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Effect of amiloride on metabolic alkalosis and hypokalaemia after cardiopulmonary bypass surgery

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This study was undertaken to investigate the effects of the potassium-retaining diuretic, amiloride, on the potassium balance and on the alkalosis which occurs in patients after open-heart surgery.

Patients who had had valve replacement operations were divided randomly into two groups, one of which received 10 mg amiloride daily in the postoperative period.

Patients who were given amiloride needed less potassium supplementation than those in the control group ($P < 0.005$) and yet maintained significantly higher plasma potassium levels ($P < 0.05$).

This small dose of amiloride also appeared to have some effect in reducing the alkalosis.

It is concluded that amiloride is a potentially useful drug after cardiac surgery.

Metabolic alkalosis and hypokalaemia are common after open-heart surgery. The former is thought to be due mainly to the transfusion of acid-citrate-dextrose blood, the citrate being metabolized to bicarbonate. It may also be partly due to hyperventilation (Bain *et al.*, 1966; Grigor, 1968). The hypokalaemia has been attributed to long-term diuretic therapy especially in patients who have valve replacement operations. This has been shown to lead to a depletion in the total body potassium despite a normal plasma level and oral potassium supplements (Mandal, Callaghan, and Sterns, 1968; Ebert, Jude, and Gaertner, 1965; Lockey *et al.*, 1966). The copious diuresis which occurs as a part of postoperative management accentuates the hypokalaemia, and the importance of adequate potassium supplementation in this situation has been emphasized by several authors (Kettlewell, White, and Saunders, 1970; Breckenridge *et al.*, 1972; Barnard *et al.*, 1966; Shanahan, Anderson, and Morris, 1969).

Amiloride is a mild oral diuretic which has potassium retaining properties (Martindale, 1972). Its exact mode of action is uncertain, but it is not a carbonic anhydrase inhibitor, nor an aldosterone antagonist (Baer *et al.*, 1967). It appears to act on the distal tubular cells of the nephron, preventing the secretion of potassium, and enhancing the excretion of sodium and bicarbonate (Guignard and Peters, 1970; Baba *et al.*, 1968; Bull and Laragh, 1968). It has been used both to correct the hypokalaemic alkalosis induced by the more powerful diuretics (Antcliffe *et al.*, 1971) and in an attempt to conserve potassium before cardiac surgery (Singh, Hurley, and North, 1969).

This study was mounted to assess its value after cardiac surgery.

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Subjects and methods

All patients who underwent valve replacement operations in this unit between 1 January 1973 and 31 July 1973 are included, except for those who had isolated aortic valve replacements who had not been taking diuretics before operation as it was found that they did not usually require postoperative diuretic therapy. Twenty-six patients were studied in all. They were divided into 3 groups, according to the number of valves they had had replaced. Within each group they were paired in chronological order and, using random number tables, one patient from each pair received 10 mg amiloride daily from the third postoperative day onward. Amiloride is an oral preparation and could not be administered until oral feeding had been established. Fourteen patients acted as controls (C) and 12 received amiloride (A).

Twenty-four hour urine collections were made and arterial blood samples taken on the 3rd, 4th, 7th, and 14th postoperative days. The urine was collected in bottles containing 50 ml toluene, 0·5 g streptomycin, and 250 mg chloramphenicol, and was kept refrigerated at 4°C until it could be analysed. Sodium, potassium,

