Br. J. clin. Pharmac. (1984), **18**, 317–324

Effect on finger tremor of withdrawal of long-term treatment with propranolol or atenolol

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1 The effect of the withdrawal of long-term β-adrenoceptor blockade on pulse rate and finger tremor was studied in 27 patients who had been treated for 2 years following an uncomplicated myocardial infarction with either atenolol, propranolol or placebo.
2 During treatment, pulse rate was significantly lower in patients treated with propranolol or atenolol compared with placebo.
3 Compared with the response in the placebo group the mean increase in tremor on withdrawal of propranolol was statistically significant for postural and for work tremor in both hands.
4 A significant increase in tremor on withdrawal of atenolol occurred only in the postural position and in a narrow frequency band (left hand, 7–11 Hz; right hand, 7–9 Hz).
5 The differences in the effect on tremor of withdrawal of treatment with propranolol or atenolol in doses which produced similar reductions in heart rate, emphasise the β_2 classification of peripheral receptors associated with normal muscle tremor but do not exclude the involvement of β_1-adrenoceptors.

Keywords tremor propranolol atenolol

Introduction

The mechanism by which β-adrenoceptor antagonists reduce essential tremor has been discussed in terms of the relative importance of antagonism at β_1- and β_2-adrenoceptors and of the relative ability of the drugs to enter the brain (Jefferson *et al.*, 1979; Calzetti *et al.*, 1982; Collier & Leigh, 1983; Abila *et al.*, 1983). Less attention has been paid to the action of β-adrenoceptor antagonists on normal tremor. We have made objective measurements of the effects of long term administration of a cardioselective and of a non-cardioselective β-adrenoceptor antagonist on normal tremor. The long-term treatment removed any doubt about the equilibration of the drugs within distribution compartments. Since the characteristics of the tremor recorded from the fingertip are different with different recording postures and could be differentially affected by β-adrenoceptor blockade, three recording postures were used.

In a clinical trial of the long term effects of β-adrenoceptor blockade, finger tremor was measured in 27 of the patients who had been taking propranolol or atenolol or placebo for 2 years and again 1 month after withdrawal of therapy. This study differed from previous investigations since: (i) the patients were not suffering from a tremor-associated disease such as essential tremor or Parkinson's disease. There was no evidence that their tremor was other than normal physiological tremor. (ii) Withdrawal from chronic therapy rather than the administration of a single or a few doses was investigated. (iii) Three forms of tremor were measured, namely rest, postural and work tremor (Birmingham *et al.*, 1977).

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Methods

All patients studied had initially been admitted to coronary care units within 24 h after a myocardial infarction and subsequently attended an outpatient clinic whilst taking part in a study of the effects of long term administration of a β-adrenoceptor antagonist after myocardial infarction (Wilcox *et al.*, 1980). The treatment regimens were either, propranolol 80 mg twice daily, atenolol 50 mg twice daily or placebo tablets twice daily. Compliance with treatment was checked by tablet counts at each visit. The trial was random and double blind. The protocol was approved by an Ethical Committee. Towards the end of the trial the patients who were attending one of the clinics were invited to have their finger tremor measured whilst on treatment and again after stopping treatment. Patients were asked to abstain from alcohol for 24 h before the measurements, which were not made at fixed times of the day. Of the 27 patients who agreed and completed the measurements, eight were being treated with propranolol, eight with atenolol and 11 with placebo (Table 1). Tremor was measured during the last month of the 2 year period of treatment and one month after the withdrawal of tablets. The withdrawal was gradual with patients taking half the daily dose during the last week of treatment. Any concomitant therapy was being taken on the occasion of the first measurement and of the second measurement.

Tremor measurement

Measurements of middle finger tremor of both hands were made using a small accelerometer (Bruel & 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).

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 and hand supported and the middle finger exerting an upward force of 1 N against the spring of a strain-gauge transducer ('work' tremor). All measurements were made with the subject seated comfortably in a quiet room. Measurements in each posture were made for one minute 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 & Kjaer, type 2635).

