The long-term treatment of hypertension with thiazide diuretics

D. G. BEEVERS

M.B., M.R.C.P.

Medical Registrar

M. HAMILTON

M.D., F.R.C.P.

Physician

J. E. HARPUR

M.B., B.S

Research Registrar

Chelmsford Group of Hospitals

Summary

Two hundred and twenty-seven cases of moderate to severe hypertension were treated with thiazide diuretics alone for periods of up to 12 years. In 80% the hypertension was adequately controlled without additional antihypertensive agents.

Hypokalaemic alkalosis was common despite potassium supplements—but caused no symptoms. The incidence of diabetes and gout was low.

It is concluded that thiazide diuretics provide excellent control of hypertension with very few side effects.

Introduction

Thiazide diuretics have been used in the treatment of hypertension since the introduction of chlorothiazide in 1957. The mode of action is obscure, but is probably unrelated to the natriuretic effect (Maronde, Milgrom & Dickey, 1969; Dollery *et al.*, 1962) and may be due to relaxation of arteriolar smooth muscle. Whilst thiazides have few clinically evident side-effects, it is commonly held that hypokalaemic alkalosis, carbohydrate intolerance and hyperuricaemia are frequent unwanted effects. The thiazides are most frequently used as an adjunct to more potent antihypertensive drugs.

Patients and methods

Two hundred and twenty-seven patients with moderate to severe hypertension (eighty-nine males, average age 52.6, 138 females, average age 52.3) were treated with a thiazide diuretic alone—usually hydroflumethiazide—and followed for periods of up to 12 years. This number does not include those hypertensives who required additional antihypertensive agents within a few months of starting thiazide therapy. The patients underwent conventional investigations in order to determine the aetiology of their hypertension (Table 1).

The mode of presentation and complications at presentation (Table 2) were the same as commonly found in any group of hypertensives, the proportion

TABLE 1. Aetiology of hypertension

Essential hypertension	198
Chronic pyelonephritis	23
Polycystic kidneys	2
Disseminated lupus	1
Parathyroid adenoma	1
Renal artery stenosis	2
Total	227

TABLE 2. Mode of presentation

Headache	70
Routine medical examination	40
Breathlessness	38
Dizziness	20
Angina pectoris	17
Pregnancy	19
Strokes	12
Coronary thrombosis	8
Grade III retinopathy	19
Grade IV retinopathy	3
Left ventricular enlargement	67
Cardiac failure	33
Blood urea at beginning of study:	
40-60 mg/100 ml	33
Over 60 mg/100 ml	1

of those presenting in the accelerated phase is naturally low as such patients usually require immediate and more potent therapy (Hamilton, 1966).

Patients were generally treated on an out-patient basis and seen within 6-weekly intervals until adequate blood pressure control was achieved, thereafter they were seen at 4-6-monthly intervals. All underwent routine clinical examination, their urine was tested and they had regular checks of their blood urea and electrolytes. Ninety-six cases had their serum uric acid checked on several occasions. The duration of follow-up is shown in Fig. 1.

Eleven cases were referred to us whilst on other anti-hypertensive agents which had failed to control their hypertension. In these cases an untreated blood pressure level was not available.

The majority (71%) of patients were treated with 200 mg of hydroflumethiazide (Hydrenox, Boots).

FIG. 1. Duration of treatment with thiazides alone (227 patients).

The remainder received smaller doses, and a few had other thiazide diuretics in equivalent doses. Potassium supplements were recommended as a routine—usually slow K (Ciba) in a dose of 1–2 tablets daily (600–1200 g daily), but 22% were given increasing doses if their serum potassium fell to very low levels. In eight cases the thiazide was given on 5 days in 7 in an attempt to lessen the hypokalaemic effect.

Results

Blood pressure control

The mean and standard error, and 95% confidence interval for the mean blood pressure before and when receiving treatment are shown in Fig. 2 and Table 3. Good control (diastolic blood pressure less than 100 mmHg) was maintained in 50%, fair control (diastolic blood pressure less than 110 mmHg) in 35% and poor control (diastolic blood pressure more than 110 mmHg) in only 15%. In all fifty-six of the 227 cases (20.2%) eventually required the addition of a more potent agent, and the time when this became necessary is shown in Fig. 5.

FIG. 2. Pre-treatment and treatment mean systolic and diastolic blood pressures.