TABLE *Details of patients included in study; until 3rd postoperative day*

Control group C)				*Preoperative drug therapy*				*Intra-operation and until 3rd post-op. day*		*Postoperative drugs until day 3 (total dosage)*		
Case No.	*Age (yr)*	*Sex*	*Operation*	*Diuretics (mg/day)*	*Potassium supplements (mEq/day)*	*Digoxin (mg)*	*Other drugs*	*Volume of blood transfused (units)*	*Sodium bicarbonate (mEq)*	*Diuretics (mg)*	*Potassium supplements (mEq)*	*Digoxin (mg)*
1	54	M	AVR	Frusemide 80	70	—	Propranolol	15	—	Frusemide 80	270	—
3	37	F	AVR MVR	—	—	0·25 daily	Warfarin	17	50	Frusemide 20	214	1·5
5	21	F	MVR	—	—	0·25 b.d.	Warfarin	9	60	Frusemide 60	170	0·625
8	51	F	MVR TVR	Frusemide 40	24	0·25 b.d. ex. Sun.	Warfarin	12	—	Frusemide 80	324	0·5
9	39	F	MVR	Frusemide 40	24	0·25 daily	—	11	150	Frusemide 60	280	0·25
10	47	F	AVR MVR	Frusemide 80	48	0·25 b.d.	—	13	100	Frusemide 60	130	—
13	41	F	AVR MVR TVR	Frusemide 40	24	0·25 b.d.	Bethanidine	16	100	Frusemide 200	225	—
14	52	F	MVR	Frusemide 40 alt. dy	24	0·25 b.d.	—	10	100	—	340	2·25
15	33	F	AVR	Frusemide 40	36	—	—	15	100	Frusemide 80	280	—
18	29	M	MVR	—	—	0·25 b.d.	—	12	100	Frusemide 100	230	0·5
22	44	F	MVR	—	—	0·25 ex. Sat. and Sun.	—	6	—	Frusemide 160	234	—
23	46	F	MVR TVR	Frusemide 40	24	0·25 b.d.	—	12	—	—	340	—
24	47	F	MVR	Frusemide 80								
			TVR	ECA 100 Spiro. 100	24	0·25 b.d.	—	12	100	Frusemide 80	280	0·5
25	39	F	MVR	Bendro-fluazide 10	16	0·25 b.d.	—	11	—	Frusemide 40	310	—

AVR = aortic valve replacement; MVR = mitral valve replacement; TVR = tricuspid valve replacement; ECA = ethacrynic acid; Spiro. = spironolactone.

chloride, and *p*H were measured on both blood and urine. In addition, titratable acidity and ammonia were estimated on the urine, and P_{CO_2} and base excess on the blood. The sodium and potassium measurements were made with an EEL 27 integrating flame photometer and chloride using an Aminco solid state automatic chloride titrator. Ammonium was measured using Berthelot's method and a Unicam colorimeter. Blood gases were estimated on a Corning EEL *p*H/blood gas analyser 165, and urinary *p*H on a Radiometer *p*H meter 22.

Fluid balance was noted each day and frusemide and ethacrynic acid were administered as often as deemed necessary on clinical grounds to both groups. Potassium supplements were given if the plasma potassium, on routine daily measurement, fell below 3·9 mEq/l. During the period of the study all patients ate a normal hospital diet, except 2 (one from each group) who were tube fed.

A few patients had their total exchangeable body potassium (K_E) measured on days 3 and 17. A known dose of radioactive ^{43}K was given orally on day 2, followed by a 24-hour urine collection, in which the radioactivity was counted by a Gammaguard 150 automatic gamma counter. A 'spot' specimen of urine was then obtained and this was both counted and analysed for total potassium. This procedure was repeated on day 16. The calculation of K_E was based on the formula first described by Corsa *et al.* (1950).

Results

Of the 14 control patients (C) 12 were women and 2 were men. In the amiloride group (A), 4 of the 12 patients were men. Two patients, one from each group, died during the study from unrelated causes.

The ages, preoperative drug therapy, total volume of blood transfused, total amount of sodium bicarbonate, and postoperative drug therapy until day 3, were compared in the two groups and the details are shown in the Table. The only significant

TABLE (Cont'd)

