Beta-adrenoceptor-blocking drugs, growth hormone and acromegaly

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Summary
Chronic treatment with oxprenolol or propranolol in active hypertensive patients was associated with elevation of serum growth hormone (GH). Propranolol, 80 mg orally, caused a marked rise in GH in 3 of 4 acromegalic patients.

Introduction
Beta-adrenoceptor-blocking agents are extensively used in the management of hypertension and ischaemic heart disease. These agents may also be used in acromegalic patients where hypertension and ischaemic heart disease occur commonly (Martins et al., 1977). There is, however, some evidence that propranolol, alone in normal subjects (Imura et al., 1971; Maclaren, Taylor and Raiti, 1975), and combined with glucagon in acromegalic subjects (Coutant, Vandeweghe and Vermeulen, 1977), may increase growth hormone (GH) concentrations. The object of this study was to determine if chronic treatment with oxprenolol or propranolol in hypertensive patients is associated with elevation of GH, and to determine the influence of propranolol alone on GH levels in acromegalic patients.

Materials and methods
Fifteen ambulatory hypertensive out-patients (aged 25–65 years) receiving chronic treatment with oxprenolol (5 patients) or propranolol and concomitant diuretic therapy in 11 patients were matched for age, sex, blood pressure control and disease state, with 15 patients receiving anti-hypertensive therapy other than β-blockers, clonidine or α-methyldopa (i.e. diuretics, vasodilators, or peripheral adrenergic neurone blocking agents). Growth hormone levels were measured by radio-immunoassay, on samples taken in the afternoon immediately following assessment at a busy clinic. Four supine patients (3 male, 1 female) with active acromegaly were given propranolol 80 mg orally, after an overnight fast, once a week following a glucose tolerance test (GTT) and had serial samples taken over 3 hours via an indwelling cannula for estimation of GH and plasma propranolol (by a gas-liquid chromatographic method). Statistical analysis was by a Wilcoxon non-parametric test and correlation by method of least squares regression.

Results
In the hypertensive group GH levels were higher (P<0·05) in oxprenolol/propranolol patients (5·8±2·1 µu/l, mean±s.e.mean) than in the control patients (0·9±0·3 µu/l) although plasma glucose levels were similar, 5·5±0·4 and 5·1±0·2 mmol/l respectively.

In acromegalic patients, glucose did not suppress the elevated GH levels. The plasma glucose did not change significantly throughout the propranolol test and in all patients, except one, D, there was a marked rise in GH following propranolol (Fig. 1). This latter patient in addition did not show any GH response to insulin induced hypoglycaemia. There was a positive correlation (r=0·63, P<0·05) between the logarithms of the percentage increase...
in GH levels (in the 3 responders) and of plasma propranolol concentration.

Discussion
In addition to dopaminergic control, the adrenergic system is an important regulator of growth hormone secretion. Alpha blockade and β-stimulation suppress GH secretion, while β-blockade augments GH secretion in both normal and acromegalic subjects (Cryer and Daughaday, 1977). Chronic elevation of GH may be cardiotoxic in acromegaly (Martins et al., 1977) although its possible effects on an ischaemic or hypertensive heart is unknown. Acute treatment with propranolol has been shown by Imura et al. (1971), and MacIaren et al. (1975), to increase GH levels, however GH did not increase in a study by Lee, Thompson and Blizzard (1974). In this study in active hypertensive patients, chronic treatment with non-selective centrally acting β-blockers was associated with elevation of GH, while a normal GH response to glucose loading has recently been noted by Day et al. (1979) in recumbent fasting hypertensive patients receiving chronic propranolol or atenolol therapy. Propranolol may increase the GH response to many stimuli including moderate exercise (MacIaren et al., 1975); however, more detailed studies are necessary to determine whether GH remains elevated for a greater part of the day in patients receiving β-blockers. It has been suggested by Sherman et al. (1978) that oral contraceptives may induce growth and hormonal secretion in otherwise silent pituitary microadenomas, which occur in 5–10% of the population, and it is also possible that term treatment with β-blockers may facilitate the development of pituitary adenoma and acromegaly.

The variability in the response of some acromegalic patients to hypoglycaemia, propranolol, glucagon, thyrotrophin-releasing hormone and L-dopa has over the last decade led to the suggestion (Cryer and Daughaday, 1969; Goldfine, 1978) that some degree of hypothalamic control of GH persists in many acromegalic patients and autonomous pituitary secretion develops in the remainder. It is possible that patient D who did not respond to either insulin/hypoglycaemia or propranolol is in the latter category. The significant positive relationship between plasma propranolol concentration and GH response in the other acromegalic patients further supports the role of the sympathetic system in GH secretion. This marked elevation of GH following propranolol, may be an important consideration when assessing GH levels, and initiating therapy with β-blockers in acromegalic patients.

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References
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