0.001$; Figure 2). These two parameters were then related to the patients' ages resulting in a positive correlation between C_{av} and age ($r^2 = 0.48$; $P < 0.0025$), and a very strong positive correlation between amiloride renal clearance and age ($r^2 = 0.71$; $P < 0.001$). Creatinine clearance was also significantly related to age (Figure 3). The steady-state plasma amiloride concentration and renal amiloride clearance were significantly correlated with the patients' creatinine clearance ($r^2 = 0.59$ and 0.76 respectively; Figure 4). There was no statistically significant difference ($P > 0.05$) in the ratio of amiloride renal clearance to creatinine clearance between the two populations (2.6 ± 0.9 elderly *vs* 2.7 ± 0.7 young), and there was no significant correlation ($r^2 = 0.003$; $P > 0.05$) between this ratio and age.

The pharmacodynamic effects of amiloride were also different between the two groups. The

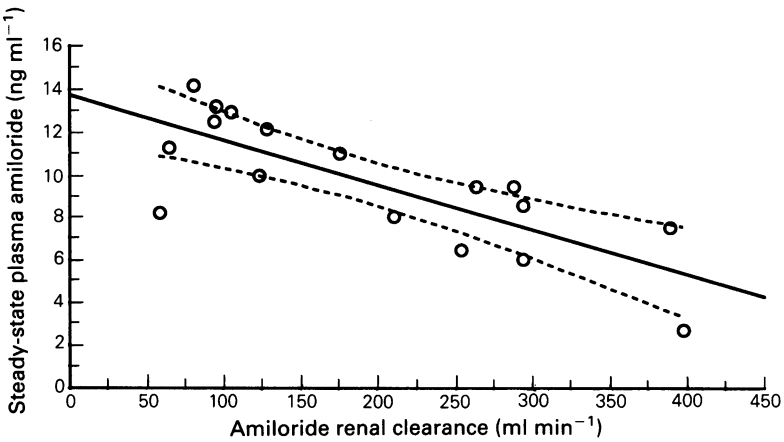

Figure 2 Relationship between amiloride renal clearance and steady-state plasma amiloride concentration. The equation to the line is: $y = -0.021x + 13.7$ ($r^2 = 0.61$; $P < 0.001$). The stippled lines indicate the 95% confidence limits about the regression line.

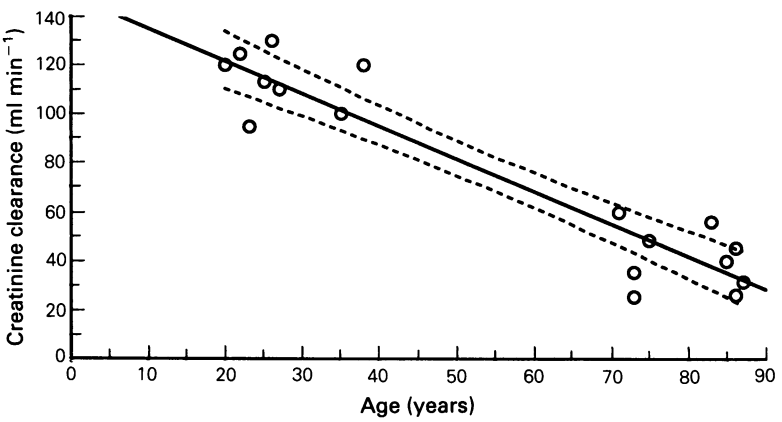

Figure 3 Relationship between age and creatinine clearance. The equation to the line is: $y = -1.34x + 148.7$ ($r^2 = 0.89$; $P < 0.001$). The stippled lines indicate the 95% confidence limits about the regression line.

interdosing interval urine volume was significantly less in the elderly compared with the young subjects (1.58 ± 0.42 l elderly *vs* 2.40 ± 0.77 l young; $P < 0.05$). In addition, sodium excretion was also significantly lower in the elderly (56 ± 30 mEq elderly *vs* 91 ± 22 mEq young; $P < 0.05$), as was potassium excretion (27 ± 17 mEq elderly *vs* 49 ± 17 mEq young subjects; $P < 0.05$). There was no difference ($P > 0.05$) in the urinary amiloride concentration between the two groups (1.18 ± 0.45 μg ml^{-1} elderly *vs* 1.45 ± 0.71 μg ml^{-1} young).