Tremor analysis

The tremor waveform, filtered to remove frequencies above 50 Hz, was analysed with a Hewlett-Packard spectrum analyser (HP3582A) and desk-top computer (HP9825A). Five-second samples were subjected to Fourier analysis and eight sequential samples from each one-minute record were averaged to yield a mean frequency spectrum covering the range 0.4 to 51.2 Hz (referred to as the 0–50 Hz band) in 0.2 Hz intervals. From this analysis the root mean square (rms) of tremor amplitude was also calculated. Results from the subjects in each treatment group for each of the tremor postures were averaged to produce group mean spectra (Figure 1) and mean rms acceleration for each posture for each hand on and off treatment. Subtraction of the frequency spectrum obtained during treatment from that obtained one month after cessation of treatment produced a subtraction spectrum for each subject. These subtraction spectra were averaged within each treatment group to produce a mean difference spectrum, + and − one standard error of the mean. The frequency of the dominant peak of each spectrum was determined using a smoothing and peak searching technique (Wharrad, 1982).

Other measurements

Pulse rate and blood pressure were recorded in each subject, whilst seated, at the clinic prior to tremor measurement.

Table 1 Composition of the three groups of patients

	Placebo *n = 11* *9 males, 2 females*	*Propranolol* *n = 8* *8 males*	*Atenolol* *n = 8* *8 males*
Mean age (s.d.) (years)	58.7 (9.2)	56.8 (12.6)	59.8 (9.2)
Mean weight (s.d.) (kg)	79.9 (8.8)	73.1 (8.8)	71.9 (11.2)
Dominant hand	9 right, 2 left	7 right, 1 left	7 right, 1 left

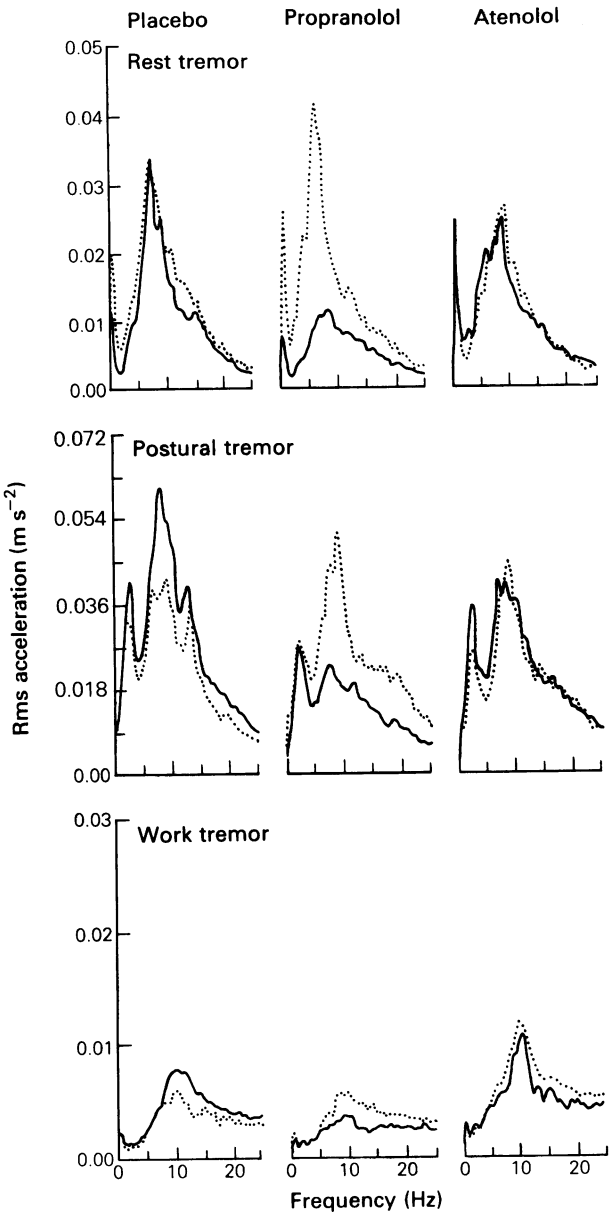

Figure 1 Mean spectra for rest, postural and work tremors of the right hand during treatment (continuous line) and 1 month after withdrawal of treatment (broken line).

Statistical analysis

The tremor values, resting pulse rates and blood pressures measured during the on-drug and off-drug periods were compared between groups using Mann-Whitney U tests.

