EFFECT OF TIMOLOL ON CLINICAL FEATURES AND ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN HYPERTHYROIDISM

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- 1 The effect of timolol, a β -adrenoceptor blocking drug on the clinical status, thyroid status and left ventricular function as measured by serial M-mode echocardiographic recordings was assessed in a double-blind randomised study in 18 hyperthyroid patients.
- 2 A significant clinical improvement was documented after 2 weeks of timolol treatment compared with placebo.
- 3 There was no evidence that timolol impaired peripheral monodeiodination of thyroxine (T₄).
- 4 There were significant increases in left ventricular fractional shortening (Fr. Sh.) and velocity of circumferential shortening (Vcf) as well as a significant decrease in the left ventricular systolic internal dimension (LVIDs) (all $P < 0.01$) in the untreated thyrotoxic patients compared with a normal euthyroid control group.
- 5 After timolol treatment (2/52) there were significant increases in LVIDs and LVIDd and a significant decrease in Vcf (all $P < 0.05$).
- 6 No further changes occurred after a further 2/52 treatment with carbimazole.
- 7 The cardiac data suggest that both an augmented sympathetic drive and a direct effect of thyroid hormone on myocardial contractility are mediators of the haemodynamic changes in hyperthyroidism.

Keywords timolol hyperthyroidism left ventricular function

Introduction

β -adrenoceptor blocking drugs are valuable in the management of hyperthyroid patients (McDevitt, 1976). They ameliorate many sympathomimetic features of the disease generally ascribed to the interaction of excess thyroid hormones with catecholamine receptors (Landsberg, 1977). The disturbed cardiac function in hyperthyroidism which responds to β -adrenoceptor blocker therapy is also associated with animal evidence suggesting an increased number of β -receptors in thyrotoxic cardiac membranes (Williams *et al.*, 1977). In addition, β -adrenoceptor blocking drugs may inhibit the peripheral monodeiodination of thyroxine (T₄) leading to a lowered serum triiodothyronine (T₃) concentration (Verhoeven *et al.*, 1977).

While human non-invasive cardiac function studies in hyperthyroidism have been documented (Nixon *et al.*, 1979) there is little data on the sequential cardiac effects of β -adrenoceptor blocking drugs during the early phase of treatment in this disease. This study describes the clinical response together with the

changes in left ventricular function in hyperthyroid patients treated with timolol. This drug, a non-selective β -adrenoceptor blocking agent without intrinsic sympathomimetic activity (Frishman, 1982) has not been studied previously in hyperthyroid patients.

Methods

Subjects

Eighteen hyperthyroid patients (15 female, three male, mean age 49.5 years $\pm$ 10.3 s.d.) were studied. All gave informed consent and the study was approved by the local Ethical Committee. Hyperthyroidism was confirmed by elevated serum concentrations of T₄ (> 150 nmol/l) and T₃ (> 3.0 nmol/l) together with an increased 4 h I¹²³ uptake ($> 40\%$). All patients were in sinus rhythm with normal conduction and no clinical evidence of cardiac failure. There was no previous history of heart disease.

Protocol

Preliminary assessment included a full clinical examination, biochemical investigation of thyroid function and an M-mode echocardiogram of the left ventricle with simultaneous recordings of electro-cardiogram (ECG), phonocardiogram (PCG) and carotid pulse. The patients were then randomly divided on a double-blind basis for treatment with timolol 10 mg twice daily [Group T (mean $\pm$ s.d. age 45 ± 11.1 , $n = 8$)] or identically matched placebo tablets [Group P (mean $\pm$ s.d. age 52.2 ± 8.5 , $n = 10$)]. After 2 weeks, carbimazole 10 mg four times daily was added, other treatments remaining unchanged. The patients were assessed at the beginning of the study, after the initial 2 week period of timolol or placebo treatment and after a further 2 week period of concomitant carbimazole. Compliance was checked by a tablet count at each visit.

1. Clinical assessment

Heart rate and blood pressure were measured supine after resting for 10 min, after standing for 2 min, and after brisk walking for 50 yds on the flat.

Blood pressure was measured by sphygmomanometer, the diastolic pressure being taken as the fiftieth phase of the Korotkof sound. A clinical hyperthyroid score index (Crooks *et al.*, 1959) was completed by two independent observers.

