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AN ASSESSMENT OF PHYSIOLOGICAL FINGER TREMOR AS AN INDICATOR OF β-ADRENOCEPTOR FUNCTION

J.M.O. ARNOLD & D.G. McDEVITT

Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Northern Ireland

1 Physiological finger tremor has been assessed as an indicator of β-adrenoceptor function.

2 Tremor was not correlated with the sex, age, weight or height of the subjects and was stable over 5 min when the hand and fingers were held horizontally. It was not increased by mental arithmetic, the Valsalva manoeuvre or 3 min exercise.

3 Satisfactory dose-response curves could be constructed for the isoprenaline enhanced increases in finger tremor.

4 In six subjects, practolol 120 mg produced a small shift to the right of the isoprenaline dose-response curve for finger tremor (dose ratio 2.1) but propranolol 40 mg was seven times more effective (dose ratio 17.1).

5 Physiological finger tremor appears to be a stable parameter which may be useful in the investigation of the selectivity of β-adrenoceptor blocking drugs.

Keywords β-adrenoceptor blocking drugs physiological finger tremor propranolol practolol

Introduction

Attempts to assess selective β-adrenoceptor blockade in man (Brick *et al.*, 1968; Briant *et al.*, 1973) have been limited by the methodology employed (McDevitt, 1977). Recently, isoprenaline enhanced physiological finger tremor has been suggested as a possible useful alternative (Perucca *et al.*, 1981; Pickles *et al.*, 1981).

Physiological finger tremor is a fine tremor in the outstretched fingers of normal subjects, with characteristic low amplitude and high frequency, which may be increased by infused catecholamines (Marsden *et al.*, 1967; Thiringer & Svedmyr, 1975). This increase is blocked by a drug with both β_1 and β_2-adrenoceptor blocking properties, but not by a β_1-selective antagonist (Larsson & Svedmyr, 1977; Perucca *et al.*, 1981), suggesting that catecholamines enhance physiological finger tremor through β_2-adrenoceptors.

The present studies assess the effect of some physiological variables on physiological finger tremor and investigate the effect of a non-selective β-adrenoceptor antagonist, propranolol and a β_1-selective antagonist, practolol, on its enhancement by intravenous boluses of isoprenaline.

Methods

Approval was obtained from the University Ethical Committee.

Finger tremor was measured by a piezo-resistive accelerometer (Devices Trem 1), weight 6 g, which was taped to the dorsum of the middle finger of the left hand. All subjects were right handed. The left arm was then comfortably supported from the elbow to the wrist on an adjustable horizontal wooden arm rest so that the pisiform bone was resting on the end of the splint. The output of the accelerometer was displayed directly through a pre-amplifier (Devices 3543) and pen recorder (Devices MX4), then integrated (Lectromed 3630) and displayed on the same recorder. A cut-off filter on the pre-amplifier was used to ignore frequences above 25 Hz. The integrator summated the positive deflections, so that the height of the ramp was proportional to the finger tremor activity over the preceding time interval (usually 10 s). All studies were performed in the morning, following a light breakfast containing no caffeine, and all the subjects were non-smokers. They rested supine, with head and shoulders comfortably supported, in a quiet temperature-controlled room (23–24°C).

Study 1

Sixteen healthy subjects (six male, 10 female; 20.4 ± 0.5 years; 64.1 ± 2.2 kg) were studied. After 30 min supine rest, the left forearm was supported, as described, on the wooden arm rest and the hand and

fingers outstretched in the same horizontal plane, so that the fingers were not touching. Finger tremor was recorded continuously for 5 min and analysed in serial 30 s epochs by analysis of variance.

A further twelve healthy subjects (eight male, four female; 21.3 ± 0.8 years; 64.9 ± 3.0 kg) were studied under the same experimental conditions. Following a 10 min rest after the recording of tremor in the horizontal plane, the left forearm was again supported in the same position on the wooden rest. With hand and fingers at an angle of +45° to the forearm, finger tremor was recorded for a further 5 min. From each recording the tremor activity over the last 30 s of minutes 1, 3 and 5 was calculated and statistically compared by analysis of variance.

