Use of amiloride as a potassium conserving agent in severe cardiac disease

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Amiloride was used as a potassium conserving agent in 24 cardiac patients requiring large doses of frusemide, and the changes in plasma and total exchangeable potassium were studied over a 6-month period. Plasma potassium rose (+0.41 mEq/l.; $P < 0.01$) and this rise was sustained throughout. Four patients had persistent hypokalaemia, but hyperkalaemia was not found. The total exchangeable potassium initially rose (+320 mEq; $P < 0.02$) over the first 3 months but fell in the last 3 months (-198 mEq; $P < 0.01$) so that at 6 months no overall change had occurred. Amiloride is thus suitable for use with frusemide as an antikaliuretic agent, provided adequate dietary intake of potassium is ensured.

Potassium depletion, as estimated by total exchangeable potassium (TEK), is common in patients with severe cardiac disease, and is thought to be due either to a fall in intracellular potassium concentration (Flear *et al.*, 1966) or to the loss of lean tissue accompanying cardiac cachexia (White *et al.*, 1969). Diuretic treatment in heart failure is frequently complicated by hypokalaemia with the associated hazards of digitalis toxicity, but in addition diuretics may directly contribute to overall potassium depletion (Lockey *et al.*, 1966). Potassium supplements generally prevent hypokalaemia but have not been shown to prevent a negative potassium balance, particularly when the more potent diuretics are used.

Amiloride, a recently introduced potassium-sparing diuretic, has been shown to prevent hypokalaemia and reduce urinary potassium loss when used with thiazides (Gombos, Freis, and Moghadam, 1966; Paterson, Dollery, and Haslam, 1968; Antcliff *et al.*, 1971), ethacrynic acid (Singh *et al.*, 1967; Yamada and Reynolds, 1970), and frusemide (Singh, Hurley, and North, 1969). This study reports the effects of replacing potassium supplements by amiloride in cardiac patients requiring treatment with frusemide. The changes in both plasma potassium and total exchangeable potassium were measured over a 6-month period.

Patients and methods

Patients

Clinical details of the 24 patients studied are summarized in Table 1. The patients selected required at least 80 mg frusemide daily as maintenance diuretic therapy, and had been established on their current regimen for at least two months before entering the trial. Potassium supplements (24-48 mEq/day) were stopped and replaced by amiloride 20 mg/day, but diet and other therapy were not altered. Patients were fully informed of the objectives of the trial, and warned to report any adverse reactions immediately; withdrawal from the trial was considered necessary if there was clinical deterioration, severe hypokalaemia, or a rise in blood urea to greater than 100 mg/100 ml.

Clinical methods

The patients attended as outpatients, initially each week, but subsequently every 2 to 3 weeks over the course of 6 months. Plasma electrolytes were determined on each attendance and total exchangeable potassium measured initially and after 3 and 6 months. Blood was taken from an unoccluded arm vein with full aseptic precautions, and plasma was separated by centrifuge within an hour. Total exchangeable potassium was estimated by the isotope dilution method (Corsa *et al.*, 1950) using ⁴³K. Potassium supplements were omitted for 24 hours before the initial estimation but it was not felt justified to discontinue diuretic therapy and this was continued as usual during the test period. 20-40 μ Ci ⁴³K in potassium chloride were given intravenously and the specific activity of urine samples passed between 22 to 24 and 24 to 26 hours was measured. Retention of the administered dose over the first 22 hours was found to be relatively constant in the first 25 estimations (96.9%, SD 1.2%) and for convenience of collection was subsequently

