PAPERS AND SHORT REPORTS

Comparison of thiazides and amiloride in treatment of moderate hypertension

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Abstract

The biochemical disturbance produced by thiazide diuretics and by amiloride during treatment of moderate hypertension were compared. Two parallel studies were initiated. In one 40 patients with newly diagnosed hypertension were treated with metoprolol and a diuretic, either hydrochlorothiazide or amiloride. In a second study 38 patients receiving longstanding treatment with hypotensives and thiazides either continued the treatment or replaced the thiazide with amiloride. Initial biochemical assessments were compared with those after two years in the study. In previously untreated patients, thiazide produced a significant fall in plasma potassium and hyperuricaemia that did not occur with amiloride ($p < 0.001$). Those patients receiving long term treatment for their hypertension who continued to take thiazides had persistent hypokalaemia and hyperuricaemia. Substitution with amiloride corrected the hypokalaemia and serum uric acid returned toward normal ranges, but this change was not statistically significant. Patients receiving long term treatment also had impaired glucose tolerance, this remained unchanged in those receiving thiazide but was corrected in those receiving amiloride.

Compared with amiloride thiazides produced undesirable but reversible biochemical changes. As control of hypertension was equally effective with both preparations, we suggest that a combination of amiloride with a beta blocker in treatment of moderate hypertension is preferred.

Introduction

Diuretics and beta adrenergic blocking agents are accepted in the treatment of mild or moderate hypertension. Thiazides are

preferred to the short acting loop diuretics and potassium sparing drugs are given mainly as adjuvants. Though potassium sparing drugs produce a mild diuresis, their hypotensive effect is similar to that induced by thiazides. Thus amiloride produces a fall in blood pressure indistinguishable from that recorded with hydrochlorothiazide or with a combination of these drugs.¹

The biochemical and other possible risks associated with thiazides cast doubt on their continued use in the treatment of hypertension. We compared the effectiveness and side effects of a thiazide and amiloride, in combination with other hypotensive drugs, over an extended period. Amiloride was chosen in preference to other potassium sparing diuretics because it has no serious side effect except for a tendency, at higher doses, to induce hyperkalaemia in patients with renal impairment and in some patients with diabetes.²

Patients and methods

Two parallel studies were initiated.

PATIENTS

Study 1—Blood pressure was measured in personnel aged 35-65 employed at the local Inland Revenue office. Hypertension (previously undiagnosed) was found in 40 subjects, who had a sustained diastolic blood pressure (Korotkoff phase V) of at least 105 mm Hg (range 105-135) on three occasions separated by at least one week.

Study 2—A total of 38 patients who had received thiazides over a long period in the treatment of hypertension were recruited from the general medical clinic. All had received a combination of hydrochlorothiazide and amiloride (Moduretic in 32 patients and Co-Betaloc in the other six) together with other hypotensives. The initial investigations were performed while patients received their usual hypotensive treatment. Duration of antihypertensive treatment including thiazides was for from three to 13 years (mean 6.15), and all had been on a stable dose for at least one year.

PROTOCOL

Study 1—After initial investigations patients were allocated at random to one of two groups: one group (20 patients) took one half

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tablet containing metoprolol 100 mg and hydrochlorothiazide 12.5 mg (Co-Betacloc) twice daily, and another group (20 patients) were prescribed metoprolol 50 mg (Betacloc) and amiloride 5 mg, both drugs twice daily (cost per 100 tablets: Co-Betacloc £9.40, Betacloc (50 mg) £1.00, amiloride £5.39). A maximum of 200 mg metoprolol was given; thereafter hydralazine, up to a maximum of 200 mg daily, was used to control blood pressure. Hydralazine was required in only four patients, two in each group.

Study 2—Patients were allocated at random to one of two groups: in one group (19 patients) treatment continued unchanged, and in the other (19 patients) thiazides were replaced by amiloride 5 mg twice daily. Prior duration of treatment was from three to 11 years (mean 5.9) in those continuing thiazide treatment and from three to 13 years (mean 6.4) in those receiving amiloride. All other drugs were continued unchanged with adjustments of dosage only according to the degree of hypertension.

All patients from both studies attended the hypertension clinic regularly where blood pressure was recorded using a Hawksley random zero sphygmomanometer.³ Biochemical tests were performed at entry and every six months over the next two years. During this time, two previously untreated patients developed wheezing that responded to bronchodilators by inhalation and two complained of claudication, which disappeared when the dose of beta blocker was reduced and hydralazine given. Three patients in study 1 who received thiazide treatment complained of impotence.