Amiloride group (A)				*Preoperative drug therapy*				*Intra-operation and until 3rd post-op. day*		*Postoperative drugs until day 3 (total dosage)*		
Case No.	*Age (yr)*	*Sex*	*Operation*	*Diuretics (mg/day)*	*Potassium supplements (mEq/day)*	*Digoxin (mg)*	*Other drugs*	*Volume of blood transfused (units)*	*Sodium bicarbonate (mEq)*	*Diuretics (mg)*	*Potassum supplements (mEq)*	*Digoxin (mg)*
2	44	F	MVR	Frusemide 40	16	0·25 daily	—	9	—	Frusemide 200	72	0·5
4	47	F	AVR MVR TVR	Frusemide 120	48	0·25 daily	—	18	—	Frusemide 60	258	0·25
6	64	M	AVR	Frusemide 40	24	0·25 b.d.	—	14	270	Frusemide 140	100	—
7	49	F	AVR MVR	—	—	—	—	16	—	Frusemide 40	250	—
11	36	M	MVR TVR	Frusemide 40 alt. dy	16	0·375 daily	Dindevan	17	—	Frusemide 120	266	0·625
12	50	M	MVR	Frusemide 40	16	0·25	—	14	120	Frusemide 40	310	0·125
16	49	F	Resuture MVR	Frusemide 40	16	0·25 daily	Warfarin	16	—	Frusemide 60	180	1·875
17	55	F	MVR	Aldactide 25	—	0·25 daily ex. Sat. and Sun.	—	9	210	Frusemide 60	310	0·75
19	56	F	AVR MVR	Frusemide 40 Mon. Wed. Fri.	8 Tues. Thurs. Sat.	0·25 b.d.	—	14	100	Frusemide 360 ECA 200	174	0·625
20	48	M	MVR	Frusemide 40	24	0·25 tid	Warfarin Salbutamol	15	200	Frusemide 180	210	0·125
21	49	F	AVR M. valvot	Bendro-fluazide 5. 3 dy/wk	16 3 dys/wk	—	—	10	70	Frusemide 140	195	1·125
26	49	F	AVR MVR	Frusemide 40	24	0·25 daily	—	9	—	Frusemide 60	270	0·75
			Age									
Group C means			41·43	Frusemide 34·29	22·57	0·37 daily		12·21	61·43	Frusemide 72·86	276·6	0·4375
Group A means			49·67	Frusemide 33·33	16·5	0·275 daily		13·42	66·67	Frusemide 121·67	231·25	0·5625
P			<0·02	>0·5	>0·5	>0·2		>0·2	>0·5	>0·1	>0·1	>0·5

difference between them is that the mean age of the amiloride patients is higher than that of the controls.

In calculating the mean dose of diuretic, only frusemide was taken into consideration as this was the predominant diuretic used throughout. Though the difference is not significant, it should be noted that the amiloride group received, on average, 48·81 mg more frusemide in the first two post-operative days than did the control group. One patient in this group was also given 100 mg ethacrynic acid, which increases the difference between the groups. The specimens on day 3 were all obtained before any amiloride had been administered.

All the patients tolerated amiloride well and no side effects were seen.

Effect of amiloride on the P_{CO_2}, *p*H, and base excess

Amiloride had no effect on the P_{CO_2}. The pattern of change in the base excess was not greatly affected by amiloride. Fig. 1 depicts the change in blood *p*H. On days 4 and 14 the blood of the control group was significantly more alkaline than that of the amiloride group ($P < 0.02$ and $P < 0.05$, respectively).

Effect of amiloride on the urinary *p*H, titratable acidity, ammonium, and hydrogen ion excretion

There was no statistically significant difference between the two groups with respect to any of these parameters.

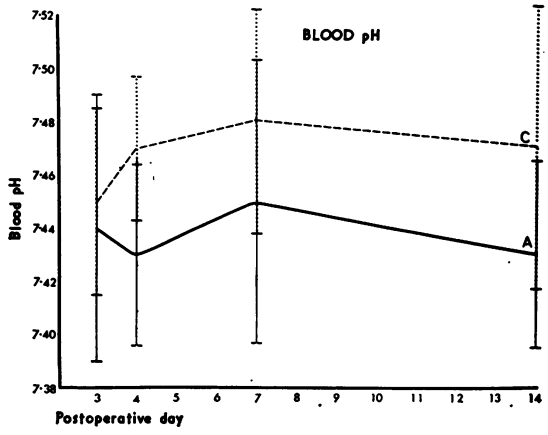

FIG. 1 *Arterial* pH (±*standard deviation*) *in the amiloride patients* (A) *and control patients* (C).

The hydrogen ion excretion was calculated as the sum of the titratable acidity and ammonium excretion (Keele and Neil, 1971) and it fell slightly on days 4 and 7.

Effect of amiloride on plasma and urinary sodium, potassium, and chloride

The plasma sodium in the control patients started at a slightly higher level than in the amiloride patients, and remained so throughout. This difference was not significant. The urinary sodium is shown in Fig. 2. The excretion of sodium was greater in the amiloride patients than in the controls on days 3, 4, and 7, but was significantly so only on day 7 ($P < 0.05$). By day 14 the excretion was the same in both groups.