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TABLE 1 *Clinical data*

Case No.	Age (yr)	Ht. (cm)	Wt. (kg)	Wt. % pred.*	Diagnosis	Diuretic treatment	Duration of treatment (yr)
Male							
1	36	177	52	74.5	Cardiomyopathy	F 160	2
2	34	183	67.5	82.5	Aortic valve replacement; mitral incompetence	F 120	2
3	48	171.5	66.25	88	Mitral stenosis; aortic incompetence	F 160	2
Female							
4	51	160	68.75	108	Mixed mitral valve disease	F 80	7
5	67	158	59	94.5	Mixed mitral valve disease	F 120	5
6	55	166	62.25	91	Mixed mitral valve disease; systemic hypertension	F 160	4
7	56	153.5	47.25	79.8	Mixed mitral valve disease	F 120	6
8	68	163	86.5	131	Mitral incompetence; ischaemic heart disease	F 80	3
9	54	158.5	64	103.5	Mitral incompetence	F 80	4
10	60	164	64.5	95	Mixed mitral valve disease; pulmonary hypertension	F 160	5
11	51	156	67	105	Mixed mitral valve disease; AVD; pulmonary hypertension	F 160	7
12	47	154.5	59	100	Mixed mitral valve disease	F 80	9
13	51	156	50	82.7	Mixed mitral valve disease	F 80	0.5
14	57	160	51.5	97	Mixed mitral valve disease	F 160	5
15	58	159.5	44	69	Mitral incompetence; systemic hypertension	F 160	2
16	38	160	79	134.5	Mitral valve replacement	F 160	0.5
17	49	157	60	100	Mixed mitral valve disease	F 80	4
18	57	159.5	56.5	88.7	Aortic valve replacement; mixed mitral valve disease; TVD	F 160	7
19	46	153.5	47	80.7	Mixed mitral valve disease; TVD	F 160	6
20	49	167	75	112	Mixed mitral valve disease	F 80	3
21	54	150	45	78	Mixed mitral valve disease; pulmonary hypertension	F 160	7
22	58	166	60	88	AVD; mixed mitral valve disease	F 120	5
23	49	156.5	50.5	83.5	Mixed mitral valve disease; TVD	F 80	6
24	46	164.5	58	89.2	AVD; mixed mitral valve disease	F 80	3

* Weight predicted from Society of Actuaries Build and Blood Pressure Study (1959).

AVD, aortic valve disease; TVD, tricuspid valve disease.

assumed at this figure. The total exchangeable potassium was calculated as the mean of the two urine samples, the average difference between the two estimates being 6.6 per cent, comparable with previous data (Staffurth, 1961).

Analytical methods

Plasma electrolytes were measured on an SMA 6/60 autoanalyser (between batch coefficient of variation 1.67%); and urinary potassium concentration on an I.L. 143 flame photometer. Radioactivity of the urine was measured in a Philips automatic well counter, counting 5 ml aliquots from each specimen for 20 minutes and comparing activity with a standard prepared from the solution originally administered. Dietary assessment was made by one observer using the method of McCance and Widdowson (1967). Statistical analysis was by Student's 't' test on paired data.

Results

Clinical effects

Amiloride was generally well tolerated, and most patients found it easier to take than potassium

supplements. A diuresis was observed in most subjects with a weight loss of 0.5–3 kg in the first week of treatment but over the ensuing weeks the weight was regained, and at the end of the trial period did not differ from the original value. The only significant side effect was an alteration in taste and nausea often persisting many hours after taking the tablets, and in 3 patients the drug was discontinued for this reason. One patient (Case 11, see below) was withdrawn from the study because of electrolyte disturbance, but no alteration in diuretic regimen was required in any other patient on clinical grounds, and digoxin toxicity was not observed. Dietary potassium intake, estimated in Cases 1 to 14, was found to be low in 5 cases (less than 60 mEq/day), but this did not appear to be directly related to low plasma potassium or total exchangeable potassium.