Results

The effect on tremor of changing from treatment with tablets to no treatment is illustrated in Figure 2. This shows for each hand in the range 0–25 Hz the mean difference spectra

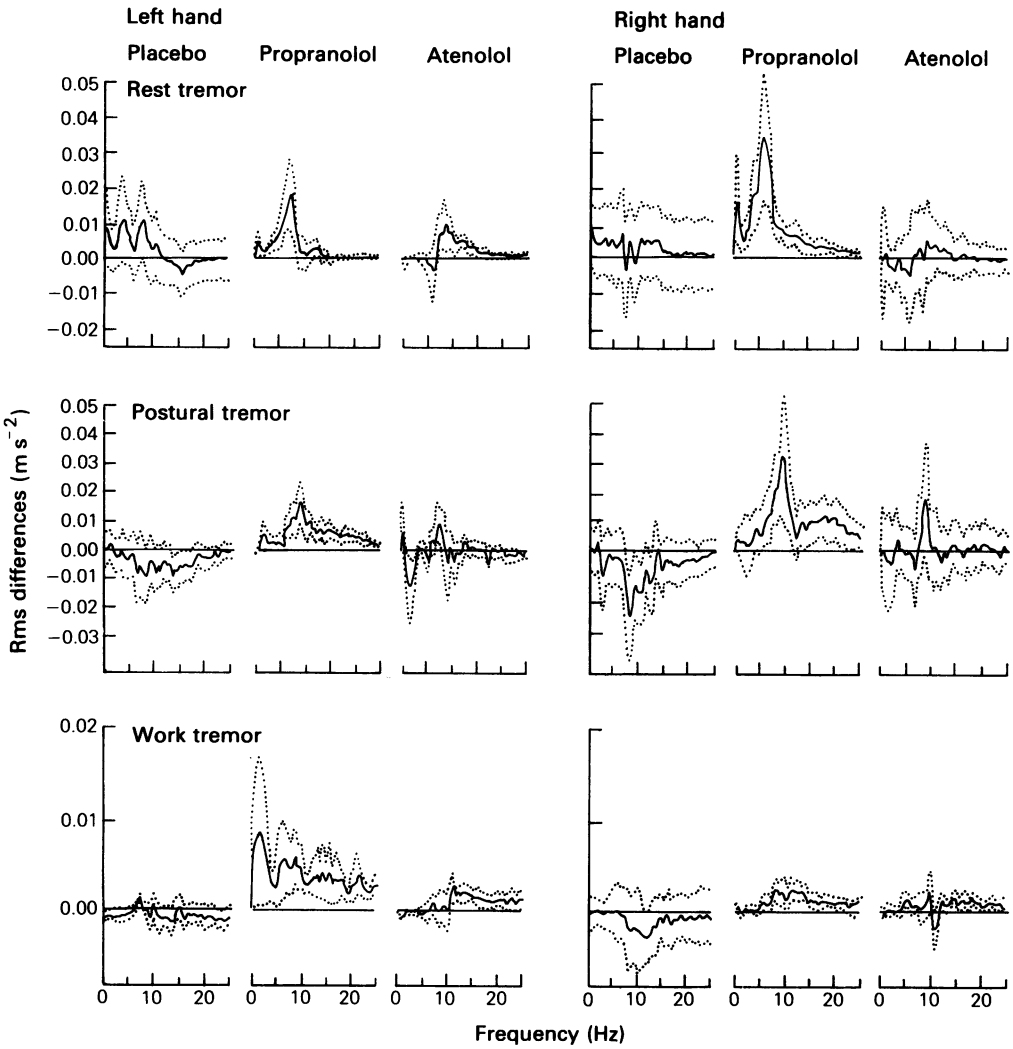

Figure 2 Mean (± s.e. mean) difference spectra for rest, postural and work tremors of both hands obtained by subtracting for each subject the tremor spectrum while taking the tablets from the spectrum obtained when treatment was withdrawn and then calculating the mean difference spectrum for each group.

