Amiloride Hydrochloride in Hypertensive Patients

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Brit. med. J., 1968, 1, 422–423

In man amiloride hydrochloride (MK-870) has been shown to be an orally effective diuretic which causes a positive potassium balance. It also enhances the saluretic effects of hydrochlorothiazide and ethacrynic acid and in addition prevents the negative potassium balance caused by these diuretics (Wilson *et al.*, 1966; Gombos *et al.*, 1966). Gombos *et al.* also studied its effects in 10 hypertensive patients, all of whom were on other antihypertensive agents. The present study was undertaken to compare the effect of amiloride hydrochloride with hydrochlorothiazide in mild hypertensives who were on no other therapy.

Patients and Methods

Previously untreated hypertensive outpatients whose systolic blood pressure was not greater than 250 mm. Hg and diastolic blood pressure not greater than 130 mm. Hg were selected. Patients with heart failure, grade 3–4 retinopathy, or a blood urea greater than 60 mg./100 ml. were not included in the trial. Before the trial began each patient had undergone the following investigations: haemoglobin and full blood count, blood urea and electrolytes, serum uric acid, serum proteins and electrophoresis, liver-function tests, urine analysis for sugar, protein, and cells, urine culture, chest *x*-ray, electrocardiogram, and intravenous pyelography. Patients were seen again when the investigations had been completed, and were re-weighed and the blood pressure was taken in the lying, sitting, and standing positions and after exercise. Each patient was then treated for three six-week periods with (*a*) amiloride (5 mg. t.d.s.), (*b*) hydrochlorothiazide (50 mg. daily), or (*c*) a combination of amiloride (5 mg. t.d.s.) and hydrochlorothiazide (50 mg. daily). The order in which the drug regimens were given was determined by random selection of sealed envelopes.

The patients were seen at three and six weeks on each regimen; the blood pressure was measured in the lying, sitting, and standing positions and after exercise, and the patients were weighed. At the end of each period of treatment blood and urine tests were repeated in order to detect any possible toxic effects of the drugs. The blood pressure, weights, and biochemical data were analysed statistically on the Elliot 4100 computer at the Royal Postgraduate Medical School.

Results

Two of the original 12 patients were unable to complete the combined diuretic regimen, having to withdraw after three days, but otherwise all patients completed the six-week periods of treatment. Table I summarizes the blood pressure and weight data on the 12 patients. It will be seen that the average blood pressures were lower on all three regimens than in the pretreatment period. The paired *t* test and, in the case of comparisons involving the combined diuretic regimen, the unpaired *t* test (as two patients withdrew from this regimen) were used to test the significance of the differences between the average blood pressures and weights on each regimen. Though the average lying blood pressure on hydrochlorothiazide (146.7/89.1 mm. Hg) was lower than that on amiloride (152.4/92.2 mm. Hg) the difference was not significant at the 5% level. The average lying blood pressure on the combination (143.9/90.6 mm. Hg) was again not significantly different from that on either diuretic alone. Comparison of the average sitting, standing, and exercise blood pressures showed no significant differences between the three regimens of treatment. Also the average lying blood pressure did not differ significantly from the average standing blood pressure on any of the three regimens. The average weight did not change significantly.

TABLE I.—*Average Blood Pressures and Weights*

	Lying		Sitting		Standing		Exercise		Weight	
	S.	D.	S.	D.	S.	D.	S.	D.	lb.	kg.
Control	176·3	104·6	168·8	105·8	168·8	108·8	181·3	106·7	165·4	75·0
Amiloride	152·4	92·2	148·7	93·5	144·7	94·1	166·2	95·3	166·4	75·5
Hydrochlorothiazide	146·7	89·1	148·9	93·5	146·7	92·1	160·2	92·3	165·9	75·3
Amiloride and hydrochlorothiazide	143·9	90·6	146·8	92·7	140·5	93·9	150·8	89·4	164·2	74·5

S. = Systolic. D. = Diastolic.
Control readings are the average for all cases for the second outpatient visit.
Treatment averages include the three- and six-week readings for all patients.

