Br. J. clin. Pharmac. (1989), **27**, 523–526

Low and conventional dose cyclopenthiazide on glucose and lipid metabolism in mild hypertension

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In a double-blind, placebo controlled, randomised parallel study we investigated the antihypertensive activity and metabolic adverse effects of three doses of cyclopenthiazide in 53 patients with mild hypertension. After a 4 week placebo washout period, patients with diastolic blood pressures between 90–110 mm Hg were randomly assigned to receive 50 μg, 125 μg and 500 μg of cyclopenthiazide or matching placebo, over an 8 week active treatment period. Blood pressure was recorded at 2 weekly intervals during the trial. Venous samples were taken for evaluation of drug effect on indices of carbohydrate and lipid metabolism just prior to, and on completion of, the active treatment period. Systolic and diastolic blood pressure decreased significantly ($P < 0.05$) with the 125 μg and 500 μg doses of cyclopenthiazide. No change was apparent in any index of glucose and lipid metabolism over time. Low and conventional doses of cyclopenthiazide lower blood pressure without alteration to the metabolic profile in the short term.

Keywords cyclopenthiazide diuretic hypertension lipids

Introduction

Hypertension is widely recognised as an important risk factor for coronary heart disease (Kannel *et al.*, 1971). However, despite the institution of effective antihypertensive therapy, results of studies to date do not reveal the expected reduction in the incidence of coronary events in hypertensive patients (Helgeland, 1980). Thiazide diuretics have been shown to induce elevations in plasma lipoproteins (Grimm *et al.*, 1981) and impair glucose tolerance (Amery *et al.*, 1978). It has been proposed that such detrimental effects on the metabolic profile could offset the benefit of blood pressure reduction (Weinberger, 1985).

Many of the reports to date reflect changes in the metabolic profile induced by high dose diuretic therapy. This placebo controlled study provided the opportunity to examine the effects of cyclopenthiazide on indices of glucose and lipid metabolism when employed in the low dose range.

Methods

Newly diagnosed hypertensives (14 patients) or those on monotherapy (39 patients) to control blood pressure, were recruited from the general practices in the Belfast area. The exclusion criteria for the study and measurement of blood pressure have been described previously (McVeigh *et al.*, 1988). Ethical approval was obtained from the local ethics committee of the Queen's University of Belfast.

During the study, patients were seen at home by the same investigator and blood pressure recorded at 2 weekly intervals for 4 weeks. At the end of the placebo periods, patients whose diastolic blood pressure was between 90 and 110 mm Hg were randomised to receive placebo, 50 μg, 125 μg or 500 μg of cyclopenthiazide and blood pressure measured at 4 weekly intervals.

At 4 weeks and again after the 8 week active treatment phase, patients attended the Department of Therapeutics after a 12 h overnight fast. Venous samples were drawn for estimation of

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Table 1 Changes in glycosylated haemoglobin and areas under glucose/insulin curves with cyclopenthiazide

Group		*Glucose area* ($mmol\ l^{-1}\ min^{-1} \times 10^{-2}$)	*Insulin area* ($mu\ l^{-1}\ min^{-1} \times 10^{-2}$)	*Glycosylated haemoglobin* (%)
Placebo	(n = 11)			
B		13.0 ± 1.5	113 ± 48	6.4 ± 0.6
F		14.3 ± 1.6	106 ± 48	6.4 ± 0.6
50 μg	(n = 12)			
B		13.0 ± 1.4	101 ± 50	6.2 ± 0.6
F		13.0 ± 1.6	105 ± 52	6.2 ± 0.7
	DM 95% CI	−1.3 (−2.8 to +0.2)	−1 (−41 to +39)	−0.2 (−0.7 to +0.3)
125 μg	(n = 13)			
B		13.5 ± 1.5	104 ± 49	6.3 ± 0.6
F		14.0 ± 1.5	103 ± 47	6.6 ± 0.9
		−0.3 (−1.7 to +1.1)	−3 (−42 to +36)	+0.2 (−0.2 to +0.6)
500 μg	(n = 11)			
B		13.6 ± 1.5	90 ± 51	6.1 ± 0.9
F		13.6 ± 1.5	113 ± 56	6.8 ± 1.1
	DM 95% CI	−0.7 (−2.1 to +0.7)	+7 (−35 to +49)	+0.4 (−0.2 to +1.0)

