COMPARATIVE TRIAL OF PROPRANOLOL AND PRACTOLOL IN HYPERTHYROIDISM

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- 1 The possible role of practolol in the management of hyperthyroidism has been studied by comparing it with propranolol.
- 2 In a double-blind cross-over trial, propranolol (40 mg), practolol (120 mg) and a placebo four times daily for one week were compared in twenty-one hyperthyroid patients by sequential analysis.
- 3 Judged by their effect on the symptoms and signs of thyrotoxicosis, both propranolol and practolol were significantly better than the placebo but no clear distinction could be made between the two active compounds.
- 4 Propranolol and practolol reduced heart rate by 24 and 17% respectively compared with placebo.
- 5 Patients generally preferred propranolol or practolol to placebo but this preference did not achieve significance with either drug.
- 6 Only in its effect on heart rate was practolol significantly inferior to propranolol, and it would appear to be a useful alternative to propranolol in the management of the peripheral manifestations of hyperthyroidism.

Introduction

On the basis of their apparently different effect on resting heart rate in patients with hyperthyroidism, distinction has been drawn between β -adrenoceptor blocking drugs without intrinsic sympathomimetic activity (propranolol, sotalol and Ro-3-3528) and those possessing such activity (alprenolol, oxprenolol, pindolol and practolol) (Turner, 1974). Drugs of the former group produce significant dose-dependent slowing of resting heart rate in such patients, whereas those of the latter group do not. The lesser effectiveness of the second group has been attributed to their intrinsic sympathomimetic activity and to the increased sensitivity to adrenergic receptor stimulation said to occur in hyperthyroidism (Turner & Hill, 1968) and it has been concluded that only those β -adrenergic receptor blocking drugs without intrinsic sympathomimetic activity are predictably effective in hyperthyroidism (Turner, 1974).

Recently, however, Carruthers, Ghosal, McDevitt, Nelson & Shanks (1974) demonstrated that practolol did have a dose-dependent effect in hyperthyroid patients on the tachycardia induced

by severe exercise, an accepted method for demonstrating the effectiveness of β -adrenoceptor blocking drugs (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; Coltart & Shand, 1970). In addition, practolol had a proportionately larger effect on exercise tachycardia than it had on resting heart rate. It was concluded that, although not as effective as propranolol, this drug might nevertheless have a potentially useful role in certain hyperthyroid patients unable to take propranolol.

We now report the results of a double-blind trial comparing propranolol and practolol in patients with hyperthyroidism.

Methods

Twenty-four outpatients (20 females and 4 males) with hyperthyroidism entered the trial after informed consent in the order they presented at the clinic. All were hyperthyroid according to standard clinical and biochemical criteria. One further patient was withdrawn as she was shown

later not to be hyperthyroid. The initial biochemical and clinical findings are shown in Tables 1 and 2. Treatment continued for a period of three weeks during which time identical tablets containing propranolol (40 mg), practolol (120 mg) or placebo were given orally four times daily for one week in randomized order. Tablets were supplied for one 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 (J.K.N.) for selected criteria before entering the trial, and at the end of each treatment week. On these occasions they were asked only if their symptoms (Table 2) were increased, decreased or unchanged during the previous week. Objective assessment of seven features of hyperthyroidism (Table 2) was then made according to an arbitrary scoring technique using 0, +, and ++ 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 the 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 access to information about heart rate. 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 (propranolol and placebo, practolol and placebo, and propranolol and practolol) and these were submitted to sequential analysis using the method described by Armitage (1960).

Results

Twenty-two patients completed the trial. One of these was excluded from the subsequent analysis because the tablet count suggested that she had not been compliant during one of the treatment

Table 1 Observations on twenty-four patients with hyperthyroidism (Mean $\pm$ s.e. mean)

Sex	Age (years)	Heart rate (beats/min)	P.B.I. * (μ g/ml)	Se thyroxinet (thyopac-4) (μ g/100 ml)	F.T.I. ‡
4M, 20F	40.7 $\pm$ 2.7	110.4 $\pm$ 3.3	12.0 $\pm$ 0.5	15.4 $\pm$ 0.7	19.0 $\pm$ 1.2

* Normal range 3.7-7.4 μ g/100 ml.

† Normal range 4.3-12.1 μ g/100 ml.

‡ Normal range 4.0-11.2 (Free thyroxine index = 'Thyopac 4'/'Thyopac 3')

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

Assessment	At onset	Improved after propranolol	Improved after practolol	Improved after placebo
Symptoms				
Palpitations	17	8	11	6
Preference for cold	11	1	3	0
Excessive sweating	17	6	6	3
Nervousness	20	12	10	4
Signs				
Widened palpebral fissure	14	4	4	2
Lid-lag	5	3	3	3
Lid-retraction	7	5	5	5
Fine tremor	18	14	9	6
Hyperkinetic movement	17	14	14	12
Warm hands and fine skin	19	9	10	5
Moist hands	18	10	11	4

Figure 1 Comparison of propranolol (○), practolol (△) and placebo in patients with hyperthyroidism — Subjective assessment.