2. Thyroid function tests

Serum was stored at -20°C and all samples measured in one assay. Total T4 (TT4) was measured by radioimmunoassay (RIA) (Challand *et al.*, 1975). Free T4 (FT4) was determined by using the 'Amerlex Free T4 Kit' (Amersham International PLC, Amersham, England). Total T3 (TT3) was measured by an automated RIA. Free (FT3) was measured by automated RIA using a rate reaction method. Reverse T3 (rT3) was measured by RIA based on the method of Hufner & Grussendorf (1976).

Serum timolol was measured by gas liquid chromatography (Tocco *et al.*, 1975) on samples obtained 4 h after administration of the drug. The detection limit of the assay was 1 ng/ml.

3. Echocardiography

M-mode echocardiograms were recorded with a Smith Kline & French Echoline using a 2.25 mm Hg focused transducer coupled to a Cambridge Multi-channel recorder.

Each investigation was performed at the same time of day and after a 10 min rest period. A careful note was made of the patient and transducer positions; these were kept constant at each subsequent investigation (all recorded by BEG).

Left ventricular dimensions were obtained just below the mitral valve after an aorta-left ventricular scan. The internal cavity dimension of the left ventricle at end-diastole (LVIDd) was measured at the peak of the R wave of the simultaneously recorded ECG and at end-systole (LVIDs) at the time of the aortic component of the second sound displayed on the simultaneous high frequency phonocardiogram. The data was measured blind by the same observer (BEG) using the leading edge method throughout. Five consecutive cardiac cycles were analysed on each occasion so as to minimise beat to beat variation in echocardiographic dimension measurements (Bett & Dryburgh, 1981).

The following parameters of left ventricular function were derived:

$$\text{Fractional shortening (Fr. Sh.)} = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd}}$$

Normalised mean velocity of circumferential fibre

$$\text{shortening (Vcf)} = \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd} \times \text{ET}}$$

Ejection time (ET) was measured from the beginning of the upstroke to the trough of the incisura of the carotid pulse tracing.

M-mode echocardiograms were also obtained using the same technique from 25 normal euthyroid volunteers (18 male, seven female, mean $\pm$ s.d. age 25 ± 6.0 years).

The reproducibility of echocardiographic dimension measurements was evaluated by recording echocardiograms in eight of the euthyroid subjects repeatedly during a six week period. The coefficients of variation at LVIDd, LVIDs, and Fr. Sh. recorded and measured blind by the same investigator (BEG) on day 0, day 1, day 7 and day 42 were 2%, 4% and 6% respectively.

Statistical analysis was performed using analysis of variance and Students' *t*-test for unpaired and paired data.

Results

1. Clinical assessment

Timolol treatment, in contrast to placebo treatment, produced a marked clinical improvement during the first 2 weeks as shown both by the significant reduction in the hyperthyroid scores and the reduction in the supine, erect and exercise induced heart rate by 20% or more (Table 1). There was a small but significant decrease in the erect systolic blood pressure in group T during this time from 140 ± 3 (s.e. mean)/79 ± 4 to 123 ± 4 /70 ± 3 mm Hg ($P < 0.05$). There were no significant changes in heart rate or blood pressure with placebo treatment during the first 2 weeks or in

Table 1 Thyroid function during timolol (T) therapy and placebo (P) for 2 weeks. Both groups received carbimazole for a further 2 weeks. Data expressed as mean $\pm$ s.e. mean

Time (weeks)	Hyperthyroid score	Pulse rate (beats min ⁻¹)	Exercise	TT4 (nmol l)	FT4 (nmol l)	TT3 (nmol l)	FT3 (pmol l)	rT3 (nmol l)
		Supine						
0 T	17.4 $\pm$ 4.0	99 $\pm$ 6	121 $\pm$ 3	213 $\pm$ 12.7	57.3 $\pm$ 9.7	7.1 $\pm$ 1.3	24.4 $\pm$ 4.4	1.6 $\pm$ 0.2
P	17.8 $\pm$ 1.84	91 $\pm$ 3	112 $\pm$ 4	185 $\pm$ 11.4	49.4 $\pm$ 6.2	6.8 $\pm$ 1.4	22.9 $\pm$ 4.8	1.1 $\pm$ 0.2
		Erect						
2 T	5.4 $\pm$ 2.3(a)	80.6 $\pm$ 5.6(b)	74 $\pm$ 2.5(c)	195 $\pm$ 13.5(d)	51.7 $\pm$ 8.4	6.4 $\pm$ 1.4	25.1 $\pm$ 6.1	1.5 $\pm$ 0.2
P	17.6 $\pm$ 2.3	75 $\pm$ 4.1(c)	93.4 $\pm$ 2.0	185 $\pm$ 11.0	50.7 $\pm$ 8.0	5.7 $\pm$ 0.6	21.2 $\pm$ 3.3	1.2 $\pm$ 0.1
4 T	-0.7 $\pm$ 2.6(a)	94.2 $\pm$ 2.3	69.4 $\pm$ 4.1(c)	134 $\pm$ 12.1	31.1 $\pm$ 5.0	3.9 $\pm$ 0.5	11.4 $\pm$ 1.8	0.8 $\pm$ 0.1
P	12.9 $\pm$ 2.6	68 $\pm$ 4.3(c)	96.1 $\pm$ 3.9	140 $\pm$ 11.4	34 $\pm$ 4.8	3.6 $\pm$ 0.2	10.5 $\pm$ 0.8	0.7 $\pm$ 0.1
Normal range	< 9	—	—	50–150	10.3–29.6	1.5–3.0	3.5–10	0.18–0.66