TABLE 3. Thiazides in hypertension

	Mean BP	Standard error of mean (SEM)	95% confidence interval (for mean BP)
Pre-treatment			
Systolic	203.4	1.8	199.9–206.9
Diastolic	120.6	1.0	118.7–122.5
On thiazides			
Systolic	161.6	1.3	159.0–164.2
Diastolic	96.8	0.7	95.4–98.2

Complications of hypertension

Those patients in whom the blood pressure became uncontrolled were given additional anti-hypertensive therapy and it is in this group that complications of hypertension are most likely to develop. The incidence of complications developing whilst on thiazides alone is shown in Table 4.

At the start of treatment thirty-four patients had a raised blood urea, but the majority did not show a rise. Six patients developed significant renal failure, but all had underlying renal disease.

Hypokalaemia

There was a marked fall in the plasma potassium in most cases as shown in Fig. 3 which compares the pre-treatment plasma potassium with the average of

TABLE 4. Complications of hypertension developing whilst on treatment with thiazides

	No. of patients
Cardiac infarct	15
Angina	32
Cardiac failure	9
Stroke	10
Renal failure	5
Blood urea at end of study	
40–60 mg/100 ml	44
Over 60 mg/100 ml	10

FIG. 3. (a) Serum potassium pre-treatment (143 patients). Mean, 4.30; SD, 0.61. (b) Serum potassium on treatment (180 patients). Mean, 3.54; SD, 0.47.

FIG. 4. Final plasma total CO₂ on treatment (157 patients).

the plasma potassium on treatment. Patients who developed a very low plasma potassium were given increasing doses of potassium supplement. However, no cases at any time developed subjective symptoms attributable to hypokalaemia. Some patients developed suspicious symptoms, but these were not altered by increasing the dose of potassium supplements and elevating the plasma potassium.

Metabolic alkalosis

During the period of observation there was a change in the method of estimation, and laboratory normals, of the plasma total CO₂ so only the most recent value is submitted—otherwise the comparison would not be real. However, Fig. 4 demonstrates that an alkalosis developed in a large number of cases: the present normal level for this laboratory is 24–32 mEq/l. The plasma total CO₂ was over 30 mEq/l in ninety-six out of 157 patients examined (62%).

Carbohydrate intolerance

Two patients had hyperglycaemia and glycosuria before starting thiazides and there was one case of renal glycosuria. After starting thiazides the two hyperglycaemic patients did not require hypoglycaemic agents, but were controlled by diet alone. Five other patients (2.2%) developed hyperglycaemia after starting thiazides—of which three required antidiabetic drugs.

Hyperuricaemia and gout

Four patients (1.7%) developed clinical gout with hyperuricaemia and one other developed an arthropathy with a normal serum uric acid. Those patients with gout were effectively treated with allopurinol or probenecid. Ninety-six patients had their serum uric acid estimated and eighteen of these were greater than 7.0 mg/100 ml giving an incidence of hyperuricaemia of 18% of estimations.

In no cases was it necessary to discontinue therapy on account of side-effects of thiazide diuretics.

Discussion

In the majority of the 227 patients who were maintained on thiazide diuretics for up to 12 years, it was possible to achieve good control of the blood pressure with no symptoms attributable to the administration of the drugs except a low incidence of diabetes and gout. The patients in this report all had a severe manometric hypertension with mean pre-treatment levels of blood pressure of 203.4 mmHg systolic and 120.6 mmHg diastolic, and many had either symptoms or objective complications of raised arterial pressure (Table 2). In spite of this the majority were adequately controlled, without recourse to more potent anti-hypertensive agents. The incidence of complications of hypertension whilst on treatment is low (Table 4), although this is partly

because those patients in whom the blood pressure became uncontrolled were given additional drugs and are no longer considered. However, it is interesting to note that, as during therapy with other drugs, the blood pressure may go out of control even after years on thiazides (Fig. 5). The incidence of side-effects of thiazide drugs, e.g. diabetes and gout, was low, and no patient required to discontinue therapy.

These results compare well with other trials from this clinic with methyl dopa (Hamilton, 1968) and clonidine (Kellett & Hamilton, 1969), in which there were a higher incidence of side-effects and an appreciable number of treatment failures.

Direct comparison of the adequacy of control of blood pressure is not possible, as in the other trials there was a larger proportion of patients with more severe hypertension including some who had failed to respond to thiazides initially.