The criteria for the design of analysis were $\theta_1 = 0.75$; $2\alpha = \beta = 0.05$ (Armitage, 1960). ▲ propranolol v. practolol.

Figure 2 Comparison of propranolol (○), practolol (△) and placebo in patients with hyperthyroidism — Objective assessment without heart rate.

The criteria for the design of analysis were $\theta_1 = 0.75$; $2\alpha = \beta = 0.05$ (Armitage, 1960). ▲ propranolol v. practolol.

weeks. Two further patients stopped taking their tablets because of side-effects and were omitted. The results of the sequential analyses for the subjective, objective without heart rate and objective including heart rate assessments for propranolol, practolol and placebo are shown in Figures 1-3 and Table 2.

Subjective assessment

Sixteen patients preferred propranolol to placebo, whereas 14 patients chose practolol in preference to placebo (Figure 1). In neither case was a significant level reached in favour of the active compound before the trial was discontinued. However, patients were almost equally divided in their choice between propranolol and practolol, nine choosing propranolol and ten practolol with two patients unable to distinguish between them.

Objective assessment without heart rate

Figure 2 shows that the trial reached a significant level in favour of both propranolol and practolol when compared with placebo, the former after 13 patients and the latter after 21 patients had taken part. No significant differences could be determined between propranolol and practolol. The observer preferred propranolol in 10 patients, practolol in nine and could not separate the effects in two.

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

Objective assessment including heart rate

Both propranolol and practolol were adjudged significantly better than placebo after 13 patients when heart rate response was included in the analysis (Figure 3). Comparing treatment between propranolol and practolol, the former drug was preferred in 15 patients but a significant difference was not shown in the 21 patients studied.

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

<i>Preference type</i>	<i>Propranolol</i>	<i>Treatment Practolol</i>	<i>Placebo</i>
Subjective (Patients')*	8	10	2
Objective without heart rate†	10	8	1
Objective including heart rate	13	8	0

* No overall preference in one patient

† No overall preference in one patient: observer could not choose between propranolol and practolol in another.

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

<i>Treatment</i>	<i>Baseline</i>	<i>Placebo*</i>	<i>Propranolol†</i>	<i>Practolol‡§</i>
Heart rate (beats/min)	110.4	103.8	78.9	86.2
s.e. mean	3.3	3.2	2.4	3.0
% reduction	—	0	24.0	17.0

	<i>t</i>	<i>P</i>
* Baseline v Placebo	2.3953	<0.05
† Placebo v Propranolol	8.7947	<0.00001
‡ Placebo v Practolol	6.1236	<0.00001
§ Propranolol v Practolol	-2.7068	<0.02

Table 5 Side-effects experienced by twenty-four patients

	<i>Propranolol</i>	<i>Practolol</i>	<i>Placebo</i>
Number of patients complaining of side-effects	10*	7	7
<i>Side effects</i>			
Headache	1	2	1
Tiredness	3	1	3
Dizziness	2	1	1
Insomnia	1	2	0
Drowsiness	0	0	1
Dreams	0	0	1
Mouth and tongue dry	1	0	0
Nausea	3	2	0
Vomiting	1	0	0
Heartburn	2	0	1
Constipation	0	1	0
Total side effects/drug	14	9	8

* Two patients discontinued propranolol because of side-effects.

The overall preferences for the three treatments selected by both the patients and the observer are shown in Table 3. Until effect of treatment on heart rate was taken into account, the patients and the observer chose propranolol or practolol an almost equal number of times. With information about heart rate included, the observer chose propranolol as most effective in thirteen patients and practolol in the remaining eight patients. Only two patients preferred placebo tablets to both of the active compounds, and the placebo was only chosen once by the observer before the heart rate was known.

The mean heart rate after placebo was slightly less than the mean baseline heart rate and the difference was significant ($P < 0.05$) (Table 4). However, the patients has considerably lower heart rates when taking both propranolol ($P < 0.00001$) and practolol ($P < 0.00001$) than when on placebo. Compared with placebo, propranolol and practolol reduced mean heart rate by 24.0 and 17.0% respectively. The effect of propranolol was significantly better than that of practolol ($P < 0.02$) but in five patients practolol reduced tachycardia more than propranolol.

Two patients stopped taking their treatment because of side-effects. Both were taking propranolol – one complained of dizziness, nausea and vomiting and the other of severe heartburn and flatulence. Altogether some fifteen patients complained of side-effects, three of them with each treatment type. These are shown in Table 5. Their distribution did not appear to differ markedly between propranolol, practolol and placebo.