INVESTIGATIONS

Before entry into either study, all patients gave informed consent to hospital investigation. This included a 50 g oral glucose tolerance test sampling for blood glucose and plasma insulin. The Kemtex 3000 automated radioimmunoassay was used for assay of insulin.

Venous blood glucose was measured by a ferricyanide reduction method (Technicon N-9a), and total body potassium by a high sensitivity whole-body counter, calibrated with ⁴²K, details of which have been described previously.⁴ Repeated measurements may be performed on the same individual with a coefficient of variation of 3.5%. Plasma sodium, potassium, urea, and creatinine concentrations were measured by standard Technicon autoanalytic techniques and serum uric acid was measured with phosphotungstic acid. Serum cholesterol was measured by the method of Stahler and his associates⁵ and triglycerides by the method of Wahlefeld.⁶

Study 1—In addition to standard investigations, patients from study 1 had samples taken for measurement of plasma renin and aldosterone activities. They were admitted to hospital for four days, during which they received a constant diet of sodium (100 mmol(mEq)) and potassium (70 mmol(mEq)). Samples were taken while patients were supine. Plasma aldosterone was estimated by radioimmunoassay method at St Mary's Hospital, London (unpublished). Plasma renin was measured by the method of Menard and Catt⁷ at the Middlesex Hospital, London.

STATISTICAL METHOD

Differences between means of two groups (initial or after two years) were calculated by unpaired two tailed *t* test. Paired *t* tests were used to compare initial results with those obtained after two years within studies. Blood glucose results of three patients in study 2 were excluded because they had mild diabetes at the start of the study and at two years. Data relating to glucose tolerance in the other patients in study 2 were normally distributed and thus analysed by the Student's *t* test.

Results

BLOOD PRESSURE

Blood pressure returned to normal in all previously untreated patients (study 1) after relatively small quantities of metoprolol (mean 125 mg) and amiloride (mean 10 mg) or a combination of metoprolol (mean 125 mg) with hydrochlorothiazide (mean 15.6 mg) daily (table). Hydralazine was needed in only four patients, two in each group, in doses of 75 mg to 200 mg daily.

Blood pressure remained within normal limits in all patients in study 2, whether continued on thiazide or converted to amiloride (table).

BIOCHEMISTRY

Study 1—In 38 of the 40 previously untreated patients with hypertension plasma renin values were low (<1.5 nmol/l/h (2 ng/ml/h)) in nine patients and normal in 27. Plasma aldosterone was normal (less than 500 pmol/l (18 ng/100 ml)) in all these patients. The remaining two patients had high plasma renin and aldosterone activities but the blood urea and serum creatinine concentrations were normal.

Control of blood pressure was achieved without biochemical disturbance in patients who received amiloride (fig 1) but with a significant fall in plasma potassium concentration ($p < 0.001$) and rise of serum uric acid concentration ($p < 0.005$) in patients given a thiazide diuretic. There was no significant change in glucose metabolism.

FIG 1—Influence of thiazide and amiloride on plasma potassium concentration in 20 patients with newly diagnosed hypertension.

Study 2—Among patients in study 2 who changed to amiloride, the plasma potassium concentration returned to normal (3.4–5.2 mmol(mEq)/l) in all who had had hypokalaemia ($p < 0.001$) whereas low values appeared or persisted in several patients who continued with thiazides (fig 2). Serum uric acid concentration returned toward nor-

FIG 2—Thiazide induced hypokalaemia corrected by substitution of amiloride in patients receiving long term treatment for hypertension.

mal but this change was not statistically significant. Glucose tolerance also differed significantly in the two groups of study 2 (table). If the criteria adopted in the Bedford survey⁸ are applied, taking a blood glucose concentration from between 6.7 to 11.1 mmol/l (120 to 200 mg/100 ml) at two hours after a 50 g glucose load to indicate impairment of glucose tolerance, then impairment of glucose tolerance de-

Clinical details of patients with newly diagnosed hypertension (study 1) and patients receiving long term treatment for hypertension (study 2)