(a) $P = < 0.005$ cf placebo(b) $P = < 0.01$ cf placebo(c) $P = < 0.0005$ cf placebo(d) $P = < 0.01$ cf pretreatmentAll thyroid hormone values at 4 weeks significantly less than those at 2 weeks ($P < 0.01$)

either group after the addition of 2 weeks of carbimazole therapy.

2. Thyroid function tests

There was a small but significant fall in total T4 during the first 2 weeks on timolol (Table 1) but there was no significant change in free T4, TT3 or free T3. In addition there was no rise in rT3 during the period. Following the introduction of carbimazole thyroid hormone concentrations fell significantly ($P < 0.01$) in both groups but many patients still had values in the hyperthyroid range at the 4 week assessment. The mean serum timolol concentration $\pm$ s.e. mean after 2 weeks of therapy in group T was 7.14 ± 0.96 ng/ml and after 4 weeks was 8.0 ± 1.82 ng/ml.

3. Echocardiography

Satisfactory M-mode echocardiograms for evaluation of left ventricular dimensions and function were obtained from 12 hyperthyroid patients (six Group T, six Group P). There were no significant differences in any echocardiographic parameter between these two groups.

There were however, significant increases in Fr. Sh. and Vcf, a significant decrease in LVIDs ($P < 0.01$), and an insignificant decrease in LVIDd in the hyperthyroid group as a whole before treatment when compared to the euthyroid control group (Figure 1).

After 2 weeks' timolol treatment (Group T) there was a significant 9% increase in LVIDd 4.6 ± 0.1 to 5.0 ± 0.1 cm ($P < 0.05$), a significant 12% increase in LVIDs 2.6 ± 0.2 to 2.9 ± 0.1 cm ($P < 0.005$) and a significant 15% decrease in Vcf 1.75 ± 0.18 to 1.49 ± 0.12 cm s⁻¹ ($P < 0.01$) with an insignificant 2% decrease in Fr. Sh. 43 ± 3 to $42 \pm 3\%$ (Figure 2). When compared to the normal volunteer group Vcf was still significantly higher following timolol treatment ($P < 0.05$) whereas no significant differences were found for LVIDd, LVIDs and Fr. Sh.

The changes in left ventricular dimensions and derived parameters of left ventricular function in the placebo treated group (Group P) during the first 2 weeks of therapy were LVIDd 5.0 ± 0.2 to 5.0 ± 0.1 cm; LVIDs 2.9 ± 0.2 to 2.9 ± 0.2 cm; Vcf 1.61 ± 0.12 to 1.60 ± 0.15 cm s⁻¹; Fr. Sh. 42 ± 2 to $43 \pm 3\%$. In contrast to the timolol treated group none of these changes was significant. No significant changes were noted in either group following treatment with 2 weeks' carbimazole when the parameters were measured at 4 weeks after entry into the study (Figure 2).

Discussion

This study has shown that timolol is clinically effective

Figure 1 Echocardiographic indices of left ventricular function in euthyroid control group (□, $n = 25$) and the hyperthyroid patients before therapy (▨, $n = 12$).

LVID_d = left ventricular end diastolic dimension

LVID_s = left ventricular end systolic dimension

Fr. Sh = fractional shortening

Vcf. = velocity of circumferential fibre shortening

Error bars represent mean $\pm$ 1 s.e. mean. * $P < 0.01$

Figure 2 Echocardiographic indices of left ventricular function in Group T (timolol, —) and Group P (placebo, ---) before treatment (0) and after 2 weeks of timolol or placebo treatment.

The addition of carbimazole therapy in both groups is shown by the hatched area.

