Beta-adrenoreceptor blocking drugs and thyroid hormones in hyperthyroid subjects

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Summary
Serum thyroid hormone concentrations were measured before and during 10 days' treatment with atenolol (200 mg/day), acebutolol (400 mg/day), oxprenolol (160 mg/day) and propranolol (160 mg/day) in 24 hyperthyroid patients. During propranolol treatment serum triiodothyronine (T3) concentrations fell significantly (P < 0.05) but there was no change in thyroid hormone concentrations in the other groups although all patients reported a symptomatic improvement.

Introduction
Beta-adrenoreceptor blocking drugs are widely used in the treatment of hyperthyroidism. Propranolol causes a fall in serum triiodothyronine (T3) concentrations in hyperthyroid patients, probably via an action on the peripheral conversion of thyroxine (T4) to T3 and reverse T3 (rT3) (Lotti et al., 1977; Kallner, Ljunggren and Tryselius, 1978; Feely et al., 1979). The action of β-adrenoreceptor blocking agents other than propranolol on circulating thyroid hormones in hyperthyroidism has not been widely studied, although the present authors have described the lack of effect of those drugs possessing the subsidiary property of partial agonist activity (ISA) (Jones, John and Jones, 1980). In order to provide further evidence on this point a comparative study of the effect of 4 different β-adrenoreceptor blocking agents in these patients has been made.

Subjects and methods
Twenty-four untreated hyperthyroid women (aged 24–55 years) were studied as out-patients after giving their informed consent. Hyperthyroidism was diagnosed in each subject by clinical criteria, by raised serum levels of T4 and T3 and by increased thyroid uptake of 131I. Patients were assessed clinically before and 10 days after treatment. The patients were divided into 4 groups of 6, receiving either atenolol (200 mg/day), or acebutolol (400 mg/day), or oxprenolol (160 mg/day) or racemic propranolol (160 mg/day) in a twice daily dosage for 10 days. No other drug was given. Venous blood samples were taken on 2 occasions before treatment and at one, 2, 4, 7 and 10 days after the first dose.

All blood samples were obtained from an antecubital vein at 10.00 hours after an overnight fast and 30 min bed rest. Samples were centrifuged promptly and serum stored at −20°C until assayed. T4 (normal range 55–150 nmol/l) was measured by radioimmunoassay using a method based on that of Challand, Ratcliffe and Ratcliffe (1975). T3 (normal range 1·3–3·5 nmol/l) was measured by solid phase radioimmunoassay (Immophase, Corning Medical, Halstead, Essex) and vacant thyroid hormone binding sites were assayed by Thyopac-3 test (T3RU) (normal range 92–117) (Radiochemical Centre, Amersham, Bucks). Free thyroxine index (FT4I, normal range 55–145 nmol/l) and free triiodothyronine index (FT3I, normal range 1·4–3·7 nmol/l) were expressed as 100 × T4 or T3 divided by the T3RU value. At the mid-point of the normal range the coefficients of variation for the assays of T4, T3 and T3RU were 8·0%, 8·5% and 1·7% respectively. For each index all samples were measured in one assay run. Data are presented as mean values ± standard error and compared by Student's t-test for paired data.
**Results**

Serum T₃ values fell significantly \( P < 0.05 \) 4 days after starting propranolol and this was sustained at 10 days (Fig. 1). Changes in FT₃I values reflected those seen in T₃ concentrations but there was no significant change in T₄ or FT₄I in the group treated with propranolol.

There was no significant change in thyroid hormone levels in the other groups (Fig. 2). Resting pulse rate was lowered \( P < 0.05 \) in the 4 groups and all patients reported a symptomatic improvement in terms of excessive sweating, nervousness, preference for cold and general wellbeing after 10 days' treatment.
Discussion

Propranolol caused a significant (P<0.05) and sustained fall in serum T₃ concentrations to approximately 75% of pre-treatment values while atenolol, acebutolol and oxprenolol had no effect on circulating thyroid hormones. The mechanism by which propranolol exerts this action is unclear. It differs from the other drugs studied in that neither is it cardioselective nor does it have ISA (Fig. 3). The subsidiary property of ISA cannot explain the lack of effect of acebutolol and oxprenolol since atenolol, which does not possess ISA, also had no effect. It is possible that other non-selective β-adrenoreceptor blocking drugs without ISA could lower serum T₃ concentrations in the same way as propranolol.

The other subsidiary property of membrane stabilizing activity (MSA) must also be considered when attempting to explain the action of propranolol on serum T₃ levels. It has been suggested from a study of euthyroid and hypothyroid subjects receiving T₄ that this effect of propranolol is related to its MSA (Heyma et al., 1980). In the present study, however, neither acebutolol nor oxprenolol lowered serum T₃ concentrations and, although these drugs are less effective than propranolol as membrane stabilizing agents, both as local anaesthetics and in their action on intracellular cardiac potentials (Vaughan-Williams and Papp, 1970; Basil et al., 1973), a fall would have been expected if the presence of MSA was important.

No clinical advantage was found in the patients' response to propranolol when compared with the other β-adrenoreceptor blocking drugs. Despite initial concern over the use of β-adrenoreceptor blocking agents with ISA in the treatment of hyperthyroidism (Turner, 1974), this finding is supported by the results of recent studies comparing propranolol with various classes of cardioselective β-adrenoreceptor blocking agents (Nelson and McDevitt, 1975; Murchison et al., 1976; Nilsson et al., 1979; Murchison, How and Bewsher, 1979). The therapeutic relevance of the fall in serum T₃ concentrations in hyperthyroid patients on propranolol is not established.

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References


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<td>Membrane stabilizing activity (MSA)</td>
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<td>+</td>
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Fig. 3. Comparison of subsidiary properties of atenolol, acebutolol, propranolol and oxprenolol. + indicates subsidiary property present, ○ indicates subsidiary property absent.

Cardioselectivity  

Partial agonist response  

Membrane stabilizing activity  

β-adrenoreceptor blocking agents (Nelson and McDevitt, 1975; Murchison et al., 1976; Nilsson et al., 1979; Murchison, How and Bewsher, 1979). The therapeutic relevance of the fall in serum T₃ concentrations in hyperthyroid patients on propranolol is not established.
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