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The comparative effects of ICI 118551 and propranolol on essential tremor

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1 The effects of the selective β_2-adrenoceptor antagonist ICI 118551 on essential tremor, heart rate and blood pressure were compared with those of propranolol.
2 ICI 118551 (150 mg daily for 7 days) and propranolol (120 mg daily for 7 days) were about equally effective in reducing essential tremor (by about 40%) and were more effective than placebo.
3 When compared with the effect of placebo, propranolol reduced blood pressure and exercise heart rate whereas ICI 118551 had no significant effect on blood pressure and produced a small but significant reduction in exercise-induced tachycardia.
4 ICI 118551 may be useful in the management of essential tremor while having fewer cardiovascular side-effects than non-selective β-adrenoceptor antagonists.

Keywords β-adrenoceptor antagonism essential tremor

Introduction

Several studies have shown that propranolol reduces the amplitude of essential tremor (Gilligan *et al.*, 1972; Winkler & Young, 1974; Jefferson *et al.*, 1979; Calzetti *et al.*, 1981, 1982). There is evidence that the effect on tremor is mediated in part by mechanisms involving β_2-adrenoceptors (Marsden *et al.*, 1967; Dietrichson & Espen, 1981; Leigh *et al.*, 1983; Findley & Cleeves, 1984). Since the effects of non-selective β-adrenoceptor antagonists cannot be confined to those which are beneficial for tremor, some unwanted effects may arise such as bradycardia, hypotension and reduced exercise tolerance (Twentyman *et al.*, 1981; Patrick *et al.*, 1985). Drugs with a more selective action on β_2-adrenoceptors may avoid some of the cardiovascular effects.

The adrenoceptor antagonist ICI 118551 has been shown to be relatively selective for β_2-adrenoceptors on isolated tissues and in animals (Bilski *et al.*, 1980; O'Donnell & Wastell, 1980; Cheah *et al.*, 1982). In man, ICI 118551 blocked isoprenaline-induced changes in forearm blood flow, diastolic blood pressure and tremor but had little effect on exercise heart rate (Harry *et al.*, 1982; Arnold *et al.*, 1985). ICI 118551 was also shown to be selective for airway β_2-adrenoceptors in healthy volunteers (Tattersfield & Cragg, 1983).

We have now compared the effects of ICI 118551 and propranolol on tremor, heart rate and blood pressure in patients with essential tremor.

Methods

Subjects

Ten adult male patients (age range 22–62 years, mean 40.7 years; all right handed) with essential tremor who were attending the outpatient clinic at the Derbyshire Royal Infirmary or University Hospital, Nottingham participated in the study

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after giving informed written consent. The protocol was approved by the Hospital Ethics Committees. The diagnosis was established on the basis of clinical history and general and neurological examination. The duration of symptoms ranged from 3 years to 29 years (mean 13 years). All the patients complained of tremor in one or both hands, and in six patients jaw or head tremor was sometimes present. When measured, five of the 10 patients had a more severe tremor in the left hand and five in the right hand. No patient was on β-adrenoceptor blockers or any other therapy at the start of the trial. Other patients with a history or evidence on examination of chronic obstructive airways disease, asthma or peripheral vascular disease were excluded.

Protocol and drugs

Drugs were administered in a double-blind cross-over manner. ICI 118551 was presented as a syrup and propranolol in tablet form. Identical tablets containing either 40 mg propranolol or placebo plus identical bottles of syrup (10 ml) containing either 50 mg ICI 118551 or placebo were administered. Patients took orally one tablet and 10 ml of syrup three times daily for 1 week.

All subjects underwent the series of 1 week periods of treatment with placebo, propranolol or ICI 118551 in an order which was randomised. A washout period of 7 days elapsed between each treatment period during which time patients took placebo tablets and syrup. On the first day of each treatment week baseline measurements of ventilatory capacity, heart rate, blood pressure (supine and standing) and tremor were made. After an exercise test had been performed treatment was begun. Subjects returned 7 days later (during which interval they had taken a treatment three times a day) and all the tests were repeated at the same time of day; the sequence of measurements was begun 90 min after the dose of treament.

Measurements

Ventilatory capacity FVC and FEV_1 were measured from the best of at least three forced expirations using a Vitalograph dry spirometer. $FEV_1 \times 100/FVC$, (FEV%), was used as an index of airway calibre.