Values are expressed as a mean percentage $\pm$ 1 s.e. mean of the pretreatment value. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$.

in the management of hyperthyroidism and that its effect continues when combined with carbimazole. As the drug is not a cardio-selective β -adrenoceptor blocking agent and does not have intrinsic sympathomimetic activity it may be inferred that its action in hyperthyroidism is similar to propranolol (McDevitt, 1976; Jones *et al.*, 1981) and nadolol (Peden *et al.*, 1981). While the latter two drugs inhibit the peripheral monodeiodination of T4 to T3 no such effect was seen in this study with timolol. The reason for the fall in T4 in Group T after 2 weeks timolol treatment is not clear but may be related to an altered distribution volume of T4 produced by the drug. In contrast, propranolol sometimes results in an increase in T4, perhaps because of a reduction in T3 and T4 clearance by this drug (Lumholtz *et al.*, 1978). These data do not exclude an effect of timolol on thyroid hormone metabolism but despite the reduction in total T4 there was no significant fall in FT4.

The haemodynamic consequences of hyperthyroidism are well described (Ueda *et al.*, 1965). Conflicting views suggest that the increase in heart rate and cardiac output are mediated either by the positive chronotropic and inotropic effects of increased sympathetic stimulation (Brewster *et al.*, 1956) or by a positive chronotropic and inotropic effect of thyroxine (Buccino *et al.*, 1967; Amidi *et al.*, 1968; Grossman *et al.*, 1971; Turner & Shenfield, 1980; Cohen *et al.*, 1981) or to a combination of both (Howitt *et al.*, 1968; Weiner *et al.*, 1969; Mazzaferri *et al.*, 1976; Rutherford *et al.*, 1979). Conversely it has been suggested that the increase in heart rate and cardiac output are secondary to changes in the peripheral circulation and blood volume induced by the hyperthyroid state (deGroot & Leonard, 1970; Merillon *et al.*, 1981).

The present non-invasive study suggests that both an augmented sympathetic drive and a direct effect of thyroid hormone on myocardial contractility are im-

portant mediators of the haemodynamic changes. The indices of left ventricular function (Fr. Sh., Vcf) in the untreated hyperthyroid group were significantly greater than in the euthyroid control group. In addition we found a significant decrease in LVIDs which contrasts with the angiographic study of Merillon *et al.* (1981). These changes in left ventricular function and dimension suggest either an increase in myocardial contractility or a decrease in afterload, Vcf and LVIDs being independent of changes in preload (Nixon *et al.*, 1982; Gault, 1978). Chronic timolol therapy, in contrast to previously published echocardiographic studies using chronic propranolol treatment in equivalent therapeutic dosages (Lewis *et al.*, 1979; Turner & Shenfield, 1980), caused a significant decrease in Vcf and significant increases in LVIDd and LVIDs, changes similar to those reported in cardiac catheterisation studies using acute propranolol treatment (Howitt *et al.*, 1968; Merillon *et al.*, 1981). In this study care was taken to minimize the biological and technical scatter inherent in the echocardiographic evaluation of left ventricular function; this may account for the different results found in the present study compared with the data of Lewis *et al.* (1979). Our study shows that the acute changes in haemodynamic function that occur with β -adrenoceptor blockade (Howitt *et al.*, 1968; Merillon *et al.*, 1981) persist with chronic treatment. The increase in LVIDs and decrease in Vcf with no significant change in systemic arterial pressure implies a decrease in myocardial contractility, a

consequence of β -adrenergic receptor blockade and associated decrease in sympathetic tone. The magnitude of these changes are greater than those expected from a decrease in heart rate alone (Hirschleifer *et al.*, 1975) and are also greater than those found with β -adrenoceptor blocker therapy in euthyroid subjects (Winkle *et al.*, 1978) thus suggesting an augmented sympathetic drive in the thyrotoxic state. The increase in LVIDd can be attributed both to the decrease in heart rate and to the normal adaptive response of the heart to a decrease in myocardial contractility. Following timolol treatment, however, the Vcf was still significantly greater than in the euthyroid group; this suggests an additional direct effect of thyroid hormone on myocardial contractility independent of an increased sympathetic drive, although no significant differences in left ventricular dimensions and heart rate were seen. These data are therefore consistent with previous studies (Howitt *et al.*, 1968; Weiner *et al.*, 1969; Mazzaferri *et al.*, 1976; Rutherford *et al.*, 1979). Timolol therapy was effective in ameliorating the clinical features of hyperthyroidism in our patients in addition to restoring towards normal the disturbed cardiovascular function in this disease.

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Reprint requests to J.M.L.

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