ment, short-term dialysis and corticosteroids have been used with some success, but no clear guide to their use exists.

We thank Dr J Anderton, renal physician, and Dr D Thomson, pathologist, Western General Hospital, Edinburgh, for their help in preparing this report.

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(Accepted 23 November 1977)

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Possible metabolic side effects of beta-adrenergic blocking drugs

Recent reports have described the increase in serum lipid concentrations that occur during thiazide treatment.^{1,2} The effects of β -adrenergic drugs on triglycerides and cholesterol are more uncertain, but an increase in triglyceride concentration has been shown during treatment with a cardioselective beta-blocker.³ We describe here the additive effect of propranolol on the thiazide-induced increase in triglyceride and urate concentrations.

Patients, methods, and results

During 1973, 785 symptom-free men, aged 40-49, with systolic blood pressures of 150-179 mm Hg and diastolic pressures below 110 mm Hg were randomised for a five-year controlled drug treatment study. Placebo was not given to the control group. All men who had had cardiovascular events or received detailed dietary instructions from other doctors and those with alcohol problems were excluded. Treatment consisted of hydrochlorothiazide 50 mg/day. Methyldopa was added in increasing doses from 250 mg twice daily to 750 mg twice daily when blood pressure remained above 140/90 mm Hg. When side effects occurred methyldopa was replaced by propranolol 40 mg to 160 mg twice a day. Generally, no detailed advice concerning diet, smoking, or weight reduction was given to any group. At three years' follow-up 145 patients were taking hydrochlorothiazide alone, 74 hydrochlorothiazide and methyldopa, and 76 hydrochlorothiazide and propranolol. Fasting serum triglycerides, cholesterol, and urate concentrations were analysed before treatment and after three years. Total serum cholesterol and triglycerides were determined by a Technicon autoanalyser,⁴ and urate by an automated uricase-peroxidase system. Differences between the means were tested by a modified *t* test accounting for unequal variances in groups.

Mean ($\pm$ SE of mean) body weight and serum cholesterol, triglyceride, and urate concentrations in men treated for three years with hydrochlorothiazide and methyldopa, and hydrochlorothiazide and propranolol

		Body weight (kg)		Cholesterol (mmol/l)		Triglycerides (mmol/l)		Urate (μ mol/l)	
		Start	3 years	Start	3 years	Start	3 years	Start	3 years
Hydrochlorothiazide and methyldopa (n = 74)	..	81.5 $\pm$ 1.2	82.7 $\pm$ 1.3	7.3 $\pm$ 0.15	7.3 $\pm$ 0.14	1.99 $\pm$ 0.12	2.07 $\pm$ 0.12	328 $\pm$ 6.5	352 $\pm$ 10.1
Hydrochlorothiazide and propranolol (n = 76)	..	80.0 $\pm$ 1.4	81.8 $\pm$ 1.4	7.1 $\pm$ 0.13	7.3 $\pm$ 0.15	1.87 $\pm$ 0.08	2.45 $\pm$ 0.14	325 $\pm$ 6.0	387 $\pm$ 9.5

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml. Triglycerides: 1 mmol/l $\approx$ 88.4 mg/100 ml. Urate: 1 mmol/l $\approx$ 16.8 mg/100 ml.

After three years on hydrochlorothiazide and methyldopa triglyceride concentration increased only insignificantly ($P > 0.10$), cholesterol was unchanged, and there was a small increase in urate concentration ($P < 0.05$) (see table). In contrast, those treated with hydrochlorothiazide and propranolol had a distinct increase (31%) in triglycerides ($P < 0.01$) and a more pronounced increase in urate concentration ($P < 0.01$). Again, the cholesterol concentration did not change significantly ($P > 0.10$). The triglyceride increase among those treated with hydrochlorothiazide and propranolol was most pronounced in patients who gained weight. Thus 24 men with a weight gain of under 2 kg had a mean increase in triglycerides of 0.50 mmol/l (44 mg/100 ml), compared with an increase of 0.96 mmol/l (85 mg/100 ml) in 15 men with a weight gain of 4 kg or more. Among those who received methyldopa instead of propranolol 15 men with a weight gain of under 2 kg showed unchanged triglyceride concentrations, while 16 men with a weight gain of over 4 kg showed a mean increase of 0.58 mmol/l (51 mg/100 ml). For all degrees of weight gain the urate values were distinctly higher in the patients who had propranolol than in those who had methyldopa, but the urate increase was not weight dependent (data available on request).

Comment

The thiazide-propranolol and the thiazide-methyldopa combinations had different effects on serum urate and triglyceride concentrations, the former producing a significantly greater increase in both serum constituents. The effect of the thiazide-methyldopa combination was very similar to that reported for thiazide alone.² These observations suggest that propranolol has an additive effect on the thiazide-induced increase in urate and triglyceride concentrations. As our two groups were not randomised, however, the results need to be confirmed, though the findings are consistent with previously reported increases in urate concentrations after treatment with beta-blockers.⁵

The study confirms our earlier observations that a substantial part of the thiazide-induced increase in triglyceride values is confined to men gaining weight.² It remains unsettled whether the increase in triglyceride and urate concentrations that is induced by thiazide and beta-blockers reduces the beneficial effect of blood pressure reduction in hypertensive patients.

The study is supported by the City of Oslo, Norwegian Drug Monopoly, and National Centre for Medicinal Product Control.

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(Accepted 6 December 1977)

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