Blood pressure Systolic and diastolic arterial blood pressures were measured with a standard sphygmomanometer after lying down for 5 min (mean of two readings) and again after 2 min standing (mean of two readings).

Tremor recording Measurements of middle finger tremor of both hands were made using a small accelerometer (Bruel and Kjaer type 4367, mass 13 g) affixed by means of a 'Perspex' ring to the terminal phalanx of the middle finger as described by Birmingham *et al.* (1977). All measurements were made with the subject seated comfortably in a quiet room. Recordings were made with (i) the forearm supported to the wrist and the hand relaxed ('rest' tremor), (ii) with the arm and hand outstretched forwards from the shoulder ('postural' tremor) and (iii) with the forearm supported and the hand extended over the front edge of the chair arm ('modified postural' tremor). Measurements in each posture were made for 1 min on each hand. The output from the accelerometer was recorded, for subsequent analysis, on one channel of an FM tape-recorder (Racal Store 4) via a charge amplifier (Bruel and Kjaer, type 2635).

Tremor analysis The tremor waveform, filtered to remove frequencies above 50 Hz to prevent aliasing, was analysed with a Hewlett Packard spectrum analyser (HP 3582A) and desk-top computer (HP 9825A). Five-second samples were subjected to Fourier analysis and eight sequential samples from each 1 min record were averaged to yield a mean frequency spectrum covering the range 0.4 to 51.2 Hz in 0.2 Hz intervals. From this analysis the root mean square (rms) of tremor amplitude was also calculated. The frequency of the dominant peak of each spectrum was determined using a smoothing and peak searching technique (Birmingham *et al.*, 1985).

Exercise heart rate Subjects were exercised on a Marquette treadmill using the Bruce continuous progressive test (Bruce, 1974). Three subjects started at stage 2 of the Bruce protocol because they were younger and fitter. The test was terminated at the end of the stage which on day 1 had elicited a heart rate of at least 150 beats min^{-1}. The ECG using 12 lead electrodes was recorded continuously onto a pen recorder. The R waves were counted over the final 30 s at each stage of the Bruce protocol to provide a measure of heart rate.

Statistical analysis Statistical analysis was by two way analysis of variance with treatment and patient as the factors. Where F tests revealed significant differences between treatments, differences were identified by t-tests on the contrast in the group means. Tremor amplitude values were log-transformed before the statistical analysis to improve the normality of the distribution (Abila *et al.*, 1985).

Results

Cardiorespiratory variables

Table 1 shows the mean changes from pretreatment values in blood pressure after 7 days' treatment with placebo, propranolol or ICI 118551 while in the supine position and while standing. Apart from a small reduction in standing diastolic blood pressure ($P < 0.05$), placebo had no significant effect on blood pressure. Propranolol significantly reduced systolic blood pressure in both postures ($P < 0.01$) and diastolic blood pressure while standing ($P < 0.01$). No significant changes in blood pressure were seen after 7 days' treatment with ICI 118551.

The mean (+1 s.e. mean) heart rates before (resting) and during the third stage of the treadmill exercise after 7 days' treatment with ICI 118551, propranolol or placebo are shown in Table 2. Treatment with propranolol significantly reduced resting heart rate ($P < 0.05$) and exercise heart rate ($P < 0.001$) when compared with placebo. The effect of treatment with ICI 118551 on resting heart rate was not significantly different from that of placebo. Exercise heart rate after treatment with ICI 118551 was slightly lower than after treatment with placebo ($P < 0.05$).

For FEV% the mean differences from placebo after 7 days' treatment both before and 3 min after the exercise test were small but significant ($P < 0.05$) for propranolol treatment (-2.4 ± 0.9 before, -4.6 ± 1.6 after) but not significant for ICI 118551 treatment (-0.51 ± 1.6 before, -2.2 ± 2.5 after).

Tremor variables

Figure 1 shows the mean reductions in rms acceleration (with s.e. mean) for the additional effects of 7 days' treatment with ICI 118551 or propranolol compared with placebo. Tremor was lower while taking the β-adrenoceptor blockers than when taking placebo in all measurement postures and for both hands, but analysis of variance showed that treatment effects were significant only for rest and postural tremor of the right hand (rest tremor $F = 6.45$, $P < 0.01$; postural tremor $F = 5.16$; $P < 0.05$).

