Effect of propranolol on thyroid homeostasis of healthy volunteers

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Summary: The effect of propranolol on thyroid status was investigated by administering the drug in 2 therapeutic doses (80 mg b.d. and 120 mg b.d.) to 8 healthy volunteers and serially measuring total and free thyroid hormones and their major binding protein. Mean free T₃ fell by 1.2 pmol/l ($P < 0.05$) whilst mean free T₄ and mean rT₃ rose by 3.3 pmol/l ($P < 0.01$) and 0.16 nmol/l ($P < 0.01$) respectively. Mean thyroxine binding globulin (TBG) fell by 1.2 mg/l ($P < 0.001$). Despite the change in free hormone levels there was no significant change in TSH. For the first time the effect of propranolol on circulating thyroid hormones and binding proteins in healthy subjects is apparent within one study. The biological significance of the change in free hormone levels is discussed.

Introduction

Beta-adrenoceptor blocking drugs (beta-blockers) have established a place in the treatment of thyrotoxicosis and it has been argued that their therapeutic effect, at least in part, may be mediated by a direct effect on thyroid hormone concentrations (Saunders *et al.*, 1978). Changes in total thyroid hormone levels have been reported in patients receiving beta-blockers for hypertension and angina (Kristensen & Weeke, 1977; Cooper *et al.*, 1982). There is then the suggestion that these drugs may directly alter thyroid status. In view of the large number of euthyroid patients taking beta-blocking agents, we felt it was important to investigate this possibility in detail. The biologically active component of circulating thyroxine (T₄) and triiodothyronine (T₃) is thought to be the free (unbound) fraction. Free T₄ and free T₃ account for only 0.03% and 0.3%, respectively, of total levels (Ekins, 1979). This study was designed to clarify the effects of propranolol on thyroid status by administering the drug in 2 therapeutic doses to healthy volunteers and monitoring not only total T₄ and T₃, reverse T₃ (rT₃), TSH and thyroxine binding globulin (TBG) but also free T₄ and free T₃.

Methods

Eight euthyroid male volunteers aged 20 to 23 y were studied. Each had a normal clinical examination, full blood count and biochemical profile. Baseline thyroid function was assessed on 2 venous samples taken a week apart. Propranolol, 80 mg twice daily, was started on day 0 and continued until day 14. On day 15, after the morning blood sample, the dose was increased to 120 mg twice daily for a further week. Propranolol was stopped on day 21. Blood was sampled for thyroid function tests on days 1, 2, 3, 7, 14, 15, 21, 22, 23 and 28 and compliance was checked by measuring plasma levels of propranolol on days 3, 7 and 15.

Total T₃, T₄ and rT₃ were measured by in-house radioimmunoassay (Black *et al.*, 1975; Evans *et al.*, 1977). Free T₄, free T₃ and TSH were measured using Amerlex kit methods and TBG by immunoelectrophoresis (Laurell, 1966). The possibility of an *in vitro* effect of propranolol on the free hormone assays was examined by assaying a sample of normal serum containing different concentrations of propranolol (range 0 to 1000 ng/ml) for free T₄ and T₃.

The increments and decrements from the mean for each individual for each day were analysed by Student's *t* test and Wilcoxon rank sum test. There was close agreement between the two statistical approaches. For consistency, as standard errors are given, the values of significance quoted are those calculated by Student's *t* test.

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Results

There was a non-significant rise in total T_4 during the treatment period and a return to baseline on stopping the beta-blocker. Total T_3 levels remained stable throughout the study (Figure 1). Despite changes in total and free thyroid hormone levels (Figure 2) there was no significant change in basal TSH concentration during the study period.

Mean free T_4 rose during the first week from a basal level of $19.8 (\pm \text{s.e.m. } 0.9)$ to $22.7 (\pm 1.0)$ pmol/l on day 7 ($P < 0.02$). With some fluctuation in absolute values, it remained elevated for the rest of the treatment period, returning to baseline on stopping the drug (Figure 2).

The mean basal free T_3 was $6.4 (\pm 0.3)$ pmol/l. There was no significant change during the period of low dose propranolol but there was a significant fall to $5.2 (\pm 0.2)$ pmol/l ($P < 0.05$) on 120 mg b.d. and a sharp rise towards the basal value on stopping the drug (Figure 2).

Reverse T_3 rose during the first week from a baseline level of $0.44 (\pm 0.02)$ to $0.57 (\pm 0.03)$ nmol/l ($P < 0.01$). It remained elevated throughout the treatment period, falling to basal levels after day 21.

TBG fell gradually from $9.4 (\pm 0.3)$ to a nadir of $8.2 (\pm 0.4)$ mg/l ($P < 0.001$) on day 22 and then showed a trend of gradual recovery during the post-treatment week (Figure 3). The change in T_4 /TBG ratio showed a very close correlation with the response of measured free T_4 ($r = 0.9$; $P < 0.001$) (Figure 4).

Figure 1 Total T_4 and T_3 and TSH levels during treatment with propranolol (hatched area) and in the follow-up week.

The addition of propranolol to serum *in vitro* increasing concentrations produced a slight but non-significant rise in measured free T_4 and had no effect on measured free T_3 .

