Br. J. clin. Pharmac. (1978), **6**, 233–237

COMPARATIVE TRIAL OF ATENOLOL AND PROPRANOLOL IN HYPERTHYROIDISM

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1 The use of atenolol, a cardioselective β-adrenoceptor antagonist, in the management of hyperthyroidism has been studied by comparing it with propranolol.

2 In a double-blind cross-over trial, atenolol (50 mg), propranolol (40 mg) and placebo 4 times daily for 1 week were compared in twenty-one hyperthyroid patients by sequential analysis.

3 Patients generally preferred atenolol or propranolol to placebo but this preference only achieved significance with propranolol.

4 Judged by their effect on the symptoms and signs of hyperthyroidism, both atenolol and propranolol were significantly better than placebo, but no distinction could be made between the two active compounds.

5 Atenolol and propranolol reduced mean heart rate by 29.8 and 27.1% respectively compared with placebo.

6 Atenolol appeared almost equally effective to propranolol in the management of the peripheral manifestations of hyperthyroidism.

Introduction

Propranolol has been shown to control the peripheral manifestations of hyperthyroidism (Shanks, Hadden, Lowe, McDevitt & Montgomery, 1969) and to be useful in various aspects of the management of the disease (McDevitt, 1977). In addition, despite initial concern that β-adrenoceptor blocking drugs with partial agonist activity would be less effective in this role (Turner, 1974), practolol was found to be almost indistinguishable from propranolol in hyperthyroid patients, although propranolol produced greater reduction of heart rate (Nelson & McDevitt, 1975). The efficacy of practolol in the management of hyperthyroidism has subsequently been confirmed (Murchison, Bewsher, Chesters & Ferrier, 1976) but its toxicity (British Medical Journal, 1975) precludes its use in this clinical situation.

Because of the possibility that patients with obstructive airways disease may develop hyperthyroidism and require the benefits of β-adrenoceptor blockade, it is important to discover whether other cardioselective β-adrenoceptor blocking drugs improve the symptoms and signs of this disease. We now report the results of a double-blind trial comparing atenolol, which has cardioselectivity in man (Vilsvik & Schaaning, 1976) with propranolol in patients with hyperthyroidism.

Methods

Twenty-two outpatients (20 females and 2 males) with hyperthyroidism were admitted to the trial in the order they presented at the clinic. All consented to participate after full explanation of the procedure. They were adjudged hyperthyroid by standard clinical and biochemical criteria (Table 1). Treatment continued for a period of 3 weeks during which tablets containing propranolol 40 mg, atenolol 50 mg or placebo were given orally 4 times daily for 1 week in randomized order. A double dummy system was used in which patients took two different tablets throughout the 3 week period. The combinations were, therefore, active propranolol plus atenolol placebo, active atenolol plus propranolol placebo or propranolol and atenolol placebos. The active and placebo tablets for each drug were identical, but the tablets for the two drugs were different. Tablets were supplied for 1 week only at a time with a known variable number of tablets in each treatment box. Patients were instructed to bring any unused tablets back to the clinic at the end of each week, so that an estimate of compliance could be made. The three treatments were allocated by a double-blind technique, so neither the patient nor the observer knew which drug had been given. No other antithyroid treatment was taken during the trial. Each patient was assessed by the same observer (JKN) for

Table 1 Observations on twenty-two patients with hyperthyroidism (mean + s.e. mean)

Sex	*Age (years)*	*Weight (kg)*	*Heart rate (beats/min)*	*T_3* (% uptake)*	*T_4† (nmol/l)*	*F.T.I.‡*
2M, 20F	46.1 ± 2.7	56.3 ± 1.6	113.3 ± 3.4	86.2 ± 1.8	201.0 ± 10.5	236.9 ± 15.3

Normal ranges: *95–122 % uptake
†54–144 nmol/l
‡51–142

selected criteria before entering the trial, and at the end of each treatment week. On these occasions they were asked only if their symptoms were increased, decreased or unchanged during the previous week. Objective assessment of seven features of hyperthyroidism was then made according to an arbitrary scoring technique using O, + or ++ for grading severity. Heart rate was measured on each visit by a nurse and was recorded on a separate sheet which was not seen by the observer until the trial was completed and his initial treatment assessments had been made. At the end of the second and third weeks of treatment, the patients' subjective treatment preferences were noted and the observer recorded his comparative preferences for the treatments on the basis of improvement in the symptomatic and objective criteria but without knowledge of heart rate changes. When the trial was completed, the patients' heart rates for each week were added to each data sheet and the observer made a further assessment of his preferences. Three preferences were thus determined—patient's subjective preference, observer's objective preference without heart rate and observer's preference including heart rate—for each comparison (atenolol and placebo, propranolol and placebo, and atenolol and propranolol) and these were submitted to sequential analysis using the method of Armitage (1960). Other statistical comparisons were made using Student's paired *t*-test and the χ^2 test.