There was no significant difference between the average blood urea in the pretreatment period (31 mg./100 ml.) and the average blood urea when either amiloride alone (32 mg./100 ml.) or hydrochlorothiazide (33 mg./100 ml.) was given. However, on the combined diuretic regimen the average blood urea rose significantly to 40 mg./100 ml. as compared with the pretreatment value ($P=0.013$). The average plasma potassium was significantly higher ($P=0.011$) on amiloride (4.6 mEq/l.) than before treatment (4.2 mEq/l.). However, no individual value was higher than the upper limit of the normal range, and the highest value recorded was 5.1 mEq/l. On hydrochlorothiazide the average plasma potassium fell to 3.7 mEq/l., which was significantly less than control ($P=0.016$), and in addition three individual values were below the lower limit of normal (3.0, 3.1, 3.1 mEq/l.). On the combined regimen the average value (4.0 mEq/l.) was not significantly different from that before treatment; only one reading was below normal (3.7 mEq/l.) and the highest value was 4.3 mEq/l.).

The average plasma chloride was not significantly different from control when amiloride was given but there was a significant fall on both hydrochlorothiazide ($P=0.03$) and amiloride + hydrochlorothiazide ($P=0.02$), there being no significant difference between hydrochlorothiazide and the combined diuretic regimen. The average plasma bicarbonate was not significantly different when patients were on amiloride, but a significant rise as compared with control was seen on hydrochlorothiazide, whereas with the combined regimen the bicarbonate was not significantly different from that found in the control period. The average blood uric acid on amiloride

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was lower than in the pretreatment period and rose while on hydrochlorothiazide, though these differences were not significant at the 5% level. However, on combining the diuretics the average uric acid was significantly higher than that observed during the control period.

Side-effects

Two patients were unable to tolerate the combined diuretic regimen. After two or three days on the two diuretics they complained of severe nausea and weakness and noticed that they had passed excessive amounts of urine. Both patients had a 6-lb. (2.7-kg.) weight loss in three days. It was felt that this was not due to any toxic effect of the individual drugs but was caused by excessive loss of salt and water. They quickly recovered when the combined diuretics were stopped. No patient complained of any symptoms when on either amiloride or hydrochlorothiazide alone. Routine tests showed abnormalities in three patients. One patient showed a rise in isocitrate dehydrogenase to 13 i.u. and an increase in gammaglobulin on the electrophoretic strip while on amiloride. The protein strip was normal after she was put on hydrochlorothiazide, but the isocitrate dehydrogenase stayed just above normal at 11 i.u. A second patient showed a slightly raised isocitrate dehydrogenase of 11 i.u. in the control period, and this remained raised on all three regimens of treatment. In addition the bilirubin rose to 1.4 mg./100 ml. on the combined regimen but fell to normal on hydrochlorothiazide alone and was also normal when the patient was on amiloride alone. A third patient had a raised isocitrate dehydrogenase before treatment began (12 i.u.) and while on amiloride (16 i.u.) and also on hydrochlorothiazide (13 i.u.); but on the combined regimen it fell to normal (3 i.u.) and was not felt to be a significant effect of either drug. The average values of these estimations are shown in Table II. No abnormality of haemoglobin, white cell count, or urine was seen on any treatment regimen.