Table 2 Table of mean dominant frequencies (Hz) and standard deviations (s.d.) on and off propranolol, atenolol and placebo treatment for rest, postural and work tremors of both hands

		Placebo		*Propranolol*		*Atenolol*		*Placebo*		*Propranolol*		*Atenolol*	
		On	*Off*	*On*	*Off*	*On*	*Off*	*On*	*Off*	*On*	*Off*	*On*	*Off*
Rest	Mean	8.3	8.3	8.7	7.5	8.7	9.2	8.2	7.6	7.7	7.8	9.0	8.3
	s.d.	2.2	1.7	1.3	1.0	1.6	1.9	1.3	1.3	1.4	2.1	2.6	2.0
Postural	Mean	9.1	9.0	8.9	9.2	9.3	8.5	8.9	8.5	9.0	8.7	8.6	9.0
	s.d.	1.7	1.4	1.8	1.2	1.8	0.7	1.5	1.9	2.0	1.1	1.7	0.7
Work	Mean	10.5	10.7	9.3	8.7	10.0	9.9	10.5	10.3	9.4	9.3	9.9	9.6
	s.d.	0.8	1.6	2.7	2.4	1.4	1.0	1.0	0.6	1.3	1.1	1.6	1.2

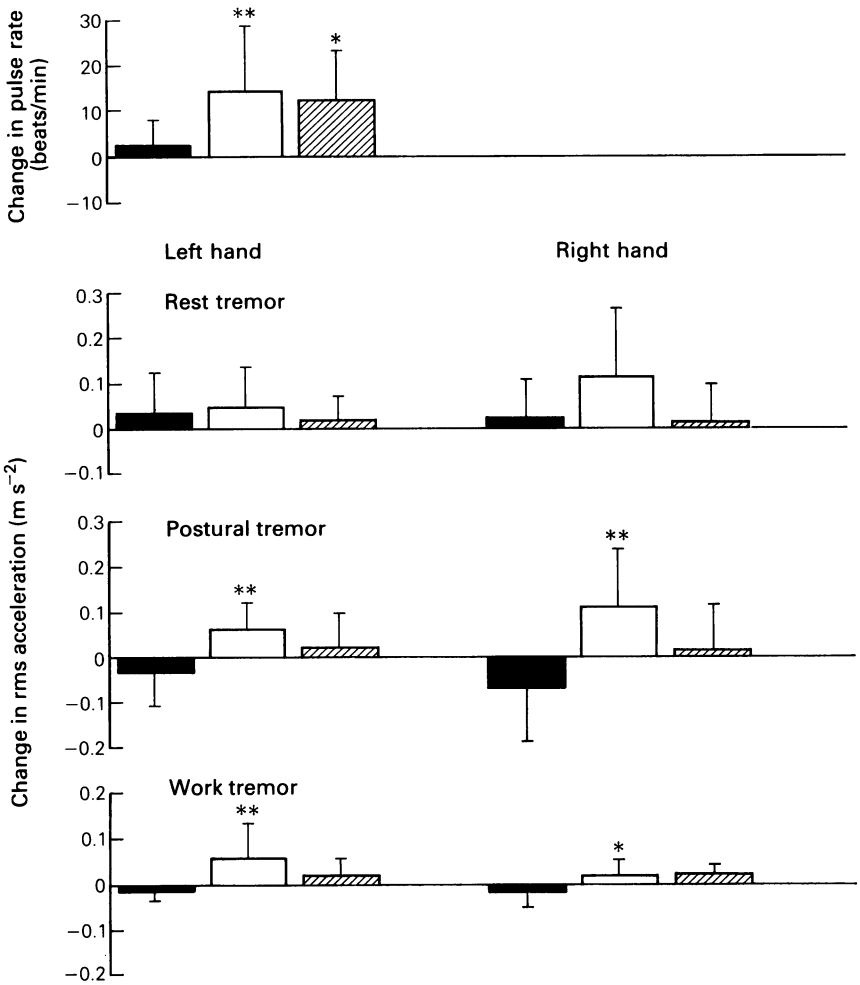

Figure 3 Mean change (+1 s.d.) in resting pulse rate (beats/min) and rms acceleration (ms^{-2}) for rest, postural and work tremors of both hands for three groups of subjects taking propranolol (□, $n = 8$), atenolol (▨, $n = 8$) or placebo (■, $n = 11$). * $P < 0.05$, ** $P < 0.1$ for tests of significant difference between groups, Mann-Whitney U test.

obtained by subtracting for each subject the tremor spectrum while taking the tablets from the spectrum obtained when treatment was withdrawn and then calculating the mean for each group. Activity above the zero line therefore indicates less tremor when the tablets were being administered. The mean difference spectra are plotted with standard errors and give a graphic indication of where the main changes in the spectra occurred. Broadly, these arose between 5 and 13 Hz. The overall impression was of an increase in tremor on withdrawal of propranolol, little change on withdrawal of atenolol and particularly in postural and work tremor, a *decrease* in amplitude on withdrawal of placebo tablets.