Study 2

Eight healthy volunteers (four male, four female; 20.6 ± 0.6 years; 65.5 ± 4.0 kg) were studied under the experimental conditions described above. With the left hand and fingers outstretched horizontally, finger tremor was measured for 1 min before, 3 min during and 1 min after mental arithmetic. Following a 10 min rest, finger tremor was measured for 1 min before, 25 s during and 1 min after the performance of a Valsalva manoeuvre. Statistical comparisons were made by Student's *t*-test for paired data.

After a further 15 min rest, the subjects received graded intravenous bolus injections of isoprenaline sulphate by the method of Cleaveland *et al.* (1972), through an intravenous line (Butterfly 19G) previously inserted into a major vein in the right forearm. The isoprenaline had been freshly prepared in saline 0.9% with sodium metabisulphite 0.1% as preservative. All the subjects were familiar with the subjective effects of intravenous isoprenaline. Heart rate was monitored continuously from chest leads through an instantaneous ratemeter (Devices 3750) and displayed by a pen recorder (Devices MX4). Changes in heart rate were, however, measured from limb lead II of an electrocardiograph (Minigraph; Cardiac Recorders Ltd.) as the shortest three consecutive R-R intervals. This was recorded during a 45 s control period before each isoprenaline bolus, and then for a further 45 s commencing 30 s after the bolus injection. Isoprenaline was administered to produce a maximum heart rate of not more than 40 beats/min. Finger tremor was measured during a 1 min control period. The hand was then allowed to rest for 1 min, the recording position re-assumed, and a continuous recording of finger tremor monitored during the injection of isoprenaline and for approximately the five minutes following. The increase in finger tremor was expressed as the percentage increase with isoprenaline, compared to control (100 × finger tremor during maximum 30 s/finger tremor during last 30 s of control period). At least four doses of isoprenaline were administered and dose-response curves were constructed for the increases in heart rate and finger tremor. From the respective regression equations, the dose of isoprenaline required to increase heart rate by 25 beats/min (I_{25}) and finger tremor by 150% (IT_{150}) were calculated. A placebo injection (0.5 ml saline, 0.9% with sodium metabisulphite 0.1%) was given blind to the subject during construction of the isoprenaline dose-response curves, and the changes in heart rate and finger tremor measured.

At least 30 min after the last dose of isoprenaline, and when finger tremor had returned to baseline, a 3 min exercise step test was performed (45 cm step at 32 steps/min). Before exercise, control finger tremor was recorded for 1 min, with the subject seated, but with the left forearm comfortably supported to the wrist on a wooden rest, and the hand and fingers outstretched in the same horizontal plane. During the last 30 s of exercise, maximum heart rate was measured from chest leads and the instantaneous ratemeter. Finger tremor was then recorded, in the same seated position, during the first 30 s immediately after cessation of exercise. Student's *t*-test for paired data was used to compare finger tremor after exercise with the last 30 s of the control period.

Study 3

Six healthy volunteers (five male, one female; 19.7 ± 0.4 years; 65.2 ± 4.2 kg) were studied on three mornings at approximately weekly intervals. Each received single blind, in a random order, a matching tablet of either placebo (PLAC), practolol 120 mg (PRACT) or propranolol 40 mg (PROP). Ninety minutes later, an intravenous line (Butterfly 19G) was inserted in the right antecubital fossa, the accelerometer placed on the middle finger of the left hand, chest and limb electrocardiograph leads attached, and a respiration transducer (Lectromed 4320) placed around the chest. After 30 min rest in the supine position with head and shoulders supported, graded bolus injections of isoprenaline sulphate were given (Cleveland *et al.*, 1972) and the changes in heart rate and finger tremor measured, as described in Study 2. Approximately four points were obtained on the dose-response curves for heart rate and finger tremor. From the regression equations the slopes were recorded, the I_{25} and IT_{150} calculated and statistical comparisons made by analysis of variance of the log transformed data. Plasma drug levels were measured before and after construction of the dose-response curves.

Results are expressed as mean ± s.e. mean.

Results

Study 1

In sixteen healthy patients, with hand held hori-

zontal, there was no significant change in finger tremor over 5 min. This was confirmed in a further twelve subjects in whom tremor was measured with hand held horizontal and at +45° (Table 1). However, finger tremor was significantly greater when the hand and fingers were held at +45° than at horizontal ($P < 0.001$), and at +45° tremor increased progressively so that at 5 min it was significantly greater than at 1 min ($P < 0.01$).