Values are expressed as mean ± s.d. and the differences of mean with 95% confidence intervals (DM 95% CI) illustrated.
n = Number in each group; B = Baseline values; F = Follow-up values after 8 weeks' therapy

total cholesterol, total triglycerides, high density lipoprotein cholesterol, apolipoprotein A_1, apolipoprotein B, and glycosylated haemoglobin levels. A 75 g oral glucose tolerance test was performed with fasting glucose and insulin samples taken initially, and then at half-hourly intervals over the ensuing 2 h. The apolipoprotein and insulin samples were centrifuged immediately at 1500 *g* for 10 min. The plasma was separated from cells and the samples stored at −20° C until a complete batch was collected prior to laboratory analysis.

Statistics

An analysis of variance was used to determine if there was a treatment difference in any variable and the Neuman-Keuls (Armitage, 1971) multiple range test was applied to determine between which treatments these occurred. Correlation among these changes were sought by least squares analysis. The level of significance was chosen at the 5% level, and comparisons were made with the corresponding placebo values unless otherwise stated. Results are expressed as mean ± s.d.

Results

The basic clinical data and blood pressure responses to treatment have been documented previously (McVeigh *et al.*, 1988). The 125 μg and 500 μg doses of cyclopenthiazide produced significant decreases in systolic and diastolic blood pressure averaging 20/11 mm Hg and 23/10 mm Hg respectively ($P < 0.05$ for both) after 8 weeks therapy.

No significant change in fasting, or 2 h, glucose and insulin concentrations were noted with treatment. Drug effects on glucose area, insulin area and glycosylated haemoglobin concentration are illustrated in Table 1.

Absolute values of treatment effect on lipid, lipoprotein and apolipoprotein A_1 and B levels are shown in Table 2. No change in any of these parameters was apparent over the treatment period. Neither was there any alteration to the important total cholesterol/HDL ratio over time. These values were (mean ± s.d.) 7.0 ± 2.3 to 7.6 ± 3.4, 7.8 ± 2.8 to 7.1 ± 3.7, 6.7 ± 2.7 to 6.8 ± 2.2, 5.9 ± 1.7 to 6.1 ± 1.6 for the placebo, 50 μg, 125 μg and 500 μg groups respectively.

Discussion

The 125 μg and 500 μg doses produced comparable decrements in blood pressure without altering any index of glucose and lipid metabolism over an 8 week treatment period.

Cyclopenthiazide is the most popular phenothiadazine derivative used for control of arterial blood pressure in the United Kingdom. Only one prior trial has examined the effect of cyclopenthiazide on lipid metabolism (Crisp *et al.*, 1980). No changes were recorded in total

Table 2 Changes in serum lipid, lipoprotein, and apoprotein concentrations with cyclopenthiazide