	Study 1						Study 2					
	Amiloride + metoprolol		Thiazide + metoprolol		p1	p2	Thiazide continued		Amiloride substituted		p1	p2
	Initial	2 years	Initial	2 years			Initial	2 years	Initial	2 years		
Blood pressure (mm Hg):												
Systolic	182 (21.9)	138 (16.5)	182 (21.6)	137 (9.1)	NS	NS	148 (22.4)	141 (18.1)	152 (25.0)	141 (14.2)	NS	NS
Diastolic	113 (10.3)	81.5 (5.6)	115 (10.1)	84.5 (4.8)	NS	NS	92 (9.9)	84.5 (11.2)	94.5 (7.2)	84.7 (7.2)	NS	NS
Plasma potassium (mmol/l)	4.0 (0.2)	4.2 (0.4)	3.9 (0.3)	3.5 (0.3)	NS	0.001	3.7 (0.4)	3.5 (0.4)	3.7 (0.6)	4.3 (0.3)	NS	0.001
Total body potassium (mmol/kg)	43.6 (6.6)	42.8 (6.5)	43.7 (9.4)	42.6 (9.4)	NS	NS	41.7 (10.2)	41.0 (10.0)	40.7 (10.4)	40.1 (10.2)	NS	NS
Serum uric acid (mmol/l)	0.36 (0.08)	0.37 (0.09)	0.36 (0.07)	0.44 (0.08)	NS	0.005	0.38 (0.08)	0.38 (0.08)	0.38 (0.08)	0.35 (0.09)	NS	NS
Blood glucose (mmol/l)*	5.4 (1.7)	4.9 (1.5)	5.2 (1.0)	5.2 (1.3)	NS	NS	4.8 (1.3)	5.3 (2.3)	5.3 (2.0)	4.5 (2.0)	NS	0.005
Plasma insulin fasting (U/l)	10.4 (5.8)	13.0 (9.3)	10.6 (5.5)	13.3 (8.9)	NS	NS	11.2 (6.2)	13.2 (8.3)	11.8 (7.8)	12.9 (8.5)	NS	NS
Body weight (kg)	72.5 (14.5)	74.0 (14.6)	73.8 (13.1)	75.3 (13.6)	NS	NS	74.8 (13.0)	72.6 (13.4)	74.2 (12.4)	75.5 (12.6)	NS	NS

p1 = Initial v initial. p2 = 2 years v 2 years.

*Two hours after oral glucose tolerance test.

veloped in five patients who continued with thiazides but disappeared in two who changed to amiloride. Glucose tolerance was normal throughout in the remaining patients. There was no association between changes in glucose tolerance and the potassium concentration or the capacity to secrete insulin, which remained normal. Values of plasma triglycerides and cholesterol did not differ significantly during these studies.

No changes were observed in either study in total body potassium or plasma insulin response to oral glucose tolerance tests. No differences in any variable were seen between any of the groups in either study before entry (table).

Discussion

The major findings in our study were that thiazides produced significant hypokalaemia, hyperuricaemia, and, in patients with long standing hypertension, glucose intolerance. These biochemical abnormalities were not observed in previously untreated patients who were given amiloride, and in patients with longstanding hypertension they were all reversible. The changes occurred despite overall maintainance of a steady body weight and normal body potassium concentration, with similar control of hypertension in all groups.

The studies were prospective with patients randomised to one of two treatment groups. To assess the initial effects of treatment and the reversibility of any undesirable biochemical changes resulting from prolonged use of thiazides care was taken to separate patients in whom hypertension was newly diagnosed from those receiving longstanding treatment. Initial measurements have been compared with those at the end of two years but most of the biochemical investigations were repeated every six months. The major changes in potassium concentrations had occurred by the end of the first six months.

Our findings confirm those of previous studies,⁹⁻¹⁰ which show that the hypokalaemia produced by thiazides is seldom associated with a significant fall in total body potassium, although severe depletion of body stores may occur.¹¹ Because severe depletion is rare, it has been assumed that a small reduction in plasma potassium (3.0-3.4 mmol(mEq)/l) is unimportant¹² but the disproportionate loss of extracellular potassium increases the ratio of intracellular to extracellular potassium, causing a change in transmembrane potential with increased cellular excitability¹³ and cardiac ectopic beats with re-entry arrhythmias.¹⁴ Ventricular tachycardia and ventricular fibrillation rarely complicate the hypokalaemia produced by thiazide¹⁵⁻¹⁶ but patients with ischaemic heart disease, particularly after a myocardial infarction, would be vulnerable to the consequences of hypokalaemia.¹⁷ In a recent analysis of acute myocardial infarction,¹⁸ ventricular tachycardia or fibrillation were present in 21% of patients with normal concentrations of potassium but in 48% of those with a concentration of 3.4 mmol/l or less. These events may contribute to the high incidence of sudden death recorded in patients with hypertension.¹⁹