Results

All twenty-two patients completed the trial, but one of them was excluded from the subsequent analysis because the tablet count suggested that she had been non-compliant during one of the treatment weeks. The results of the sequential analysis for the subjective and objective assessments for atenolol, propranolol and placebo are shown in Figures 1–3.

Subjective assessment (Figure 1)

The trial reached a significant level in favour of propranolol compared to placebo after twenty-one patients. With atenolol, thirteen patients preferred the active compound to placebo and three patients could not distinguish between them. In comparing the two active compounds, eleven patients chose propranolol, eight atenolol and two could not distinguish between them.

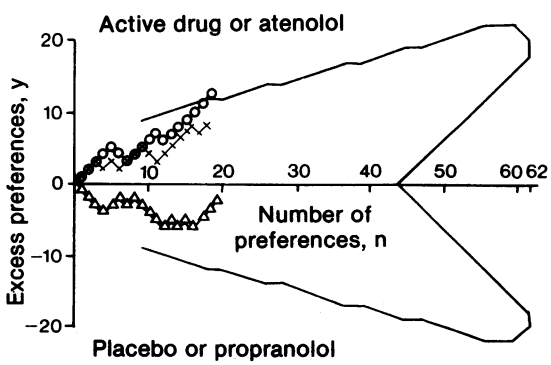

Figure 1 Comparison of atenolol (×), propranolol (○) and placebo in patients with hyperthyroidism—subjective assessment. (△) Atenolol *v* propranolol. The criteria for design of analysis were $\theta_1 = 0.75$; $2\alpha = \beta = 0.05$ (Armitage, 1960).

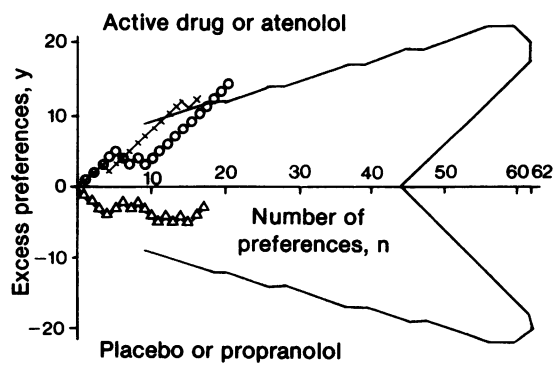

Figure 2 Comparison of atenolol (×), propranolol (○) and placebo in patients with hyperthyroidism—objective assessment without heart rate. (△) Atenolol *v* propranolol. The criteria for the design of the analysis were $\theta_1 = 0.75$, $2\alpha = \beta = 0.05$ (Armitage, 1960).

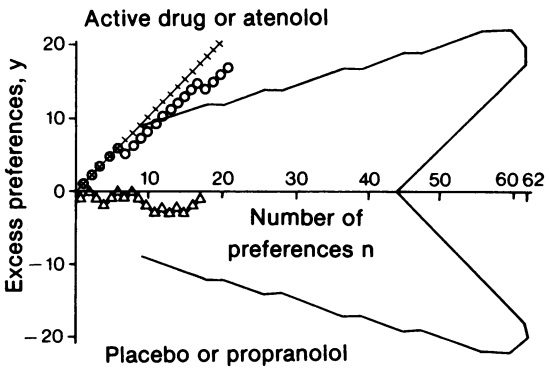

Figure 3 Comparison of atenolol (×), propranolol (○) and placebo in patients with hyperthyroidism—objective assessment including heart rate. (△) Atenolol *v* propranolol. The criteria for the design of the analysis were $\theta_1 = 0.75$; $2\alpha = \beta = 0.05$ (Armitage, 1960).

Objective assessment without heart rate (Figure 2)

Both atenolol and propranolol were adjudged significantly better than placebo before effect on heart rate was known, the former after 16 patients and the latter after nineteen patients had been studied. No significant differences could be determined between atenolol and propranolol: the observer preferred atenolol in seven patients, propranolol in ten patients and could not separate their effects in four patients.

Objective assessment including heart rate (Figure 3)

Again the trial reached a significant level in favour of both atenolol and propranolol when compared with placebo, after ten and twelve patients respectively. Differentiation between the two active drugs was again impossible: atenolol was preferred in eight patients, propranolol in nine and in four no separation could be made.

Analysis of the effects of treatment on individual symptoms and signs is shown in Table 2. Active treatment was significantly more effective than placebo in improving fine tremor, hyperkinetic movement and moist hands: in the latter case, this was confined to propranolol only.

The overall preferences for the three treatments selected by both the patients and the obscrver are shown in Table 3. It can be seen that both types of assessment could distinguish clearly between active and inactive treatments, but that distinction between the two active treatments could not be made even with effects on heart rate included.