In the total 28 subjects, finger tremor showed significant interindividual differences ($P < 0.01$), but was not significantly different between the sexes (14 male, 14 female). Neither was it correlated with the age (range 18–27 years), height (range 157–187 cm) or weight (range 51–83 kg) of the subjects.

Table 1 Finger tremor measured over last 30 s of minute 1, 3 and 5, with hand held horizontal or at +45°. Measurements are integrator ramp height in mm. Mean of 12 subjects ± s.e. mean

	1 min	*3 min*	*5 min*
Horizontal	20.4 ± 5.0	17.0 ± 4.4	18.4 ± 5.4
+45°	37.3 ± 7.5*	43.5 ± 9.6*	46.8 ± 9.3*†

* $P < 0.001$ when compared to horizontal at corresponding times

† $P < 0.01$ when compared to +45° at 1 min.

Study 2

Finger tremor was significantly reduced from control throughout a 3 min period of mental arithmetic (control 35.4 ± 9.8 mm; arithmetic 27.0 ± 10.4 mm; $P < 0.01$) during which heart rate rose by 15.7 ± 3.7 beats/min. During the Valsalva manoeuvre, finger tremor was significantly decreased with a minimum activity over a 10 s period of 6.1 ± 2.2 mm compared to 9.0 ± 2.3 mm during an average control 10 s period ($P < 0.05$). The finger tremor during the first full 30 s after the manoeuvre tended to be increased (40.0 ± 11.1 mm) but was not significantly different from the control 30 s (26.9 ± 6.9 mm). The 3 min exercise step test increased heart rate to 175 ± 10 beats/min but did not significantly alter finger tremor (control 38.5 ± 8.5 mm; exercise 43.3 ± 6.6 mm).

Following intravenous bolus injections of isoprenaline, breathing changed at 25.0 ± 0.7 s, heart rate was maximum at 47.1 ± 1.4 s, and finger tremor was maximum at 138.4 ± 5.1 s (Figure 1). With the larger doses, up to 25 min was required for finger tremor to return to control values.

Dose-response curves were constructed for the isoprenaline-induced increases in heart rate and finger tremor, the latter of which are shown in Figure 2. In every subject, finger tremor was increased by at least 150%. The dose of isoprenaline (IT_{150}) required