Discussion

Previously reported changes in total thyroid hormone levels in euthyroid subjects receiving propranolol may be summarized thus: total T_3 may fall whilst reverse T_3 , and on higher doses, total T_4 may rise. These changes, however, have never previously been described in one study (Cavalieri & Rivers, 1981). Lotti *et al.* (1977) and Faber *et al.* (1979) noted a fall in T_3 with propranolol 40 to 120 mg/d and the latter group also recorded a rise in reverse T_3 , but neither group found a change in total T_4 levels. Kristensen & Weeke (1977) and Cooper *et al.* (1982) reported raised total T_4 levels in patients receiving propranolol for essential hypertension and angina pectoris respectively; five of the six described by Cooper *et al.* (1982) also had raised levels of rT_3 but both groups of patients had normal total T_3 levels. The changes in total hormone concentrations found in our study – the rise in rT_3 , the non-significant rise in T_4 and the stable T_3 levels – are compatible with the observations of others.

Kristensen & Weeke (1977) included measurements

Figure 2 Response of free T_4 and T_3 and reverse T_3 during treatment with propranolol (80 mg b.d. and then 120 mg b.d.) and in the follow-up week. Day 0 is the mean of two basal values for each volunteer. * $P < 0.05$; ** $P < 0.01$.

Figure 3 Response of TBG and change in T_4 /TBG ratio during treatment with propranolol (80 mg b.d. and then 120 mg b.d.) and in the follow-up week. Day 0 is the mean of two basal values for each individual. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

of free T_4 and free T_3 in their study of 15 patients starting propranolol for essential hypertension. Their results differ from ours in that they observed a rise in free T_4 but no change in free T_3 . Their patients were taking other antihypertensive drugs and the authors base their report on 2 blood samples for each individual taken 30 days apart, two factors which may have reduced the sensitivity of their study.

In this report, changes in free thyroid hormones paralleled those described for total circulating hormones, and for the first time the effects of propranolol on thyroid hormones, total and free, and their major binding protein are apparent in one study. Most T_3 and rT_3 is produced by the monodeiodination of T_4 in peripheral tissues – liver and kidney – rather than in the thyroid (Chopra *et al.*, 1978). The changes in free T_4 , free T_3 and rT_3 presented here provide strong supporting evidence for an inhibitory influence of

propranolol on 5' monodeiodinase. This enzyme is responsible for the monodeiodination of T_4 to T_3 (Chopra *et al.*, 1978) and rT_3 to T_2 , hence T_3 production falls and rT_3 clearance is reduced if its activity is inhibited. The mechanism by which propranolol exerts this inhibitory effect is unclear. The property is not confined to propranolol but is shared by some other beta-blockers (Perrild *et al.*, 1983). DL-propranolol, which has no known beta-blocking activity, has also been reported to decrease T_3 and increase rT_3 levels (Heyma *et al.*, 1980).

The fall in TBG that occurs during propranolol therapy was first noted by Wilkinson *et al.* (1983). It occurs in euthyroid subjects and in thyrotoxic patients once rendered euthyroid. It cannot be attributed to changes in plasma volume as serum albumin levels remain unaffected. The very close correlation between the T_4 /TBG ratio (an estimate of free T_4) and the measured free hormone (Figure 4) suggests that the fall in TBG does not invalidate the use of the T_4 /TBG ratio in patients taking propranolol. Furthermore, this close correlation affords independent evidence supporting the argument that the rise in free T_4 is genuine and not explained by an effect of propranolol on the free T_4 assay. In contrast, there was no correlation between the change in T_3 /TBG ratio and the response of free T_3 .

Interpretation of the biological significance of an 18% fall in free T_3 and a concurrent 20% rise in free T_4 is complicated by the lack of a definitive standard by which to assess thyroid status. In euthyroid subjects, serum levels of free T_4 and free T_3 remain remarkably constant with time (unpublished data). A fall of 1.2 pmol/l in free T_3 and a rise of around 3.0 pmol/l in free T_4 in absolute terms in healthy volunteers is unphysiological. The net effect of these divergent responses on metabolism depends upon the relative potencies of free T_4 and free T_3 . It has been estimated that T_4 is 2 to 4 times less potent in stimulating calorogenesis than T_3 , and that T_4 has no catabolic activity (Perrild *et al.*, 1983). Therefore the overall effect may be that there is a net fall in catabolic activity.

At present the two most sensitive indicators of 'adequacy' of circulating thyroid hormone levels are the serum TSH level and its response to thyrotrophin releasing hormone (TRH). In this study, there was no significant change in TSH levels. Cooper *et al.* (1982) included TRH stimulation in their series of patients on high-dose propranolol; they obtained normal or blunted, rather than exaggerated, TSH responses to TRH stimulation. Thus there is no evidence as yet to suggest that the pituitary appreciates treatment with propranolol as drug-induced hypothyroidism but the definitive test awaits the discovery of a sensitive assay of biological activity of thyroid hormones at the tissue level.

Figure 4 Correlation of estimated free T_4 (T_4 /TBG ratio) and measured free T_4 during the study period (on and off propranolol). $r = 0.9$; $P < 0.001$.

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