Amiloride in Primary Hyperaldosteronism with Chronic Peptic Ulceration

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Prolonged treatment with the aldosterone antagonist spironolactone is well-established in the syndrome of hypertension with aldosterone excess and low plasma renin ("primary" hyperaldosteronism) and is usually effective in lowering the blood pressure and correcting the electrolyte abnormalities in cases with adrenocortical adenoma or micronodular hyperplasia (Brown *et al.*, 1965, 1969, 1971b, 1972; Spark and Melby, 1968; Crane and Harris, 1970). While serious side effects are in our experience rare, spironolactone may cause epigastric discomfort, and in one patient gastric ulceration developed during therapy and rapidly healed when the drug was withdrawn (Brown *et al.*, 1971 b).

We report the use of an alternative potassium-conserving diuretic, amiloride, in a patient with primary hyperaldosteronism in whom spironolactone could not be tolerated because of severe epigastric pain associated with peptic ulceration.

Case History

A 70-year-old housewife was referred to this unit because of hypertension associated with hypokalaemia. She gave a 10-year history of episodic epigastric pain relieved by antacids and vomiting; there had been one haematemesis five years previously. Barium meal examination on the present admission suggested fibrosis of the lesser curvature of the stomach indicative of old ulcerative disease. The duodenal cap appeared normal but there was coarsening of the postbulbar mucosa with possible ulceration. Fibroscopy (Mr. C. MacKay) disclosed a rigid antrum due to chronic scarring with no break in the mucosa and no evidence of neoplasia.

The serum electrolyte pattern associated with hypertension strongly suggested primary hyperaldosteronism (see table), and this was confirmed by raised plasma aldosterone levels accompanied by low plasma renin and angiotensin II concentrations. Quadric analysis (Ferriss *et al.*, 1970; Aitchison *et al.*, 1971) indicated the presence of an adrenocortical adenoma rather than hyperplasia ($P < 0.02$) but the patient was reluctant to undergo surgery and in view of her age this was not pressed. An initial trial of spironolactone (300 mg daily) had to be abandoned after two weeks because of exacerbation of the epigastric pain and nausea, and it was subsequently decided to study the effect of amiloride.

METHODS

All "untreated" values (see table) were obtained before therapy or after withdrawal of hypotensive drugs, diuretics, or potassium supplements for at least four weeks; all values assessed during treatment were obtained four weeks or more after the start of amiloride. The blood pressure measurements were made at outpatient attendances after the subject had lain quietly for five minutes. In order to reduce observer bias the special sphygmomanometer designed by Rose *et al.* (1964) was used. For the estimation

Clinical Findings in the Patient Under Study. Figures are Means ($\pm$ S.D.)

	Before Treatment	During Treatment	P <
Blood pressure (mm Hg):			
Systolic	168.8 (24.7)	142.4 (14.7)	0.02
Diastolic	99.5 (11.2)	82.2 (5.7)	0.001
Serum:			
Na (mEq/L)	144.7 (1.9)	139.9 (2.7)	0.001
K (mEq/L)	2.21 (0.34)	4.22 (0.32)	0.001
Cl (mEq/L)	98.2 (1.2)	104.7 (1.9)	0.001
HCO ₃ (mEq/L)	32.0 (2.1)	23.7 (1.4)	0.001
Urea (mg/100 ml)	47.7 (4.5)	57.9 (6.1)	0.001
Plasma:			
Renin (units/L)	4.7 (1.4)	8.3 (3.0)	0.05
Angiotensin II (pg/ml)	7.4 (2.5)	19.4 (10.6)	0.05
Aldosterone (ng/100 ml)	23.9 (4.8)	52.0 (11.3)	0.05
Body weight (kg)	53.9	52.3	
Total body water (L)	29.4	26.0	
Na _E (mEq)	2,515	2,045	
K _E (mEq)	1,574	1,822	
K _T (mEq)	1,732	2,063	

of renin, angiotensin II, and aldosterone, the patient was admitted to hospital and fed a fixed diet containing between 138 and 145 mEq Na and 50 and 58 mEq K daily. After three or more days of this diet venous blood samples were obtained between 08:30 and 10:00 hours after overnight recumbency and fasting.

Plasma renin and angiotensin II concentrations, total exchangeable sodium (Na_E), total body potassium (K_T), and total body water were estimated as previously (Brown *et al.*, 1965, 1972); total exchangeable potassium (K_E) using ⁴²K as described by Davies and Robertson (1973); plasma aldosterone by radioimmunoassay (Fraser, *et al.*, 1973).

Oral amiloride was given in divided doses of 40 mg daily for six weeks, and the patient was readmitted for further biochemical assessment.

RESULTS

The exacerbation of the epigastric pain which occurred during spironolactone therapy subsided within three days of stopping the drug. Symptoms remained quiescent during amiloride treatment, and no untoward side effects were reported. Systolic and diastolic blood pressures were significantly reduced, there was a highly significant fall in serum sodium and bicarbonate, while serum potassium, chloride, and urea levels rose (table). Concomitantly there was a fall in Na_E and total body water, and a rise in K_E and K_T. Mean plasma concentrations of renin, angiotensin II, and aldosterone increased significantly during therapy. Subsequently it was possible to reduce the dose of amiloride to 20 mg daily, and the patient remained well controlled after six months of therapy.