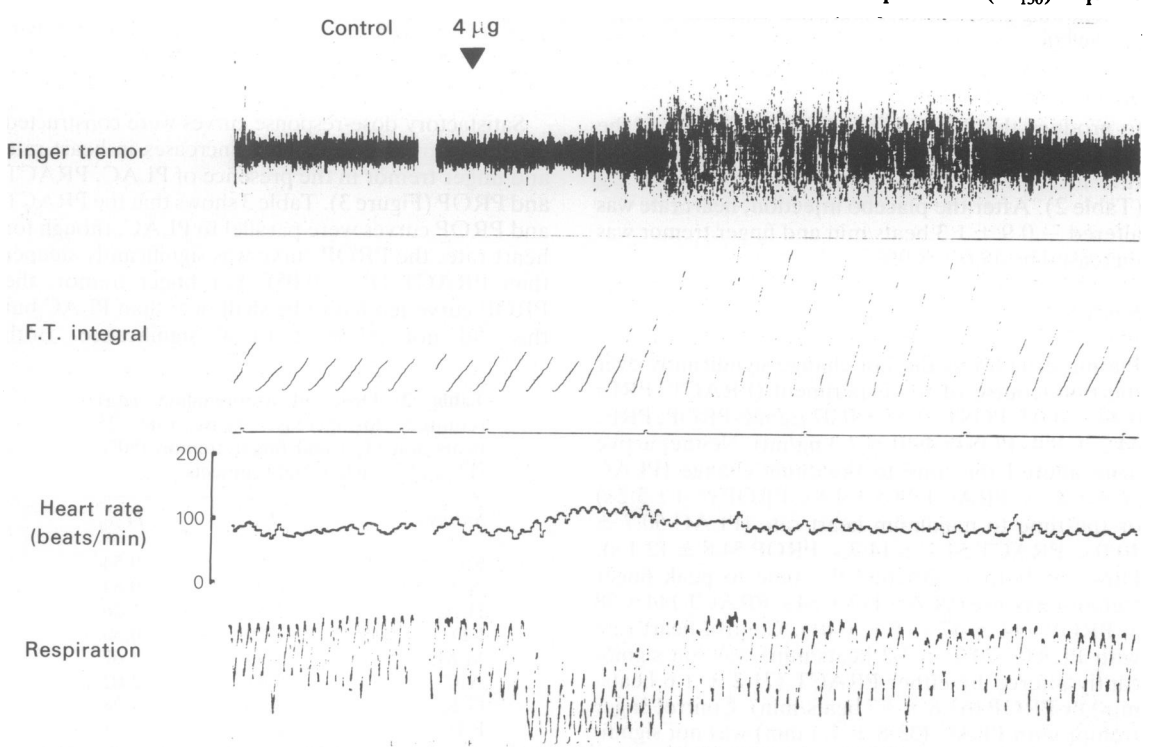

Figure 1 Recording of finger tremor, heart rate and respiration changes during a control period and an intravenous bolus injection of isoprenaline sulphate (4 μg). This is marked in minutes below the tracing of finger tremor integral.

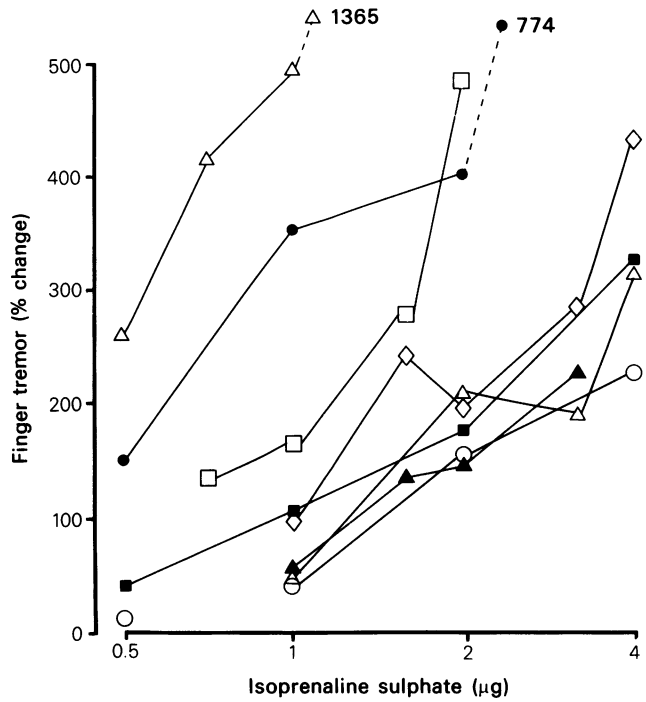

Figure 2 Dose-response curves, in eight subjects, of the percentage increase in finger tremor (hand horizontal) following graded intravenous bolus injections of isoprenaline sulphate. Each subject is represented by a different symbol.

to produce this increase was 1.24 ± 0.20 μg and the isoprenaline dose (I_{25}) required to produce a heart rate increase of 25 beats/min was 2.04 ± 0.38 μg (Table 2). After the placebo injection, heart rate was altered − 0.9 ± 1.3 beats/min and finger tremor was increased by 45.6 ± 8.9%.

Study 3

Plasma drug levels did not change significantly over the time course of the experiment (PRACT, PRE: 0.44 ± 0.07; POST: 0.47 ± 0.07 μg/ml; PROP, PRE: 44.2 ± 8.4, POST: 49.0 ± 7.3 ng/ml). Neither active drug altered the time to breathing change (PLAC 26.6 ± 4.2 s, PRACT 28.5 ± 4.8 s, PROP 26.4 ± 5.2 s) or the time to maximum heart rate (PLAC 50.7 ± 10.0 s, PRACT 54.2 ± 14.7 s, PROP 54.8 ± 12.1 s). However both lengthened the time to peak finger tremor response (PLAC 117 ± 34 s, PRACT 144 ± 38 s, PROP 144 ± 47 s, $P < 0.01$). Control heart rate with PLAC (70.7 ± 3.2 beats/min) was not significantly altered by either PRACT (71.2 ± 1.6 beats/min) or PROP (63.8 ± 3.7 beats/min). Control finger tremor with PLAC (33.8 ± 4.4 mm) was not significantly altered by either PRACT (37.0 ± 7.4 mm) or PROP (31.4 ± 6.8 mm).