Discussion

In this study, there were substantial differences between the two groups in their handling of amiloride both pharmacokinetically and pharmacodynamically. Whereas there was no difference in serum creatinine between the two groups, creatinine clearance was significantly reduced in the elderly, consistent with literature reports (Rowe *et al.*, 1976). Steady-state conditions for amiloride had been achieved as the C_{min} and 24 h plasma concentrations were similar within both groups. The minimum and maximum attained plasma amiloride concentrations were much higher in the elderly, as was the steady-state plasma concentration, even when corrected for differences in body weight. The average increase in the steady-state plasma concentration of 61% is less than the increase observed by Sabanathan *et al.* (1987) of approximately 100%; this may be a consequence of the different population groups studied (e.g. nonhospitalized *vs* hospitalized).

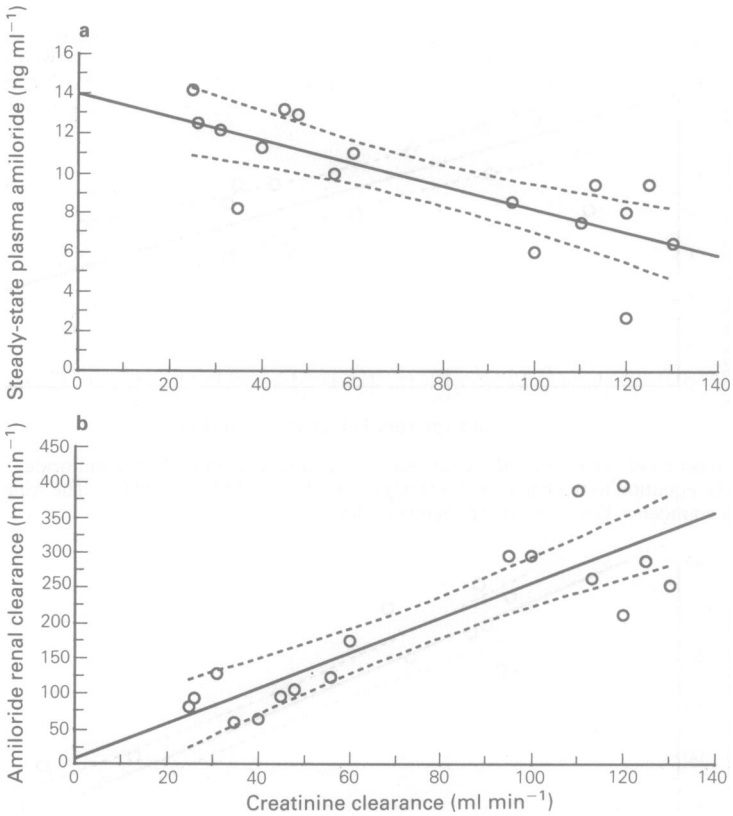

Figure 4 a) Relationship between steady-state plasma amiloride concentration and creatinine clearance. The equation to the line is: $y = -0.059x + 14.0$ ($r^2 = 0.59$; $P < 0.001$). The stippled lines indicate the 95% confidence limits about the regression line. b) Relationship between amiloride renal clearance and creatinine clearance. The equation to the line is: $y = 2.48x + 7.94$ ($r^2 = 0.76$; $P < 0.001$). The stippled lines indicate the 95% confidence limits about the regression line.

However, the data are consistent with those of Spahn *et al.* (1987) who compared the disposition of amiloride between healthy controls and patients with varying degrees of renal failure.