Group		*Total cholesterol (mmol l^{-1})*	*Total triglycerides (mmol l^{-1})*	*HDL-C (mmol l^{-1})*	*LDL-C (mmol l^{-1})*	*APO A_1 (mmol l^{-1})*	*APO B (mmol l^{-1})*
Placebo	(n = 11)						
B		5.4 ± 0.8	1.3 ± 0.6	0.9 ± 0.2	4.1 ± 0.8	1.8 ± 0.5	1.2 ± 0.2
F		5.2 ± 0.6	1.3 ± 0.5	0.8 ± 0.4	3.9 ± 0.5	1.8 ± 0.6	1.1 ± 0.2
50 μg	(n = 12)						
B		6.4 ± 0.6	1.5 ± 0.5	0.9 ± 0.3	5.0 ± 0.8	1.7 ± 0.4	1.4 ± 0.2
F		6.2 ± 0.8	1.6 ± 0.6	1.1 ± 0.4	4.6 ± 0.9	1.6 ± 0.2	1.3 ± 0.2
	DM 95% CI	+1.0 (−0.5 to +2.5)	+0.3 (−0.8 to +1.4)	(+0.3 (−0.7 to +1.3)	+ 0.7 (−1.0 to +2.4)	−0.2 (−0.7 to +0.3)	+ 0.2 (−0.4 to +0.8)
125 μg	(n = 13)	6.1 ± 0.8	1.5 ± 0.7	1.0 ± 0.3	4.5 ± 0.9	1.7 ± 0.3	1.3 ± 0.2
B		5.9 ± 0.8	1.7 ± 0.9	1.0 ± 0.3	4.3 ± 0.7	1.8 ± 0.6	1.4 ± 0.3
F	DM 95% CI	+0.7 (−1.0 to +2.4)	+0.4 (−0.6 to +1.4)	+0.2 (−0.5 to +0.9)	+0.4 (−0.6 to +1.4)	0.0 (−0.6 to +0.6)	+0.3 (−0.6 to +1.2)
500 μg	(n = 11)						
B		5.1 ± 0.9	1.0 ± 0.4	0.9 ± 0.2	3.8 ± 0.1	1.7 ± 0.3	1.1 ± 0.3
F		5.2 ± 0.7	1.2 ± 0.7	1.0 ± 0.4	3.8 ± 0.8	1.7 ± 0.3	1.2 ± 0.2
	DM 95% CI	0.0 (−1.0 to +1.0)	−0.1 (−0.8 to +0.6)	+0.2 (−0.5 to +0.9)	−0.1 (−0.6 to +0.4)	−0.1 (−0.8 to +0.6)	+0.1 (−0.4 to +0.6

Values are expressed as mean ± s.d. and the differences of means with 95% confidence intervals (DM 95% CI) illustrated.
n = Number in each group; B = Baseline value; F = Follow-up values after 8 weeks' therapy

cholesterol, total triglyceride, HDL-cholesterol or LDL-cholesterol levels with the 500 μg dose employed. Our results confirm and extend these findings, as in addition, no change was noted in apolipoprotein A_1 or apolipoprotein B levels over time.

The mechanisms whereby thiazide diuretics alter the lipid and lipoprotein profiles are unknown. Haemoconcentration, hypokalaemia (Perez-Stable & Caralais, 1983) and insulin resistance (Ames & Hill, 1982) have been proposed as important contributing factors. Cyclopenthiazide is unique among phenothiadazine diuretics in that microgram doses will produce comparable natriuretic and diuretic activity to milligram doses of related compounds (Beling *et al.*, 1983). This factor may provide a possible explanation for its lack of effect on the metabolic profile documented in this trial.

It has been recognised for many years that a deterioration in glucose tolerance can accompany the use of thiazide diuretics to treat hypertension (Furman, 1981). There is mounting evidence to suggest that the impairment of glucose metabolism may in part, be dose related with use of these drugs. In a recent study, no increase in fasting glucose was documented after 16 weeks therapy with 25 mg of hydrochlorothiazide (Helgeland *et al.*, 1986), confirming the findings of longer term trials which employed low to moderate doses of thiazide diuretics in essential hypertension (Berglund *et al.*, 1986). No relationship was observed between the decrease in serum potassium with the 500 μg dose (0.6 mmol l^{-1}) (McVeigh *et al.*, 1988) and alteration in any index of glucose and insulin metabolism.

The observed neutral effect of cyclopenthiazide on lipid and glucose metabolism in the short term study requires confirmation. In view of the small numbers involved in this study, the negative findings could represent a type II statistical error especially in relationship to glycosylated haemoglobin. Therefore we are undertaking a larger study which will enable us to determine the long term beneficial antihypertensive activity and possible adverse metabolic effects of low dose cyclopenthiazide therapy.

We are indebted to all those general practitioners in the Belfast area who helped with recruitment for this study. We are grateful to Mr B. Sheridan of the Endocrine Laboratories, Royal Victoria Hospital, for analysis of the insulin samples. We would like to thank Napp Research Centre for supplying the cyclopenthiazide and placebo medications for this trial.

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(Received 25 May 1988, accepted 3 January 1989)