Plasma electrolytes

The overall effect of amiloride on electrolytes is summarized in Table 2; there was a small but sig-

TABLE 2 Mean plasma electrolytes and blood urea before and during treatment with amiloride

	Na ⁺ (mEq/l.)	K ⁺	Cl ⁻	HCO ₃ ⁻	Urea (mg/100 ml)
Before treatment	139.46	3.54	97.08	28.70	38.50
Amiloride	138.80	3.95	97.04	28.20	42.00
SD of difference	2.48	0.51	2.40	1.91	10.15
P	NS	<0.01	NS	NS	NS

nificant increase in plasma potassium (mean +0.41 mEq/l., $P < 0.01$) but no change in any of the other parameters measured. This increase in potassium was present after one week of treatment, and persisted without any significant change for the remainder of the study. The initial potassium readings were lower than expected (mean 3.54 mEq/l.), probably because of the care taken in venepuncture, avoiding factors which may give falsely high readings in routine measurements. Details of individual potassium levels are shown in Tables 3 and 4; in 4 patients (Cases 5, 7, 11, and 17) plasma potassium remained less than 3.7 mEq/l. throughout, though there was no evidence of clinical deterioration or digoxin intoxication. In one patient (Case 11), however, the potassium fell to less than 3.0 mEq/l. and the blood urea rose to 105 mg/100 ml, so that amiloride had to be discontinued after 3 months' treatment. The small rise in blood urea observed in most patients was not significant; the blood urea did not rise above 70 mg/100 ml in any other patient.

Total exchangeable potassium

The patients studied fell into two groups; the first (group A) in whom measurements were made before and during treatment with amiloride, and the second (group B) in whom measurements were obtained only when therapy had been established. Details of group A are shown in Table 3. A significant increase in total exchangeable potassium occurred in the first 3 months of treatment ($P < 0.02$), but over a further 3 months there was a fall in 6 of the 9 patients, and the total exchangeable potassium at 6 months did not differ significantly from the original value. In group B (Table 4) there was no significant change between the third and the sixth month of treatment, but when the figures of the two groups were combined a significant fall in total exchangeable potassium was found over this period ($P < 0.01$). These findings are summarized in Table 5 from which it is concluded that though treatment with amiloride was associated with an initial rise in total exchangeable potassium, this was not sustained over a longer period of study.

TABLE 3 Group A: plasma potassium and TEK before and during six months treatment with amiloride

Case No.	Plasma K ⁺ (mEq/l.)			Total exchangeable potassium (mEq)		Δ Total exchangeable potassium 3 mth†	Δ Total exchangeable potassium 6 mth
	0	3	6 mth	Before treatment	% pred.*		
1	3.8	4.4	4.9	2120	66.5	-100	-190
2	3.9	4.5	4.2	2680	74	+670	+450
4	3.8	4.2	4.1	2219	94	+510	+315
5	2.8	3.4	3.4	2210	—	+270	-360
6	4.3	4.0	3.8	2450	98	+415	-225
7	2.3	3.1	3.4	1700	79	+105	-15
8	3.9	4.2	4.1	2120	—	-290	—
9	4.9	4.7	4.5	2070	90	+590	+60
10	3.0	3.8	—	2020	82	+210	—
11	2.5	3.2	—	2100	94	+270	—
12	3.1	3.2	4.0	2380	106.5	-50	-140
13	3.3	4.3	3.9	1960	86.5	+390	-130
14	3.6	4.1	—	2025	93	+1200	—

* Predicted values for total exchangeable potassium obtained from Flear *et al.* (1966).

† Δ total exchangeable potassium indicates change in total exchangeable potassium compared to the initial reading.

TABLE 4 Group B: effect of amiloride on plasma potassium and total exchangeable potassium in patients in whom initial total exchangeable potassium was not obtainable

Case No.	Plasma K ⁺ (mEq/l.)			Total exchangeable potassium (mEq) 3 mth treatment	Δ Total exchangeable potassium 6 mth treatment*
	0 mth	3 mth	6 mth		
3	3.7	4.4	4.9	2625	+95
15	3.3	3.8	4.0	1850	-40
16	3.5	4.6	3.9	2362	
17	3.5	3.1	3.4	2795	-225
18	3.6	3.8	4.1	2120	+130
19	3.7	3.8	3.7	1700	+225
20	4.5	3.5	4.4	3190	+85
21	3.9	3.9	3.8	2045	-150
22	3.3	4.2	3.6	2150	-460
23	3.7	4.3	4.2	2515	-275
24	3.9	3.7	—	1995	

* Δ total exchangeable potassium indicates change in total exchangeable potassium compared to reading at 3 months.