Quantitative analysis

Two basic quantitative parameters, an overall measure of amplitude (rms acceleration) and the frequency of the dominant peak were derived from the spectra for each patient in each group. The means of these values for frequency are shown in Table 2. The mean differences in amplitude between on and off treatment are shown in the lower three block diagrams in Figure 3. The Mann-Whitney U test was used to compare the effect of withdrawal of propranolol or atenolol with the effect of stopping placebo treatment. Significant increases in postural ($P < 0.01$, both hands) and work tremor ($P < 0.01$, left hand

Table 3 Table of significant differences (Mann-Whitney U test) of amplitude changes in tremor on withdrawal of tablets in β-adrenoceptor blocked groups compared with the placebo group for different frequency bands in the frequency spectrum

		Left hand			*Right hand*		
	Frequency band (Hz)	*Rest tremor*	*Postural tremor*	*Work tremor*	*Rest tremor*	*Postural tremor*	*Work tremor*
Propranolol	0–50	NS	**	**	NS	**	*
	5–7	NS	NS	NS	NS	NS	NS
	7–9	NS	*	NS	NS	**	*
	9–11	NS	*	NS	NS	**	*
	11–13	NS	*	NS	NS	*	**
Atenolol	0–50	NS	NS	NS	NS	NS	NS
	5–7	NS	NS	NS	NS	NS	NS
	7–9	NS	*	NS	NS	*	NS
	9–11	NS	*	NS	NS	NS	NS
	11–13	NS	NS	NS	NS	NS	NS

* $P < 0.05$, ** $P < 0.01$, NS–not significant

and $P < 0.05$, right hand) on withdrawal of propranolol were detected. On stopping treatment with placebo there were small increases in rest tremor, and *decreases* in postural and work tremor, however none of these small changes was statistically significant. There were no significant changes in frequency (Table 2) on withdrawal of atenolol, propranolol or placebo.

Band analysis

Visual inspection of the mean difference spectra showed that the major changes on withdrawal of the treatments were often in a much narrower band than the full frequency range (0–50 Hz) of the spectrum. Analysis was therefore repeated for 2 Hz bands between 5 and 13 Hz. Table 3 summarises the statistically significant changes. In the resting position there were no differences between tremor on propranolol or atenolol compared with that of the placebo group. For postural tremor, propranolol reduced tremor between 7 and 13 Hz, usually to a greater extent in the right hand. For work tremor the difference occurred only in the right hand; the difference in overall rms referred to above (Figure 3) was not sustained for the left hand on 5-13 Hz band analysis. This was because, as inspection of Figure 2 confirms, the main difference occurred below 5 Hz.

Statistical analysis of the change in the overall spectrum (0–50 Hz) while on atenolol revealed no difference compared with placebo (Figure 3), but band analysis uncovered a significantly lower amplitude of postural tremor in a narrow frequency band (7-11 Hz, left hand; 7–9 Hz, right hand, $P < 0.05$) while on atenolol.

Cardiovascular changes

Resting pulse rates were higher 1 month after withdrawal of treatment in six of the propranolol group, seven of the atenolol group and four of the placebo group. Mean increases of 13–14 beats/min (Table 4) were noted on withdrawal of atenolol ($P < 0.05$) and propranolol ($P < 0.01$). The placebo-treated group showed no significant change. Systolic and diastolic blood pressures did not change significantly in any of the treatment groups.

Discussion

Since the early reports of Winkler & Young (1971), Gilligan *et al.* (1972) and Winkler &

Table 4 Mean resting pulse rates measured on and off treatment

	Placebo (n = 11)		*Propranolol (n = 8)*		*Atenolol (n = 8)*	
	On	*Off*	*On*	*Off*	*On*	*Off*
Mean	72.4	74.2	62.8	76.3	65.8	79.3
s.d.	10.8	11.2	10.4	11.5	9.8	8.8

Young (1974) of the efficacy of propranolol in the treatment of essential tremor, there have been many assessments of the comparative effectiveness of different β-adrenoceptor antagonists. Subjective and objective scoring methods were used by Jefferson *et al.* (1979) and Leigh *et al.* (1983) in comparisons of propranolol, atenolol, sotalol and metoprolol to lead them to conclude that antagonism at peripherally-located β_2-adrenoceptors is the primary mechanism of reduction of essential tremor. Measurement of tremor by accelerometry has been used in single dose studies (Calzetti *et al.*, 1981; Abila *et al.*, 1983; Collier & Leigh, 1983) or after equilibration in repeated dose studies (Dietrichson & Epsen, 1981; Calzetti *et al.*, 1982; Larsen *et al.*, 1982). The conclusions have ranged from the view that antagonism at peripherally located β_2 receptors is sufficient to explain the results, to a gradual realisation that antagonism at β_1-receptors accessible to the more lipid soluble compounds could also be a significant factor.