We have used high doses of thiazides in most cases as it was found at the beginning of the period of observation that patients who showed a poor response to small doses initially, often responded to a higher dose. This is contrary to the findings of other workers who demonstrated a flat dose-response curve in a short term investigation (Crans-ton *et al.*, 1963). However, the antihypertensive effect of the majority of drugs is augmented by an increased dose.

Hypokalaemia occurs almost invariably, may be profound, and is persistent, often despite large doses of potassium supplement. In view of the absence of symptoms attributable to hypokalaemia here and elsewhere (Maronde *et al.*, 1969) it has been suggested that potassium supplements are unnecessary (Healy *et al.*, 1970). We have used potassium supplements as a routine because many patients may subsequently require digitalis therapy or develop an acute potassium-losing condition (e.g. gastro-enteritis) which might precipitate a serious hypokalaemia. Large quantities of potassium supplements are inconvenient and may in themselves give rise to side-effects and trials are being performed on potassium-retaining agents. There is no doubt that a marked metabolic alkalosis also occurs, sometimes even when the plasma potassium is within the lower range of accepted normal: when potassium supplements are increased the alkalosis is usually reversed, and it is possible that the degree of alkalosis is a better measure of the total body content of potassium than is a simple measure of the plasma potassium, especially as potassium is mainly an intracellular ion.

The incidence of thiazide-induced diabetes was lower than commonly reported, although a similar incidence has been found elsewhere (Kohler *et al.*, 1970). Furthermore, the two patients who were diabetic before starting treatment did not require

FIG. 5. The time at which additional anti-hypertensive therapy became necessary.

TABLE 5. Comparison of thiazides with other anti-hypertensive agents in trials done at this clinic

Agent	No. of patients	No. discontinuing drug because of side effects (%)	Adequate BP control (%)
Thiazide	227	0	80
Methyldopa (Hamilton, 1968)	222	5	91
Methyldopa	44	7	80
Clonidine	40	28	50

any additional anti-diabetic drugs and none of the patients in either group required insulin. Great emphasis is placed in weight reduction in obese hypertensives, which is also an effective means of treating maturity-onset obese diabetics.

We have found a lower incidence of hyperuricaemia than has been reported elsewhere. Breckenridge (1966) reported hyperuricaemia in 58% of hypertensives on treatment and in 27% of untreated hypertensives, although he used slightly different criteria of normal, and also more patients had impaired renal function. Clinical gout was rare (1.7%) in this survey and provided the blood pressure is well controlled, it is desirable to treat the gout and continue the thiazides.

Acknowledgments

We would like to thank The Chelmsford Medical Education and Research Trust for the provision of the Research Registrar's salary, and Mrs A. Oldfield for secretarial help.

References

- BRECKENRIDGE, A. (1966) Hypertension and hyperuricaemia. *Lancet*, **i**, 15.
- CRANSTON, W.I., JUEL-JENSEN, B.E., SEMMENCE, A.M., HANDFIELD JONES, R.P.C., FORBES, J.A. & MUTCH, L.M.M. (1963) Effects of oral diuretics on raised arterial pressure. *Lancet*, **ii**, 966.
- DOLLERY, C.T., PENTECOST, B.L. & SAMAAH, N.A. (1962) Drug-induced diabetes. *Lancet*, **ii**, 735.
- HAMILTON, M. (1966) *Symposium on Antihypertensive Therapy*, pp. 196–206. Springer Verlag, Berlin.
- HAMILTON, M. (1968) Some aspects of the long-term treatment of severe hypertension with methyl dopa. *Postgraduate Medical Journal*, **44**, 66.
- HEALY, J.J., MCKENNA, T.J., CANNING, B.St.J., BRIEN, T.G., DUFFY, G.J. & MULDOWNY, F.P. (1970) Body composition changes in hypertensive subjects on long-term diuretic therapy. *British Medical Journal*, **1**, 716.
- KELLETT, R.J. & HAMILTON, M. (1969) *Catapres in Hypertension*, p. 197. Butterworths, London.
- KOHNER, E.M., DOLLERY, C.T., LOWY, C., SCHUMER, B. & SAMUELS, C. (1970) Diabetogenic effect of long-term diuretic therapy. *Symposium of the Seventh Congress of International Diabetes Federation*, 23 August, p. 107.
- MARONDE, R.F., MILGROM, M. & DICKEY, J.M. (1969) Potassium loss with thiazide therapy. *American Heart Journal*, **16**, 16.