Comment

Amiloride is a pyrazine-carbonyl-guanidine unrelated chemically to other known diuretic or potassium-conserving agents (Bull and Laragh, 1968; Lant *et al.*, 1969). It appears to have a direct effect on distal convoluted tubules independently of the presence or absence of aldosterone; hence its action is less specific in syndromes of aldosterone excess than that of spironolactone. Nevertheless, the effects seen here during long-term amiloride therapy are closely similar to those we have previously reported during prolonged spironolactone therapy in other cases (Brown *et al.*, 1964, 1965, 1972). The fall in arterial pressure accompanying reduction in Na_E, with converse increases in K_E and K_T are in accord with current views relating sodium balance to the pathogenesis of hypertension (Brown *et al.*, 1971a, 1971c). Braren *et al.* (1968) described the use of amiloride preoperatively in a patient with an aldosterone-secreting adenoma. They gave 20 mg daily for 5 days followed after an interval of 2 days by 40 mg daily for 5 days, both in conjunction with the 10-mEq Na, 90-mEq K diet. On this regimen there was a rise in total body potassium, hypokalaemia was corrected, and serum sodium and bicarbonate fell. However, plasma renin activity which was previously undetectable remained so, and there was no fall in arterial pressure.

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References

- Aitchison, J. *et al.* (1971). *American Heart Journal*, 82, 660.
 Braren, C. H., Campbell, R. G., Hashim, S. A., and Van Itallie, T. B. (1968). *American Journal of Medicine*, 45, 480.
 Brown, J. J., *et al.* (1969). *Proceedings of the Royal Society of Medicine*, 62, 1258.
 Brown, J. J. *et al.* (1971a). *British Medical Bulletin*, 27, 128.
 Brown, J. J. *et al.* (1972). *British Medical Journal*, 2, 729.
 Brown, J. J., Davies, D. L., Lever, A. F., Peart, W. S., and Robertson, J. I. S. (1964). *British Medical Journal*, 2, 1636.
 Brown, J. J., Davies, D. L., Lever, A. F., Peart, W. S., and Robertson, J. I. S. (1965). *Journal of Endocrinology*, 33, 279.
 Brown, J. J., Ferriss, J. B., Fraser, R., Lever, A. F., and Robertson, J. I. S. (1971b). In *Medical Uses of Spironolactone*, ed. G. M. Wilson, p. 27. Amsterdam, Excerpta Medica.
 Brown, J. J., Fraser, R., Lever, A. F., and Robertson, J. I. S. (1971c). *Abstracts of World Medicine*, 45, 549, 633.
 Bull, M. B., and Laragh, J. H. (1968). *Circulation*, 37, 45.
 Crane, M. G., and Harris, J. J. (1970). *American Journal of Medical Sciences*, 260, 311.
 Davies, D. L., and Robertson, J. W. K. (1973). *Metabolism*. In press.
 Ferriss, J. B. *et al.* (1970). *Lancet*, 2, 995.
 Fraser, R., Thomson, S., and Young, J. (1973). In press.
 Lant, A. F., Smith, A. J., and Wilson, G. M. (1969). *Clinical Pharmacology and Therapeutics*, 10, 50.
 Rose, G. A., Holland, W. W., and Crowley, E. A. (1964). *Lancet*, 1, 296.
 Spark, R. F., and Melby, J. C. (1968). *Annals of Internal Medicine*, 69, 685.

Unilateral Renal Hypoplasia with Hypertension (Ask-Upmark Kidney)

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Congenital unilateral renal hypoplasia with hypertension was first reported by Ask-Upmark (1929). Habib *et al.* (1965) reported nine more cases of this rare condition, which they called "segmental hypoplasia of the kidney." It has a typical histological picture, affects primarily children and young adults, and is sufficiently characteristic for it to be diagnosed and treated accordingly. A case is reported here.

Case Report

The patient, a 17-year-old girl, was admitted to hospital in 1966 because of severe headaches, vertigo, and general fatigue of two months' duration. Her blood pressure was 220/115 mm Hg supine and 220/150 mm Hg erect. The appearance of the retina was normal. A chest radiograph showed moderate enlargement of the left ventricle, and the electrocardiogram showed left ventricular hypertrophy. The blood urea was 45 mg/100 ml, creatinine clearance 65 ml/min, and the urinary sediment contained 3-4 leucocytes. There was no proteinuria and urinary cultures were sterile. The haemoglobin was 14 g/100 and the white blood cells 8,000 with a normal differential count. Liver function tests were normal. An intravenous pyelogram showed that the right kidney was 3.5 cm smaller than the left, the upper right calyx showed signs of clubbing, and the upper and lower poles showed lobulation. The dye concentration appeared equal on both sides. A renogram after intravenous injection of 15 μ Ci ^{131} I-labelled orthoiodohippurate showed diminished concentration and prolonged transit time in the right kidney. The angiotensin infusion test was negative and the Stamey test gave equivocal results. Renoangiography showed normal renal arteries on both sides but a paucity of vessels in the upper pole of the right kidney with lack of arborization and a tapering of the arterioles (fig. 1). In the nephrographic phase the effect was stronger on the right side, suggesting a paradoxical nephrographic effect (fig. 2).

A tentative diagnosis of contracted right kidney after pyelonephritis was unsatisfactory in view of the peculiar shape of the small kidney, the absence of a history of recurrent urinary tract infections, and the absence of anomaly of the urinary tract. Bilateral renal biopsy specimens showed some sclerosis of the arteries and

arterioles, more prominent on the left side. In line with current opinion in 1966 it was decided that the patient was unlikely to benefit from right nephrectomy, and she was treated conservatively.

During the next four years the patient had recurrent urinary tract infections. Despite control of her hypertension with methyl-dopa and a low salt diet grade II hypertensive changes developed in the retina, the blood urea rose progressively to 70 mg/100 ml, and her creatine clearance decreased to 40 ml/min. Traces of protein appeared in the urine. Selective renin studies in 1970

FIG. 1—Nephroangiography shows paucity of vessels to upper pole of right kidney, with lack of arborization and tapering of the arterioles.

FIG. 2—Nephrographic phase: stronger dye on right side.

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