

β -Adrenoreceptor antagonists in essential tremor

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SUMMARY Three different β -adrenoreceptor antagonists—propranolol, sotalol, and atenolol—were compared in a double-blind study with placebo in nine patients with essential tremor. All three drugs produced an equal reduction in standing pulse rate but atenolol was less effective in reducing tremor than propranolol and sotalol. These results suggest that the reduction in tremor produced by β -adrenoreceptor antagonists is mediated by an effect on peripheral β_2 -adrenoreceptors.

Several studies have shown that the β -adrenoreceptor antagonist propranolol reduces the amplitude of essential tremor (Winkler and Young, 1971; Dupont *et al.*, 1973; Morgan *et al.*, 1973; Tolosa and Loewenson, 1975; Young *et al.*, 1975; Jefferson *et al.*, 1979). The mechanism of this pharmacological effect is unknown, since propranolol may act on peripheral (Marsden *et al.*, 1967) or central nervous system β -adrenoreceptors (Myers *et al.*, 1975; Day *et al.*, 1977; Taylor *et al.*, 1978) blocking both β_1 and β_2 sites. Furthermore, propranolol possesses a membrane stabilising ("quinidine-like") effect (Morales-Aguilera and Vaughan Williams, 1965) which may contribute to its therapeutic action in essential tremor.

The past decade has witnessed the introduction of several β -adrenoreceptor antagonists which may be useful in investigating the precise site and mode of action of propranolol in essential tremor. These alternative β -adrenoreceptor antagonists differ from propranolol in various ways and may, for example, be devoid of membrane stabilising activity or may be cardioselective, blocking predominantly β_1 -receptors. Some of these drugs also show poor penetration of the blood-brain barrier, with little or no central nervous system activity.

In the present study, the effect of propranolol in essential tremor has been compared with the effect of a cardioselective β -adrenoreceptor antagonist (atenolol), and with a nonselective β -antagonist which possesses no membrane stabilising activity and which enters the brain with difficulty (sotalol).

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Patients and methods

Nine patients with essential tremor were studied. The diagnosis of essential tremor was made on the basis of a characteristic postural tremor of the upper limbs without other neurological abnormalities. All patients had normal thyroid, cardiac, renal, and hepatic function. The main clinical features of the nine patients are presented in Table 1.

Propranolol (Inderal), sotalol (Sotacor), atenolol (Tenormin), and placebo were given orally in a randomised double-blind trial, each drug or placebo being taken for two weeks before the degree of tremor was assessed clinically. Optimum doses of propranolol for each individual were established before the random phase of the trial and ranged from 60–160 mg per day, in divided doses. Equivalent doses of sotalol and atenolol were used according to the ratios propranolol=1, sotalol= $1\frac{1}{2}$, and atenolol= $\frac{2}{3}$. Individual daily doses of sotalol ranged from 80–240 mg and of atenolol from 50–100 mg. Propranolol was ad-

Table 1 Clinical details of nine patients with essential tremor

Patient	Age (yr)	Sex	Family history	Length of history (yr)
1	73	F	—	10
2	66	M	—	16
3	44	F	—	6
4	45	F	+	30
5	31	F	+	17
6	57	F	—	4
7	72	F	—	6
8	59	M	—	34
9	56	F	+	30

ministered three to four times daily, sotalol thrice daily, and atenolol twice daily. The order of administration of the three drugs was randomised.

Clinical assessment was performed within two to four hours of the previous oral dose of drug or placebo at the end of each two weeks of medication. Measurements were made by the same examiner (DJ) in the same surroundings and at approximately the same time of day. After a 10 minute period of rest in the supine position, the supine and standing pulse rate and blood pressure were measured. Tremor was assessed objectively by scoring the degree of tremor of the outstretched hands and by rating tests of handwriting, drawing, and a timed performance test which involved threading rings onto a peg, as described elsewhere (Jefferson *et al.*, 1979). The scores obtained in individual tests were added to give a total objective tremor score. Each patient was invited to assess the severity of his or her manual tremor at each visit by marking a linear analogue scale (subjective tremor score) and to comment on the overall subjective effects of the previous two weeks of medication.

Drug compliance was monitored by counting the number of tablets which remained in the container at the end of each two week period. The responses of pulse rate and blood pressure to the different treatment schedules were compared using the Student's *t* test for paired data. A non-parametric statistical method (Wilcoxon's test of paired differences) was used to compare the objective tremor scores on the different drugs with those on placebo, which were also subjected to analysis of variance with linear contrast.

Results

Drug compliance, as judged by tablet counting, was excellent throughout the study, and no patient complained of side effects during the different periods of medication.

PULSE RATE AND BLOOD PRESSURE (FIGS. 1 AND 2)

All drugs caused a reduction in the supine ($P < 0.001$) and standing ($P < 0.001$) pulse rate when compared with placebo. There was no difference between the effects of the individual drugs, suggesting that all three were producing a similar degree of blockade of cardiac chronotropic β_1 -adrenoreceptors.