In our group of 10 patients, five had a more severe tremor in the left hand and five in the right hand. This made it more appropriate to look at the effect of the drugs on the most severely affected hand only. Figure 2 shows the mean difference (with s.e. mean) between 7 days' treatment with placebo and treatment with the β-adrenoceptor blockers for tremor of the most severely affected hand measured in the three different postures. A two way analysis of variance of the log transformed data gave F values for treatment effect of 1.29 for rest tremor, 4.74 ($P < 0.05$) for postural tremor and 6.21 ($P < 0.01$) for modified postural tremor. Paired comparisons showed that both propranolol and ICI 118551 reduced modified postural tremor ($P < 0.05$) and propranolol also had a small but significant effect on postural tremor ($P < 0.5$).

Table 3 shows the mean percentage reductions in tremor of the most severely affected

Table 1 Mean changes (with s.e. mean) in blood pressure (mm Hg) after 7 days' treatment with ICI 118551, propranolol or placebo

	ICI 118551		*Propranolol*		*Placebo*	
	Supine	*Standing*	*Supine*	*Standing*	*Supine*	*Standing*
Systolic	-2.3	2.9	-11.0**	-17.6**	-6.2	-4.7
s.e. mean	2.1	3.6	2.0	3.4	4.4	3.1
Diastolic	4.1	-1.3	-8.0	-9.8**	-2.4	-6.0*
s.e. mean	2.1	2.9	4.0	2.9	1.7	2.3

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; before treatment compared with seventh day.

Table 2 Mean heart rates (with s.e. mean) before (resting) and during the third stage of the exercise test, on the seventh day of treatment with ICI 118551, propranolol or placebo

	ICI 118551	*Propranolol*	*Placebo*
Resting	61.0 ± 10.5	*56.1 ± 10.9	62.6 ± 9.6
During third stage	*125.1 ± 12.5	***109.4 ± 12.8	134.8 ± 11.4

*$P < 0.05$, ***$P < 0.001$, compared with placebo, paired t-tests.

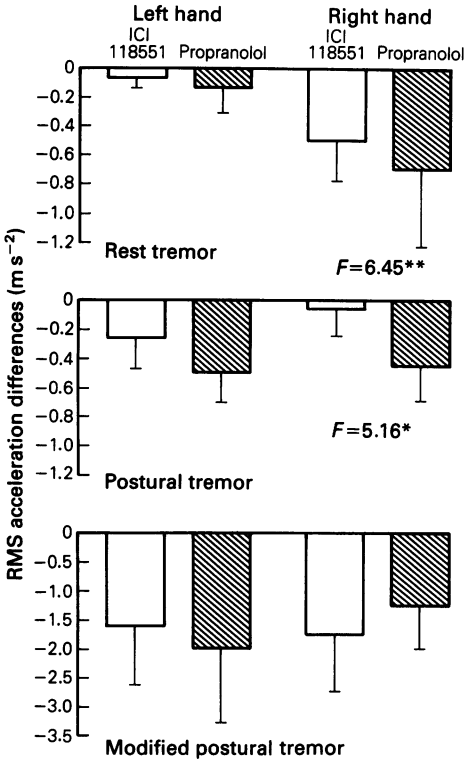

Figure 1 The difference between the effect on tremor of 7 days' treatment with placebo, ICI 118551 or propranolol expressed as the mean (−1 s.e. mean) rms acceleration differences from placebo for rest, postural and modified postural tremor for left and right hands. (*F* values derived from analysis of variance of log transformed data, $*P < 0.05$, $**P < 0.01$.)

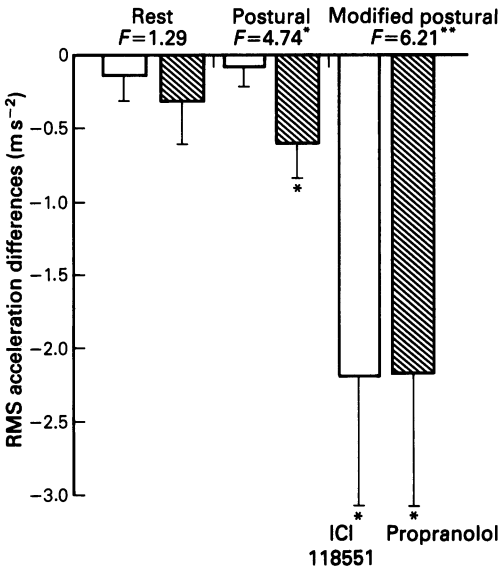

Figure 2 The difference between the effect on tremor of the most severely affected hand of 7 days' treatment with placebo, ICI 118551 or propranolol expressed as the mean rms acceleration differences from placebo (−1 s.e. mean) for rest, postural and modified postural tremor. (*F* values for treatment effect derived from analysis of variance of log transformed data, $*P < 0.05$, $**P < 0.01$; individual drug effect compared by *t*-test, $*P < 0.5$.)