In humans, approximately 50% of an oral dose of amiloride is recovered in urine as unchanged amiloride (Weiss *et al.*, 1969). The remainder of the dose probably represents either unabsorbed drug or biliary and or intestinal clearance, as several investigators have recovered up to 50% of the dose in faeces after oral dosing (Weiss *et al.*, 1969; George, 1980; unpublished observations). Metabolism of amiloride is considered not to occur. The reason for the reduced urinary recovery of amiloride in the elderly must remain speculative, as the total body clearance of amiloride and its absolute bioavailability are not known. Spahn *et al.* (1987) also found a reduced urinary recovery of amiloride in patients with renal failure, however the 48 h urine collection time period was too short to enable complete recovery of amiloride as its half-life was 55 h. Sabanathan *et al.* (1987) found no difference in the urinary recovery of amiloride between young healthy controls and elderly hypertensive patients. If amiloride were completely absorbed and the unrecovered dose was cleared at a normal rate by extrarenal processes, then a three-fold reduction in renal clearance would result in a significant increase in the amount eliminated by extrarenal mechanisms and a significant reduction in the amount eliminated by renal mechanisms, as was observed. However, if poor absorption is the factor contributing to the faecal recovery of amiloride, then reduced renal clearance would still result in the same amount of amiloride excreted in urine during a dosing interval at steady-state. Our results raise the possibility of reduced absorption of amiloride in geriatric patients, which could be a result of the ageing

process, their concurrent disease or concomitant medication. The available data do not allow us to differentiate between these possibilities.

It is apparent that renal function is the major factor influencing the disposition of amiloride. There was a highly significant, strong, negative correlation between age and creatinine clearance, a relationship which has been previously decribed (Lindeman *et al.*, 1985). The strong correlations between age and steady-state plasma amiloride concentration, and between age and renal amiloride clearance were due to a decline in renal function with age. Renal clearance was markedly reduced (three fold) in the elderly patients and there was a very strong positive correlation between amiloride renal clearance and creatinine clearance, in which 76% of the variance could be explained. The slope of the relationship (2.5) indicates that amiloride undergoes substantial renal tubular secretion which represents its major clearance mechanism by the kidney and by extrapolation, the body. The slope found in this investigation was almost identical (2.55) to that reported recently by Spahn *et al.* (1987). Amiloride is an organic base and is secreted by the proximal tubule via the organic base system, as cimetidine and other organic bases reduce its renal clearance in man (Somogyi *et al.*, 1989) and in animals (Besseghir & Rennick, 1981; Rennick *et al.*, 1984; Somogyi *et al.*, 1989). The outcome of these correlations is that renal function is the most important pathophysiological parameter controlling the disposition of amiloride.

There is uncertainty in the literature regarding the effect of age on renal tubular function. Reidenberg and colleagues (1980) found that the ratios of the renal clearances of procainamide and *n*-acetylprocainamide to creatinine clearance, in patients receiving procainamide, declined significantly with age, whereas the same group (Drayer *et al.*, 1981) could not confirm this with anothe organic base, cimetidine. In this study, there was no difference in the amiloride renal clearance to creatinine clearance ratio between the two populations and there was no correlation between this ratio and age. The reason for the apparent decline in tubular function with age reported for procainamide and its active metabolite is unknown. Our data do not support the hypothesis of age having a differential influence on renal tubular and glomerular functions.

The reductions in urine volume (34%), sodium excretion (39%) and potassium excretion (45%) in the elderly compared with the young subjects, were all of similar magnitude suggesting a common underlying mechanism. Even though the elderly were receiving potent diuretic therapy, in the form of frusemide, their response was suppressed. This is unlikely to be a consequence of reduced drug delivery into the lumen of the tubule, the site of diuretic effect (Lant, 1985). Other factors such as hospital stay, fluid and electrolyte intake, disease state (e.g. diabetes) and other drugs are likely to have contributed to this pharmacodynamic difference. In addition, the effect of frusemide on the pharmacodynamics of amiloride remains to be determined, but it is unlikely that it affected amiloride's pharmacokinetics. However, it should be noted that potassium was retained to a significantly greater degree in the elderly patients indicating that a reduced amiloride dosage should be considered in this group of patients.

In conclusion, amiloride disposition is markedly altered in the elderly, a consequence of reduced renal function. Potassium excretion was also much lower in the elderly suggesting that the dose could be reduced in the elderly, a dosing strategy currently being considered by the pharmaceutical industry.

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