TABLE II.—*Biochemical Data*

	Sodium (mEq/l.)	Potassium (mEq/l.)	Chloride (mEq/l.)	Bicarbonate (mEq/l.)	Urea (mg./100 ml.)	Uric Acid (mg./100 ml.)	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K. A. Units)	Isocitrate Dehydrogenase (I.U.)
Normal range ..	136–149	3·8–5·2	100–107	24–30	14–38	2·0–7·0	0·1–0·8	4–11	3–8
Control	141 (±2)	4·2 (±0·4)	102 (±3)	28 (±2)	31 (±8)	5·5 (±1·5)	0·4 (±0·1)	8 (±4)	7 (±2)
Amiloride ..	140 (±3)	4·6 (±0·4)	103 (±4)	27 (±2)	32 (±10)	5·1 (±1·0)	0·5 (±0·2)	7 (±2)	8 (±4)
Hydrochlorothiazide	140 (±3)	3·7 (±0·4)	99 (±5)	30 (±2)	33 (±9)	6·4 (±1·3)	0·5 (±0·2)	7 (±2)	9 (±4)
Amiloride and hydrochlorothiazide ..	139 (±3)	4·0 (±0·2)	98 (±4)	29 (±1)	40 (±8)	6·8 (±1·3)	0·7 (±0·3)	8 (±3)	7 (±3)

Normal range shows 80% confidence limits.
For each treatment average ± one standard deviation calculated from one estimation at the end of the treatment period.

Discussion

Amiloride in a daily dose of 15 mg. had a hypotensive effect similar to that of 50 mg. of hydrochlorothiazide. When the drugs were combined the hypotensive effect was not significantly increased.

The reduction in average lying blood pressure on amiloride (23.9/12.4 mm. Hg) and on hydrochlorothiazide (29.6/15.5 mm. Hg) is of the same order as found by Cranston *et al.* (1963), who compared the effects of bendrofluazide, cyclopenthiazide, and chlorthalidone in hypertensive patients.

Our results compare with those of Gombos *et al.* (1966), who studied the effects of amiloride and hydrochlorothiazide in 10 hypertensives who were already on other antihypertensive drugs. They found no significant difference between the hypotensive effect of amiloride, hydrochlorothiazide, or the two drugs in combination. There was no significant difference in body weight on the three regimens and biochemical changes were similar to those seen in the present study.

The combination of a potassium-sparing diuretic such as amiloride or triamterene with a thiazide promises to be a satisfactory way of avoiding hypokalaemia in patients who require long-term diuretic therapy. It may also be dangerous because of the risk of hyperkalaemia. This may occur if potassium supplements are continued after a potassium-sparing diuretic is started, and has also been reported when these drugs are used alone. The risk of hyperkalaemia is increased in the presence of renal impairment. Cohen (1966) reported a rise in average serum potassium in 10 elderly men with congestive heart failure who were treated with a combination of 100 mg. of triamterene and 0.5 g. of chlorothiazide. In five patients the serum potassium rose above 6 mEq/l. In addition he reported the death of two patients in whom hyperkalaemia induced by a mixture of triamterene and hydrochlorothiazide was thought to have contributed. Deaths have also been reported due to hyperkalaemia with spironolactone (Sjoberg and Kreisle, 1962).

The potency of the diuretic combination demands care in the choice of dose to avoid excessive salt loss, as occurred in two patients in this study. This disadvantage could probably be overcome by using smaller doses of each agent.

Though amiloride reduces serum uric acid when given alone it does not prevent the hyperuricaemia caused by thiazides.

Summary

The hypotensive effect of amiloride hydrochloride (MK-870) was investigated in mild hypertensive patients by means of a crossover trial comparing the effects of amiloride (15 mg. daily), hydrochlorothiazide (50 mg. daily), and amiloride (15 mg. daily) + hydrochlorothiazide (50 mg. daily). Amiloride was found to have a mild non-postural hypotensive effect indistinguishable from that of hydrochlorothiazide. The combination of the two agents produced no further hypotensive effect. This particular combination of the agents was thought to be too potent, as two patients had to withdraw owing to excessive diuresis and the average blood urea rose significantly while on the two diuretics. However, it was noted that when the two agents were combined the plasma potassium remained near pretreatment levels, whereas with hydrochlorothiazide alone the plasma potassium tended to fall and on amiloride alone it rose.

We are grateful to the Department of Haematology, Royal Postgraduate Medical School, for carrying out serial estimations of haemoglobin, packed cell volume, and white blood count; and to Merck Sharp & Dohme for the supply of amiloride hydrochloride tablets.

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