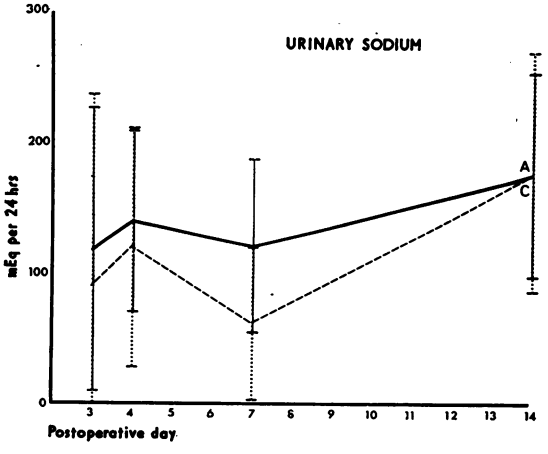

FIG. 2 *Sodium excretion* (±*standard deviation*).

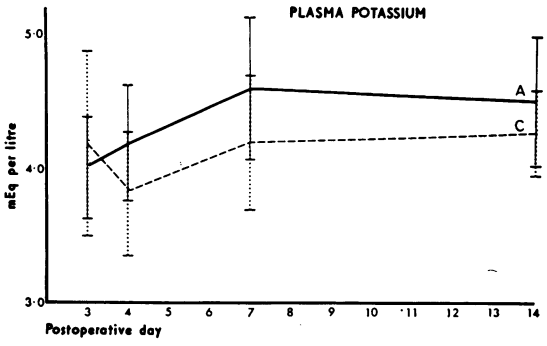

FIG. 3 *Plasma potassium* (±*standard deviation*).

Plasma potassium was slightly lower on day 3 in the amiloride group, but on days 4, 7, and 14 it was higher than in the control group (Fig. 3). The difference was significant at the 0·05 level on days 4 and 7.

There was no significant difference between the urinary potassium in the two groups before amiloride was started on day 3. Subsequently, however, the amiloride patients excreted considerably less potassium than the controls ($P < 0.02$, $P < 0.01$, and $P < 0.05$ on days 4, 7, and 14, respectively) (Fig. 4).

A similar pattern was seen in the urinary sodium/potassium ratio. The ratio was much greater in the

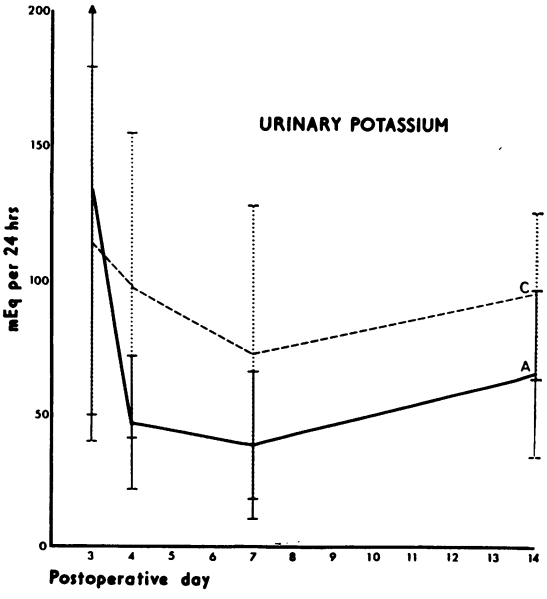

FIG. 4 *Potassium excretion* (±*standard deviation*).

amiloride group on days 7 ($P < 0.02$) and 14 ($P < 0.05$).

No difference between the groups was seen with either plasma or urinary chloride.

Effect of amiloride on fluid balance and drug therapy

The fluid balance in the two groups was essentially the same. However, the patients given amiloride required less frusemide than the control group from day 8 onwards, the P values being less than 0·05 on days, 8, 9, 11, and 13, when frusemide alone is considered.

Fig. 5 shows the mean dose of potassium supplement required by the two groups. From day 5 onward the amiloride patients needed strikingly less potassium than did the control patients ($P < 0.005$ on days 5 and 7, and $P < 0.001$ on day 6 and from day 8 to 14). This is much greater than would be accounted for by the difference in the dosage of frusemide.