The mean heart rate after placebo was not significantly less than the initial baseline reading (Table 4). However, both atenolol and propranolol reduced heart rate significantly compared to placebo. Compared to placebo, atenolol reduced mean heart rate by 29.8% and propranolol by 27.1%: again the difference between the two active compounds was insignificant.

Twenty-one of the twenty-two patients complained of side-effects during at least one of the treatment periods. These are shown in Table 5. They were distributed fairly evenly between the three treatment types and neither active drug appeared to have any particular adverse effects.

Discussion

Using a similar experimental design, it has been shown previously that propranolol (Shanks *et al.*, 1969; Nelson & McDevitt, 1975) and practolol (Nelson & McDevitt, 1975) are effective in controlling the peripheral manifestations of hyperthyroidism. This present study confirms the efficacy of propranolol and indicates that atenolol, a cardioselective β-

Table 2 Incidence of symptoms and signs in twenty-two patients with hyperthyroidism

Assessment	*At onset*	*Improved after propranolol*	*Improved after atenolol*	*Improved after placebo*	*Difference (χ^2 test)*
Symptoms					
Palpitations	15	10	8	5	NS
Preference for cold	12	2	0	3	NS
Excessive sweating	12	7	4	3	NS
Nervousness	19	9	7	3	NS
Signs					
Lid-lag	11	6	6	3	NS
Lid-retraction	11	2	6	3	NS
Fine tremor	20	18	11	3	$P<0.001$
Hyperkinetic movement	17	12	10	4	$P<0.02$
Warm hands and fine skin	21	7	7	7	NS
Moist hands	20	18	10	7	$P<0.02$

Table 3 Overall preferences for individual treatments in twenty-one patients

Preference	*Atenolol*	*Treatment* *Propranolol*	*Placebo*
Subjective (Patients')*	6	9	2
Objective without heart rate†	6	10	1
Objective including heart rate‡	8	9	0

*No overall preference in three patients: one subject could not choose between atenolol and propranolol.
†No overall preference in two patients: observer could not choose between atenolol and propranolol in two subjects.
‡Observer could not choose between atenolol and propranolol in four subjects.

Table 4 Effect of the treatments on heart rate in twenty-one patients

Treatment	*Baseline*	*Placebo*	*Atenolol*	*Propranolol*
Heart rate (beats/min)	113.3	108.8	76.4	79.3
s.e. mean	3.4	3.8	3.7	4.0
% reduction	—	0	29.8	27.1

	t	P
Baseline *v* Placebo	1.941	>0.05
Atenolol *v* Placebo	—8.993	<0.0001
Propranolol *v* Placebo	—7.339	<0.0001
Atenolol *v* Propranolol	—0.857	>0.4

Table 5 Side effects experienced by twenty-two patients

	Atenolol	*Propranolol*	*Placebo*
Number of patients complaining of side effects	12	11	9
Side effects			
Headache	1	2	3
Tiredness	1	1	0
Dizziness	0	2	1
Insomnia	1	1	0
Drowsiness	1	1	1
Mouth dry	1	1	0
Sore throat	2	1	1
Nausea	3	2	1
Dyspepsia	1	1	0
Breathlessness	1	0	0
Pruritus	2	1	1
Skin rash	0	0	2
Eye symptoms	0	1	1
Leg cramps	0	0	1
Total side effects/drug	14	14	12

adrenoceptor antagonist, also ameliorates the symptoms and signs of hyperthyroidism.

Comparison of the effects of atenolol and propranolol revealed few differences between them. When the study was discontinued, propranolol had reached a level of significant preference over placebo by subjective assessment, which atenolol had not, but overall patients did not distinguish between the two active treatments. On objective assessment, atenolol was adjudged significantly better than placebo more rapidly than propranolol. Their mean effect on heart rate was almost identical, but propranolol may have improved the symptoms of excessive sweating, fine tremor and moist hands more often than atenolol—in

only the latter case was this difference significant. In response to a general enquiry as to whether they had improved with treatment, sixteen of the twenty-one patients said they had after taking propranolol, fifteen after atenolol and only seven after placebo.

There seems little doubt then that atenolol will be effective in controlling the peripheral manifestations of hyperthyroidism and, if other aspects of the patient's clinical condition suggest that a cardioselective β-adrenoceptor antagonist is desirable, it should be used in preference to propranolol.

It is interesting that a cardioselective drug is as effective as a non-selective one, although this confirms the previous findings with practolol (Nelson & McDevitt, 1975; Murchison *et al.*, 1976). There was some suggestion that sweating, fine tremor and hand signs were less well controlled, but without more evidence it would be wrong to ascribe this to selectivity.

We are grateful to Dr W.O. Simpson, Pharmaceuticals Division, Imperial Chemical Industries Ltd, for the supply of propranolol, atenolol and placebo tablets.

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(Received August 22, 1977)