The serum uric acid concentration is known to be high in more than a quarter of patients with untreated hypertension,²⁰⁻²¹ and we confirm this finding. Glomerular filtration is usually

normal but urate excretion low, indicating a tubular defect. Whether this is due to a fall in renal blood flow is debated²¹⁻²² but peripheral and renal vascular resistances are significantly higher in hypertensive patients with a raised uric acid concentration than in those with normal values.²² As hypertension and hyperuricaemia are both associated with an increased risk of vascular disease,²³⁻²⁴ the question arises as to whether hyperuricaemia, induced by thiazides, results in further vascular damage. In this and other studies²⁰⁻²¹ the incidence of hyperuricaemia was more than doubled by administration of these drugs.

Impairment of glucose tolerance is evident only after prolonged treatment with thiazides. Lewis and his colleagues found no change in glucose tolerance after one year of treatment with thiazides²⁵ but significant deterioration after six years.²⁶ Berglund and Andersson²⁷ were unable to confirm this progression but relied in their study on measurements of fasting blood glucose and values at 60 minutes after a glucose load. We found no change in glucose metabolism in previously untreated patients over two years but significant impairment of glucose tolerance in several patients receiving long term treatment with thiazides. It was surprising to find that glucose tolerance returned to normal in those patients receiving long term treatment in whom thiazides were replaced by amiloride. Few patients with impaired glucose tolerance progress to frank diabetes²⁸ and thiazides rarely cause overt clinical diabetes. However, the importance of even minor degrees of glucose intolerance is evident from the Whitehall survey,²⁹ which showed that over seven and a half years the mortality from coronary heart disease was doubled in those subjects with an initial two hour glucose concentration above 5.3 mmol/l after a glucose load. Known diabetics were excluded but so also were patients receiving treatment for hypertension, a group particularly at risk.

Although amiloride may produce hyperkalaemia in elderly patients or in those with renal impairment, this was not encountered with the relatively small doses used in our study and we suggest that moderate hypertension is best treated with a combination of beta blocker and amiloride to avoid the problems associated with thiazide treatment.

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Successful treatment of middle aged and elderly patients with end stage renal disease

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Abstract

Many patients over the age of 55 with end stage renal disease in the United Kingdom are denied dialysis or transplantation. Although the reasons are complex, anticipation of a poor prognosis for these patients might explain why most British renal units impose an arbitrary age limit on the acceptance of patients for treatment. A study was therefore conducted to examine the prognosis and quality of life of 64 patients (mean age 59.6 years, range 55-72) accepted into our renal replacement programme from the beginning of 1975. The five year survival of the patients was 62.0%, with 78.1% of the survivors either having successful transplants or caring for themselves using home haemodialysis or continuous ambulatory peritoneal dialysis.

The results show that in terms of survival, economics, and rehabilitation it is both feasible and reasonable to

treat middle aged and elderly patients with end stage renal disease. These patients should therefore not be denied dialysis or transplantation on the basis of age alone, and the lack of resources and other factors that allow this state to persist in Britain should be rapidly redressed.

Introduction

The renal failure service in the United Kingdom is notorious for its inability to treat enough patients with end stage renal disease.¹ Middle aged (55-65 years) and elderly patients (>65) fare particularly badly, as only 18% of renal units in Britain² do not impose an age limit on the acceptance of patients for treatment. Britain provides treatment for less than one third of the number of middle aged and less than one twelfth of the number of elderly patients with end stage renal disease who are treated in neighbouring large European countries such as West Germany, France, and Italy, although the incidence of the disease in these age groups is the same in Britain as in these other countries.³

Various reasons for failure to treat these patients aged over 55 (and in some areas, also patients aged under 55) have been suggested.⁴ These include lack of resources, shortage of kidneys for transplantation, selection of patients by nephrologists, and failure of general physicians to refer patients to renal units. Anticipation of a poor prognosis for these middle aged and elderly patients and concern about their quality of life may be other factors in allowing arbitrary age limits to persist as a criterion of patient selection.

The purpose of this paper is to establish the prognosis and

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