There was no significant difference in the dose of digoxin received by the two groups.

Effect of amiloride on total exchangeable body potassium

No significant difference was found in the K_E between patients who had received amiloride and those who did not, but the number of patients in whom the K_E was measured was small. Singh *et al.* (1969) found little difference in the K_E of their patients over a two-week period and concluded that this length of time was too short for a significant difference to occur.

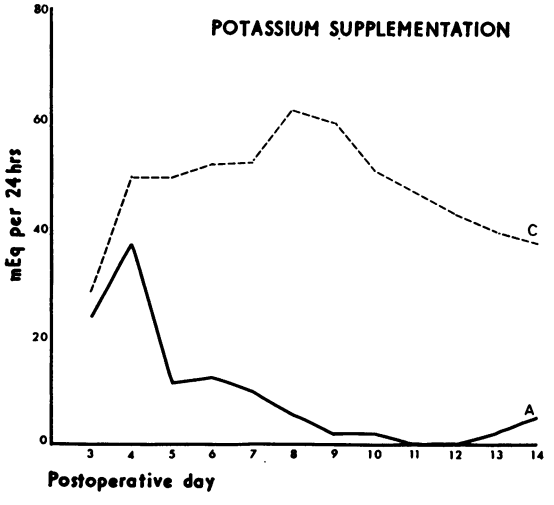

FIG. 5 *Mean daily dose of potassium supplement.*

Discussion

The mode of action of amiloride on the distal tubule of the kidney is uncertain. However, Guignard and Peters (1970) suggest that it prevents the excretion of potassium from the cells and also inhibits the uptake of sodium by acting on the luminal membrane causing it to become impermeable to these ions. This leads to retention of potassium and to a natriuresis. The excretion of hydrogen ions is simultaneously decreased because of the inactivity of the transport mechanism at the luminal border of the cell.

After open-heart surgery, though the patients are alkalotic, they excrete an acid urine. This may be attributed to the exchange of intracellular potassium for extracellular hydrogen and sodium ions. The potassium is excreted, leading to a depletion in the total body content of this ion (Jamieson and Kay, 1965). There is a higher concentration of hydrogen ion in the cell as a result of this interchange, and it has been postulated that it is the low intracellular *p*H of the tubular cells which is responsible for the secretion of an acid urine (Grigor, 1968; Adler, 1971).

Bull and Laragh (1968) showed that amiloride caused an increase in the excretion of bicarbonate in conjunction with the natriuresis (Baer *et al.*, 1967).

In the situation described, amiloride would, therefore, be expected to lead to the following: a rise in plasma and total body potassium, with a fall in potassium excretion. Plasma sodium, blood *p*H, and hydrogen ion excretion would fall and sodium excretion in the urine would rise.

A pronounced effect was seen on the potassium balance. The amiloride patients required much less potassium supplementation than did the control patients, and yet maintained their plasma potassium levels well above those of the controls. This was due to a significant decrease in the urinary excretion of potassium.

The plasma sodium of the amiloride group began and remained lower than that of the control group, but never significantly so. The lower value would be expected as a result of the natriuretic properties of amiloride. The increased excretion of sodium was confirmed on day 7 but it was the same in both groups on day 14. However, the sodium/potassium ratio in the urine was significantly different between the two groups on both days 7 and 14.

The blood *p*H became significantly lower in the amiloride patients. This indicates that amiloride does have an effect on the alkalosis. The decreased hydrogen ion excretion on days 4 and 7 is probably responsible for this. The P_{CO_2} was little different between the two groups of patients. A larger dose of amiloride may well have a more

significant effect on the alkalosis than the 10 mg used here, the recommended dosage being 10 to 40 mg daily.

No patient in this series had a plasma potassium above the upper limit of normal.

It is unfortunate that, at present, no parenteral preparation of amiloride is available, since its use, intravenously, earlier in the postoperative period would offer even greater advantages.

Conclusions

From the results of this study, it appears that amiloride is a potentially useful drug after cardiac surgery, both from its action in decreasing the metabolic alkalosis, and in reducing the amount of potassium supplementation needed, while maintaining plasma potassium levels within normal limits.

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