hand after each of the three 7 day treatments (ranges shown in brackets). Treatment with either β-adrenoceptor blocker gave mean reductions of about 40% when tremor was measured with the hand outstretched (modified postural tremor). More variable responses were seen when tremor was measured with the hand relaxed (rest tremor) or with the arm outstretched (postural tremor).

No treatment had a significant effect on the frequency of the dominant peak of the tremor spectra.

Discussion

For patients with essential tremor who need treatment, propranolol, a non-selective β-adrenoceptor antagonist, is commonly used. The results of this investigation show that the

Table 3 Mean percentage reductions in tremor of the most severely affected hand after 7 days' treatment (ranges shown in brackets)

	ICI 118551	*Propranolol*	*Placebo*
Rest	−15.8 (+189 to −94)	−0.8 (+231 to −74)	−7.3 (+61 to −75)
Postural	−34.7 (+43 to −93)	−20.7 (+59 to −82)	−15.5 (+74 to −89)
Modified postural	−47.0 (+18 to −95)	−40.1 (+20 to −92)	−6.3 (+97 to −71)

selective β_2-adrenoceptor antagonist ICI 118551 is also effective in reducing tremor. In a comparable study, with the same dose schedule except that the drugs were taken for 2 days rather than for 7 days, Huttenen & Larsen (1984) recorded percentage reductions in hand tremor of 43% ICI 118551, 35% propranolol and 6% placebo, which are similar to those now reported. In the present study, the patients were asked subjectively to rate their tremor at the end of each treatment period and six patients felt that their tremor was most improved during the week when they were taking ICI 118551 compared with three when taking propranolol and two when taking placebo.

β-adrenoceptor blockade gave the largest reductions in tremor when the hand was outstretched and the arm supported (modified postural tremor); the effect on rest and postural tremor was smaller and more variable. It is usual for patients with essential tremor to have one hand more severely affected than the other, in this group five had a more severe tremor in the left hand and five in the right hand. The analysis of tremor amplitude for the more severely affected hand reduced the variation in drug effect seen when left and right hands were considered separately.

The β_2-selectivity of ICI 118551 in doses of 40 or 50 mg has been reported for adrenoceptors associated with tremor and for adrenoceptors in other tissues in man (Arnold *et al.*, 1985; Tattersfield & Cragg, 1983; Huttenen & Larsen, 1984; Fitzgerald *et al.*, 1982). Our results also demonstrate that ICI 118551 is relatively selective for β_2-adrenoceptors in man since at doses having an equivalent effect on tremor, exercise heart rate (an indicator of β_1-adrenoceptor function; McDevitt, 1977) was reduced by a mean of 25.4 beats min^{-1} by propranolol compared with 9.7 beats min^{-1} by ICI 118551. Tattersfield & Cragg (1983) showed that in man a single dose of 50 mg ICI 118551 did cause a significant displacement of the bronchial airway dose-response curve to salbutamol. In the present study although 7 days' treatment with ICI 118551 did not significantly reduce FEV% before or after exercise (and propranolol produced only a small but significant reduction) both drugs reduced tremor of the outstretched hand to a significant extent. James *et al.* (1986) have reported abolition by a single 50 mg dose of ICI 118551 of the increase in tremor induced by public speaking in normal volunteers.

Whether a patient with essential tremor should be treated with a β-adrenoceptor blocker often depends upon weighing the beneficial effects on tremor against the cardiorespiratory side-effects. The well-reported cardiovascular effects of β-adrenoceptor blockers including hypotension, bradycardia and reduced exercise tolerance (Pearson *et al.*, 1979; Twentyman *et al.*, 1981; Patrick *et al.*, 1985) may be unacceptable. However ICI 118551 had no significant effect on supine and standing blood pressures and resting heart rate and a relatively small effect compared with propranolol on exercise tachycardia. For an equivalent effect on tremor the cardiovascular side-effects produced when treating patients with ICI 118551 are likely to be less than with non-selective β-adrenoceptor therapy.

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