Satisfactory dose-response curves were constructed for the isoprenaline induced increases in heart rate and finger tremor in the presence of PLAC, PRACT and PROP (Figure 3). Table 3 shows that the PRACT and PROP curves were parallel to PLAC, though for heart rate, the PROP curve was significantly steeper than PRACT ($P < 0.05$). For finger tremor, the PROP curve tended to be shallower than PLAC but this did not reach statistical significance. Both

Table 2 Dose of isoprenaline (μg) required to increase heart rate 25 beats/min (I_{25}) and finger tremor 150% (IT_{150}) for each of eight subjects

Subject	I_{25}	IT_{150}
S.G.	1.88	0.54
A.M.	0.93	0.84
H.A.	1.86	1.26
I.D.	1.29	0.50
M.M.	1.94	1.67
A.C.	3.41	2.02
G.K.	3.86	1.28
P.R.	1.12	1.81
Mean	2.04	1.24
s.e. mean	0.38	0.20

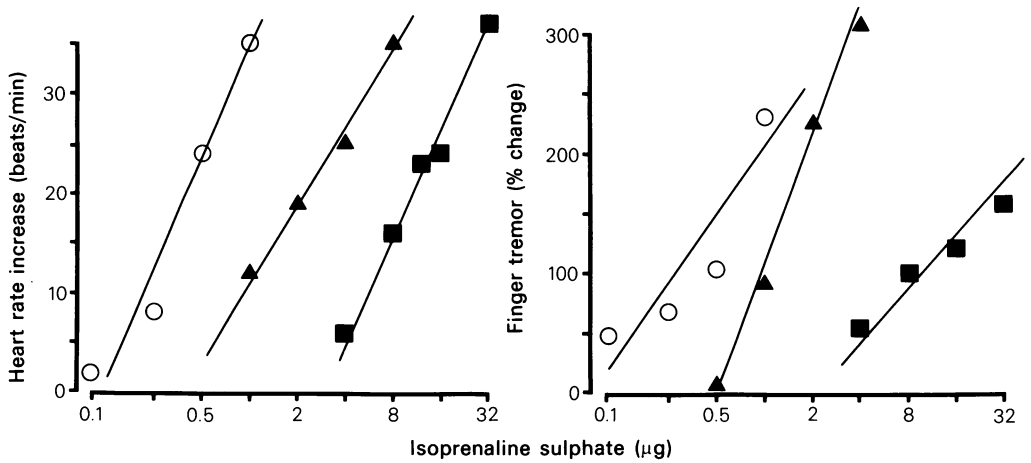

Figure 3 Dose-response curves of one representative subject (Y.W.) for the increases in heart rate and finger tremor produced by intravenous bolus injections of isoprenaline sulphate in the presence of placebo (O——O), practolol 120 mg (▲- - ▲), and propranolol 40 mg (■——■).

PRACT and PROP significantly displaced the heart rate curves to the right, increasing the I_{25} (geometric mean) from 1.42 to 6.82 μg ($P < 0.01$) for PRACT, and to 25.79 μg ($P < 0.01$) for PROP (Table 4). The shift by PROP was significantly greater than that by PRACT ($P < 0.01$). Similarly both PRACT and PROP significantly displaced the tremor curves to the right, increasing the IT_{150} (geometric mean) from 1.34 to 2.80 μg ($P < 0.05$) for PRACT and to 22.87 μg ($P < 0.01$) for PROP. Again the shift by PROP was significantly greater than by PRACT ($P < 0.01$).

Dose ratios (DR) were calculated for heart rate and finger tremor at the I_{25} and IT_{150} doses of isoprenaline and are shown for PRACT and PROP in Table 5. PROP had an approximately equal effect on heart rate (DR 18.2) and finger tremor (DR 17.1). PRACT, however, had over twice the effect on heart rate (DR 4.8) that it had on finger tremor (DR 2.1). For both variables the effect of PRACT was less than PROP, so that for finger tremor PROP (DR 17.1) had an effect over 8 times greater than PRACT (DR 2.1).