TABLE 5 Effect of amiloride on total exchangeable potassium in groups A and B

	Δ Total exchangeable potassium*		
	0-3 mth	0-6 mth	3-6 mth
Mean difference	+320.0	-26.0	-198.5
SD of difference	384.1	259.1	266.6
P	<0.02	NS	<0.01
	n=13	n=9	n=18

* Δ total exchangeable potassium is the change in total exchangeable potassium over the periods indicated.

Discussion

The place of potassium conserving agents in diuretic therapy has not been clearly established. Except in occasional situations their diuretic action is too weak for use alone, and dangerous hyperkalaemia may occur (Yamada and Reynolds, 1970). They are therefore generally used in combination with potassium-losing diuretics, and on theoretical grounds seem more suitable for maintaining potassium balance than potassium supplements alone. However, their effective use requires an adequate potassium intake which may not always be present in patients with severe heart disease. In this study 5 of 14 patients had a low dietary potassium, and similar findings have been reported in geriatric patients (Dall and Gardiner, 1971) and in patients with liver disease (Senewiratne and Sherlock, 1968), either from anorexia or a poor choice of food. As stressed

by the latter authors, simple dietary advice can greatly augment potassium intake, and is essential in long-term diuretic treatment, especially when potassium-conserving agents are used.

Amiloride has been shown to be an effective antidiuretic agent when used with thiazides, ethacrynic acid, and frusemide in short-term studies, potentiating the diuresis of these drugs while reducing urinary potassium loss by up to 50 per cent. Plasma potassium generally rises, and long-term studies have confirmed that amiloride prevents the usual fall in plasma potassium accompanying thiazide treatment (Paterson, *et al.*, 1968; McNay, MacCannell, and Oran, 1970; Antcliff *et al.*, 1971). However, when used in combination with ethacrynic acid, this effect is less consistent and hypokalaemia may occur (Senewiratne and Sherlock, 1968; Yamada and Reynolds, 1970).

In this study the use of a standard dose of amiloride in place of potassium supplements was associated with a small but significant rise in plasma potassium in most patients, which was maintained throughout the 6-month period. The low plasma potassium levels present in 12 patients on their previous regimen suggested that the potassium supplements given were inadequate for the dose of frusemide used. Amiloride therefore seems to have been more effective in maintaining plasma potassium than conventional doses of potassium supplements in these patients. Nevertheless, hypokalaemia was found in a few patients so that continued electrolyte monitoring is essential. In two of these patients plasma potassium rose to the normal range when the dose of amiloride was increased to 40 mg/day, and it may be that with more potent diuretics amiloride should be used in higher doses than generally recommended by the manufacturers, particularly as the most dangerous side effect, hyperkalaemia, is rarely found in combination therapy.

In addition to the effects on plasma potassium, amiloride has been shown to reverse the hypochloralcaemic alkalosis of diuretic treatment, probably by promoting the renal excretion of bicarbonate (Reynolds and Pelle, 1966). Though this has been confirmed with thiazides (Antcliff *et al.*, 1971) in long-term treatment, it was less consistently found with ethacrynic acid (Yamada and Reynolds, 1970) and in the present study no significant change in plasma bicarbonate occurred, most patients remaining alkalotic. A rise in blood urea was however found in most patients, though this was not significant overall. It was not progressive or associated with any clinical deterioration and probably represents a fall in renal plasma flow consequent on the diuresis rather than any diuretic nephrotoxic action of the drug (Lieberman, Ito, and Reynolds, 1969).