The salient features of the present investigation of the effects on normal finger tremor of the withdrawal of long-term administration of β-adrenoceptor antagonists were that in the group of subjects on propranolol, tremor amplitude was less than when the drug was withdrawn, this was true for postural and for work tremor over a wide frequency range; in the group of subjects taking atenolol, a small reduction was found only in postural tremor over a narrow frequency band.

Measurements of resting pulse rate in the patients confirmed that placebo treatment did not change mean resting heart rate significantly whereas treatment with either β-adrenoceptor blocker reduced mean resting heart rate significantly to the same extent. In the same way, reductions of standing and supine pulse rates were used by Jefferson *et al.* (1979) and equal reductions of sitting pulse rate (Dietrichson & Espen, 1981), or inhibition of standing tachycardia (Calzetti *et al.*, 1982; Abila *et al.*, 1983) were used to establish equivalence of cardiac β-adrenoceptor blockade.

Though equivalence of the drugs appeared to have been achieved at cardiac sites there was nevertheless a pronounced difference in effects on tremor. It has been established by many studies (for example McDevitt & Nelson, 1978; Conway *et al.*, 1976; Perucca *et al.*, 1981) that in cardiac-equivalent doses atenolol is less potent than propranolol at β_2-adrenoceptor sites. Thus the greater tremor-attenuating effect of propranolol may be due to its greater potency as a β_2-adrenoceptor antagonist.

Although a peripheral β_2-adrenoceptor antagonist explanation is supported by the effect of propranolol and the lack of effect of atenolol on isometric work tremor (whether considering wide or narrow band analysis), atenolol did significantly reduce finger tremor in a narrow frequency band when the arm was outstretched. Thus it might be inferred that frequency band analysis is sufficiently sensitive to detect the effect of the weak β_2-adrenoceptor antagonist potency of atenolol or that postural tremor is mediated in part by a β_1-adrenoceptor mechanism. It may also mean that the β_2-adrenoceptors at extra-cardiac sites are more sensitive to or more accessible to the drugs. It is interesting in this context that Perucca *et al.* (1981) noted that the decrease in tremor due to propranolol was proportionately greater than the bradycardia seen during exercise, suggesting that β_2-adrenoceptors in the periphery had a greater affinity for propranolol than the β_1-adrenoceptors in the heart.

Probable differences in distribution between the CNS and in the periphery must be considered. Propranolol is known to be more lipophilic than atenolol (Woods & Robinson, 1981) and appears in brain tissue at concentrations 10 to 20 times those of atenolol after chronic oral administration (Neil-Dwyer *et al.*, 1981). It should be noted that metoprolol, a cardioselective antagonist which enters the CNS can reduce essential tremor (Jefferson & Marsden, 1980; Larsen *et al.*, 1982; Calzetti *et al.*, 1981).

There seems to be agreement on the lack of effect of β-adrenoceptor blockade on the frequency of tremor. Larsen *et al.* (1982) reported no change in the frequency (8.3 Hz) of tremor in their patients, and Calzetti *et al.* (1982) found no change in frequency in essential tremor. In our normal subjects the dominant frequency was not shifted by cardioselective or non-selective blockade. The use of different frequency bands for amplitude analysis proved to be useful in that the overall rms and narrow bands analysis were differentially able to detect differences between the forms of tremor recorded in different postures. The tremor recorded with the arm outstretched was the most sensitive to β-adrenoceptor blockade.

We believe our results indicate that tremor is not associated solely with the activation of β_2-adrenoceptors in the periphery; it is possible that β_1-adrenoceptors having either a peripheral or a central location could be involved.

We wish to thank those physicians who allowed us to study their patients.

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(Received February 17, 1984, accepted May 20, 1984)