Discussion

Physiological finger tremor is distinct from other types such as essential or Parkinsonian tremor (Young & Shahani, 1978). It has a characteristic peak frequency, 8–12 Hz, which remains constant even when the amplitude is enhanced by isoprenaline (Perucca *et al.*, 1981). The accelerometer used in the present study is small and lightweight and being piezo resistive is sensitive over the range of frequencies studied. The measured changes in acceleration were

Table 3 Slopes of the dose-response curves for the isoprenaline induced increases in heart rate and finger tremor in the presence of placebo (PLAC), practolol 120 mg (PRACT) and propranolol 40 mg (PROP) for each of six subjects. Geometric means are shown with the appropriate standard errors

	Heart rate			*Finger tremor*		
Subject	*PLAC*	*PRACT*	*PROP*	*PLAC*	*PRACT*	*PROP*
P.McG.	7.7	7.8	12.4	146.4	188.0	96.5
M.C.	17.0	8.7	13.1	105.7	67.3	61.3
S.R.	11.7	5.8	9.8	66.0	48.9	45.7
Y.W.	14.9	10.8	14.6	74.3	108.7	70.7
A.W.	11.4	11.7	21.8	66.2	58.3	53.5
P.J.	12.1	12.4	16.3	59.3	59.3	73.5
Geometric mean	12.1	9.2	14.2*	81.5	78.3	64.7
s.e. mean	+ 1.4	+ 1.2	+ 1.7	+ 12.2	+ 18.3	+ 7.5
	− 1.3	− 1.0	− 1.5	− 10.6	− 14.8	− 6.8

* $P < 0.05$ when compared to PRACT

Table 4 Dose of isoprenaline (μg) required to increase heart rate 25 beats/min (I_{25}) and finger tremor 150% (IT_{150}) in the presence of placebo (PLAC), practolol 120 mg (PRACT) and propranolol 50 mg (PROP) for each of six subjects. Geometric means are shown with the appropriate standard errors

	Heart rate (I_{25})			*Finger tremor (IT_{150})*		
Subject	*PLAC*	*PRACT*	*PROP*	*PLAC*	*PRACT*	*PROP*
P.McG.	2.19	13.40	27.68	1.00	2.28	20.81
M.C.	1.55	10.08	29.88	0.75	3.85	30.23
S.R.	1.48	10.93	37.67	1.52	7.53	25.35
Y.W.	0.56	3.48	14.85	0.55	1.26	15.48
A.W.	2.51	4.25	23.42	3.62	1.93	15.93
P.J.	1.16	4.59	26.78	2.46	3.04	35.91
Geometric mean	1.42	6.82**	25.79**†	1.34	2.80*	22.87**†
s.e. mean	+ 0.35	+ 1.85	+ 3.58	+ 0.45	+ 0.80	+ 3.44
	− 0.28	− 1.45	− 3.14	− 0.34	− 0.62	− 2.98

* $P < 0.05$, ** $P < 0.01$ when compared to PLAC
† $P < 0.01$ when compared to PRACT

integrated and quantified as millimetres of integrator ramp height. The output of the accelerometer reflects the displacement times the square of the frequency of the tremor and as the frequency of the tremor remains constant these changes in acceleration are proportional to displacement. Thus the integrator ramp height is a measure of total finger tremor activity.

We have demonstrated that within a narrow age range, physiological finger tremor is not significantly correlated with age, sex, weight or height. We have also shown that with the hand held horizontal, tremor does not vary over a 5 min period. When the wrist dorsiflexed to 45°, baseline tremor is significantly greater and progressively increased over a 5 min period. For this reason, subsequent measurements were made with the hand horizontal to ensure a steady baseline. Under these circumstances tremor was significantly reduced during a 3 min period of mental arithmetic and during a Valsalva manoeuvre, but was unchanged after 3 min of strenuous exercise. Mental arithmetic produces a strong sympathetic stimulus (Brod *et al.*, 1959) and in the present study was effective in increasing heart rate. During and immediately after the Valsalva manoeuvre, sympathetic outflow increases (Sharpey Schafer, 1965), and although tremor decreased during the manoeuvre it tended to increase afterwards, though the latter was not statistically significant. Strenuous exercise also results in a strong sympathetic stimulus and in mild to moderate exercise it has been demonstrated that the rise in plasma catecholamines is mainly due to an increase in plasma noradrenaline and not adrenaline (Christensen & Brandsborg, 1973). It would, therefore, appear that finger tremor is not significantly enhanced by these increases in sympathetic tone but may even be depressed. This is compatible with the observation that intravenous noradrenaline does not enhance finger tremor (Marsden *et al.*, 1967). The fact that exercise did not increase finger tremor suggests that low frequency ballistocardiac vibrations did not significantly contribute to the measured tremor signal.