Discussion

It has been shown previously that propranolol (40 mg four times daily orally) is effective in blocking the peripheral manifestations of hyperthyroidism (Shanks, Hadden, Lowe, McDevitt & Montgomery, 1969). The results of this present study confirm the effectiveness of propranolol in this situation and indicate that practolol (120 mg four times daily orally) also ameliorates the symptoms and signs of thyrotoxicosis. Practolol was adjudged to have almost equal effect to propranolol on the individual parameters measured and therefore it was not surprising that both the patients and the observer did not distinguish clearly between the two active drugs while preferring both to the placebo in most instances. Both propranolol and practolol reduced the heart rate significantly more than did placebo, by 24.0 and 17.0% respectively, and this latter difference probably accounts for

the overall preference for propranolol over practolol of 3:2.

Practolol (400 mg orally) has been shown to be the minimum dose required to produce near maximum reduction of exercise tachycardia throughout a 24 h period, and in addition, there is little inter-individual variation in the blood practolol levels produced in normal subjects by this dose (Carruthers, Kelly, McDevitt & Shanks, 1974). However, with propranolol there may be up to twenty-fold variation in plasma concentration in patients receiving the same oral dose and 160 mg daily may not produce maximum blockade (Shand, 1974). Hence, if individual dose ranging was carried out in each hyperthyroid patient with both drugs for maximum effect, the difference between the efficacy of propranolol and practolol might be greater than that found in the present study with fixed doses.

Previous reports of clinical studies in hyperthyroidism with β -adrenoceptor blocking drugs with intrinsic sympathomimetic activity have given variable results. Epstein & Pimstone (1971a) considered practolol to be as effective as propranolol in treating fifteen thyrotoxic patients in a single-blind study but details of dosage and methodology are not recorded; in addition, they described the successful use of practolol in hyperthyroid heart failure (Epstein & Pimstone, 1971b). Recently in eleven patients, using a modified Wayne Therapeutic Index, practolol (200 mg, 12 hourly) was thought to produce some improvement, though significantly less than propranolol (40 mg, 6 hourly). However, no placebo treatment was used and practolol only reduced the pre-treatment pulse rate by 6% in comparison with 20% reduction by propranolol (Distiller, Joffe & Seftel, 1973). Pindolol has also been reported to produce subjective improvement in about half of a group of hyperthyroid subjects given 15 or 30 mg in an uncontrolled study for one week; it also reduced heart rate significantly (Schelling, Scazziga, Dufour, Millinkovic & Weber, 1973). In contrast, only five out of sixteen thyrotoxic patients chose oxprenolol (40 mg, 8 hourly) in preference to identical placebo tablets after one week's treatment with each and the doctors preferred the active compound only four times (Gibberd & Staffurth, 1973). Again, the mean pulse rate was only 8% lower on oxprenolol than on placebo.

In an acute study in five hyperthyroid patients, intravenous propranolol (0.2 mg/kg) and practolol (0.4 mg/kg) produced reductions of resting heart rate (14.4 and 7.2% respectively) and of exercise heart rate (25.1 and 18.1% respectively) (Carruthers *et al.*, 1974). The effectiveness of practolol compared to propranolol was only 50%

in reducing resting heart rate, but was 72% in reducing exercise heart rate. In this present study, propranolol and practolol reduced mean heart rate by 24.0 and 17.0% respectively, and practolol had 71% of the effectiveness of propranolol after one week's therapy. Although the relative doses of the two drugs were different in the two studies, the effects of practolol on heart rate after chronic administration appear to be reflected better by its acute effects on exercise heart rate than on resting heart rate.

It has been suggested that β -adrenoceptor blocking drugs with intrinsic sympathomimetic activity may be harmful in patients with thyrotoxicosis (Turner & Hill, 1968) because of potential interaction between this activity and increased sensitivity to catecholamines. However, no serious adverse reactions were reported by patients taking practolol in this study and no patient stopped taking practolol because of side-effects. No substantial differences in side-effects between the three treatments were seen except for two patients who discontinued

propranolol because of predominantly gastrointestinal symptoms.

In view of its cardiospecificity compared to propranolol, the results of this trial relating to practolol are surprising but they would indicate that practolol is an effective drug for blocking the peripheral manifestations of thyrotoxicosis. Its relative inferiority to propranolol is less than might have been anticipated and, in fact, this was not shown to be significant apart from effect on heart rate. It is concluded that practolol, and perhaps other β -adrenoceptor blocking drugs with intrinsic sympathomimetic activity, may be usefully employed in thyrotoxicosis in patients in whom the administration of propranolol is contraindicated.

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