Changes in plasma potassium are known to bear little direct relation to variations in body potassium as a whole (Flear, Cooke, and Quinton, 1957), and this is evident in the present study where no overall change in total exchangeable potassium occurred despite a persistent rise in plasma potassium. The measurement of total exchangeable potassium in patients with cardiac disease is complicated by the delay in equilibration of the potassium isotope which occurs in all oedematous states (O'Meara *et al.*, 1957). Adequate equilibration may not occur for up to 48 hours, so that the 24-hour reading used for the convenience of the patients in this study may underestimate the absolute total exchangeable potassium by 5 to 10 per cent, but still enables valid comparisons of serial changes in total exchangeable potassium to be made in each patient.

The clinical significance of the changes in total exchangeable potassium observed in the present study is not clear, particularly in the absence of any corresponding change in body weight. Its initial rise suggests that over the first 3 months a positive potassium balance was more effectively maintained than with the previous potassium supplements. The later fall in total exchangeable potassium is similar to the findings of Senewiratne and Sherlock (1968) in cirrhotic patients, and Croxson, Neutze, and John (1972) in cardiac patients. In both these studies, one-fifth of the patients failed to maintain potassium balance with amiloride; whether this represents a loss of efficacy of the drug or merely reflects the continued wasting associated with the disease itself could only be clarified by a more extensive study.

The efficacy of an antikaliuretic agent must be measured by the extent to which it maintains both plasma potassium levels and a positive potassium balance. In the first respect, amiloride compares favourably with the other potassium conserving agents, spironolactone and triamterene (Lant, Smith, and Wilson, 1969; Yamada and Reynolds, 1970), but few studies are available for a comparison of the effects of these drugs on potassium balance as a whole. Most studies of potassium balance have been concerned with the use of thiazides in hypertension, and the results may not be directly applicable in the treatment of oedema. Even in this situation, the evidence that diuretics lead to a fall in total exchangeable potassium is conflicting (Anderson *et al.*, 1971; Down *et al.*, 1972), possibly because little attention is paid to what may be a significant variation in potassium intake. Nevertheless, McKenna *et al.* (1971) found a consistent fall in patients on thiazides and were able to compare the effect of potassium supplements, spironolactone, and triamterene; the first two prevented a fall in total exchangeable potassium but triamterene did not.

In cardiac disease, the information is more limited. Potassium supplements when given in large doses (96 mEq/day) promoted a rise in total exchangeable potassium in preoperative cardiac patients (White, 1969), and this suggests that conventional doses of potassium are insufficient to maintain a satisfactory balance in patients needing a potent diuretic regimen. Spironolactone used in a similar group of patients prevented any fall in total exchangeable potassium (White, 1969), but short-term balance studies have indicated that additional potassium supplements may be necessary in some patients (Ross, 1961). The information from the present study and those of Senewiratne and Sherlock (1968) and Croxson *et al.* (1972) suggest that amiloride can be used as the sole anti-kaliuretic agent in the long-term treatment of patients on potent diuretics, and that it may be more effective than the potassium supplements in doses currently used.

Conclusion

Amiloride has been used successfully as the sole potassium conserving agent in the long-term treatment of patients with severe cardiac disease who required large doses of frusemide as maintenance therapy. Plasma potassium rose to the normal range in most patients, and the changes in total exchangeable potassium observed suggest that a negative potassium balance was prevented. Side effects, mainly gastrointestinal, were few, and limited treatment in 4 patients only. The initial rise in plasma potassium and total exchangeable potassium suggests that amiloride may be more effective than conventional doses of potassium supplements, but with large doses of frusemide hypokalaemia may occur and continued electrolyte monitoring is essential. A significant number of patients with cardiac disease may have a poor potassium intake, and simple dietary advice is important when large doses of diuretics are used.

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