Table 5 Dose ratios of practolol 120 mg (PRACT) and propranolol 40 mg (PROP) for heart rate and finger tremor calculated at the I_{25} and IT_{150} doses of isoprenaline

	PRACT	*PROP*
Heart rate	4.8	18.2
Finger tremor	2.1	17.1

Satisfactory dose-response curves were drawn for the increases in isoprenaline enhanced finger tremor. These increases were expressed as a percentage change since the baseline finger tremor may vary (i) between experiments due to intersubject variation; (ii) from day to day within-subject variation, or (iii) by replacement of the accelerometer. Care was therefore taken to place the accelerometer in the same position on every subject and forearm position was standardized from the pisiform bone as described. The dose-response curves obtained showed intersubject differences but each subject had a maximum finger tremor increase of at least 150%. As the heart rate rise to isoprenaline is a limiting response, much larger increases in finger tremor were not elicited in all subjects. Nevertheless the dose of isoprenaline required to increase finger tremor by 150% (IT_{150}) is comparable to that required to increase heart rate by 25 beats/min (I_{25}) and further comparisons and dose ratios were calculated at these levels.

It has been noted previously that cardioselective β-antagonists are less potent than non-selective β-adrenoceptor antagonists in blocking the tachycardia of intravenous isoprenaline boluses (DePlaen *et al.*,

1976; Perucca *et al.*, 1981) and this may be partly due to a contribution from reflex withdrawal of cardiac vagal tone (Arnold & McDevitt, 1982). Although not measured directly in this study, the doses of practolol and propranolol used have previously been shown to have comparable effects on an exercise tachycardia (McDevitt *et al.*, 1977) suggesting that the two drug doses are equipotent at β_1-adrenoceptors. Lertora *et al.* (1975) have also shown that, at the plasma levels obtained in the present study, practolol is highly selective for β_1-receptors as it did not block the forearm vasodilator response to intra-arterial infusions of isoprenaline. This is comparable to our finding that finger tremor was blocked to only a small extent by practolol. We have also shown that dose-response curves may be constructed for isoprenaline induced increases in finger tremor in the presence of propranolol. Furthermore, propranolol was over eight times more effective than practolol in its effect on the finger tremor enhancement by isoprenaline.

Previous workers (Perucca *et al.*, 1981; Pickles *et al.*, 1981) were unable to obtain a parallel shift of the dose response curve with propranolol 40 mg. They measured finger tremor at 45° and expressed the isoprenaline-induced changes in arbitrary units, but it is not clear how these were derived. With propranolol 10 mg they did obtain parallel shifts of a similar nature to those we have described for propranolol 40 mg and the changes produced by atenolol and metoprolol were also similar to those we have described for practolol. One possible disadvantage of the described methods is the use of boluses of isoprenaline. Due to the suddenness of the haemodynamic changes, boluses of isoprenaline are poorly tolerated when the heart rate rise is large, and may also be associated with ventricular ectopics in some people (Cleaveland *et al.*, 1972). In addition, following a bolus of isoprenaline the change in finger tremor reaches a short-lived peak. Therefore, isoprenaline infusions may be a preferable technique when examining finger tremor. This may allow greater heart rate increases to be tolerated and stable finger tremor changes to be measured. We have shown that isoprenaline infusions can be used to demonstrate parallel shifts of the finger tremor dose-response curve in the presence of atenolol 25 mg and propranolol 10 mg (Arnold *et al.*, 1983). It is also possible that a more selective β_2-adrenoceptor agonist than isoprenaline might produce a smaller tachycardia and allow fuller finger tremor dose-response curves to be constructed.

In summary, physiological finger tremor appears to be a stable parameter which is not enhanced by increases in sympathetic outflow. It is enhanced by intravenous isoprenaline for which satisfactory dose-response curves can be constructed. The non-selective β-adrenoceptor antagonist, propranolol 40 mg, was more than eight times more potent in blocking isoprenaline enhanced finger tremor than the selective β_1-adrenoceptor antagonist, practolol 120 mg.

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