Both sotalol and atenolol reduced the mean supine and standing systolic blood pressure compared with placebo ($P < 0.05$) but there was no difference between the mean systolic pressures during treatment with propranolol, atenolol, and

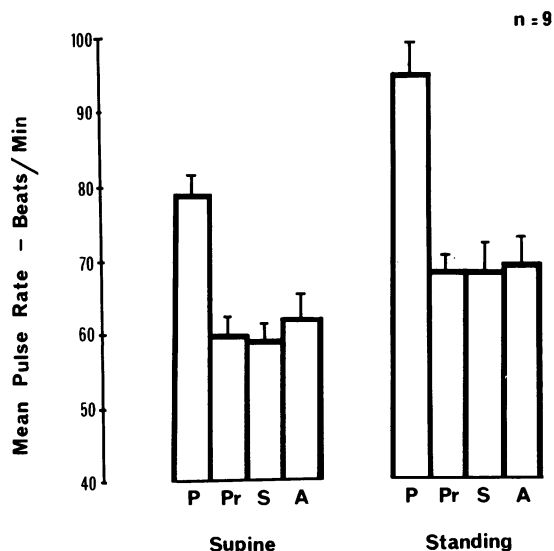


Fig. 1. Mean pulse rate (± 1 SEM) in nine patients with essential tremor during treatment with placebo (P), propranolol (Pr), sotalol (S), and atenolol (A). Using Student's *t* test for paired data, both supine and standing pulse rates are reduced compared with placebo by propranolol, sotalol, and atenolol ($P < 0.001$). There is no difference ($P > 0.1$) between the effects of the different drugs.

sotalol ($P > 0.1$). The mean supine diastolic blood pressure during treatment with sotalol was reduced compared with placebo ($P < 0.05$) but did not differ significantly from the effect of propranolol or atenolol ($P > 0.1$). The mean standing diastolic blood pressure was not reduced significantly by any of the three drugs when compared with placebo ($P > 0.1$).

TREMOR

All three β -adrenoreceptor antagonists produced a reduction in the total objective tremor score when compared with placebo (Table 2) ($P < 0.01-0.02$). Sotalol and propranolol produced the same reduction in objective tremor score but atenolol reduced the mean tremor score by a smaller amount compared with sotalol and propranolol.

When the patients' subjective tremor scores (Table 3) were examined using Wilcoxon's test, atenolol was no better than placebo in reducing tremor ($P > 0.1$) whereas sotalol produced a definite subjective improvement ($P < 0.05$) and propranolol nearly did ($P < 0.1$). However, analysis of variance with linear contrast showed sotalol and propranolol to be more effective than atenolol.

Although none of the patients, when directly

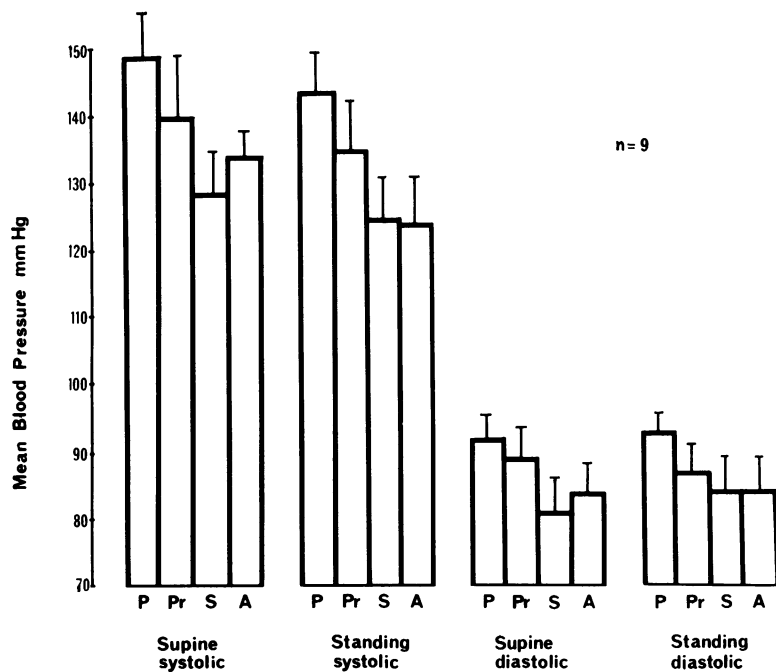


Fig. 2. Mean (± 1 SEM) supine and standing systolic and diastolic blood pressures in nine patients with essential tremor during treatment with placebo (P), propranolol (Pr), sotalol (S), and atenolol (A). Using Student's *t* test for paired data, supine and standing systolic blood pressure are reduced compared with placebo during treatment with sotalol ($P < 0.05$) and atenolol ($P < 0.05$). Mean supine diastolic blood pressure is reduced compared with placebo during treatment with sotalol ($P < 0.05$). Mean blood pressures during treatment with the different drugs do not differ significantly from each other.

Table 2 Changes in objective tremor score during treatment with placebo, propranolol, sotalol, and atenolol

Patient	Placebo	Propranolol	Sotalol	Atenolol
1	17	11	11	14
2	17	10	12	12
3	1	0	2	1
4	9	7	6	4
5	8	4	3	8
6	13	8	6	12
7	18	14	16	15
8	5	3	1	1
9	8	2	4	6
Mean score	10.7	6.6	6.8	8.1
± 1 SEM	1.98	1.55	1.71	1.81

(Maximum tremor score=25)

Tremor is reduced compared with placebo during treatment with propranolol ($P < 0.01$), sotalol ($P < 0.01$), and atenolol ($P < 0.02$). There is no difference between the effect of the three drugs ($P > 0.01$) using Wilcoxon's test, but analysis of variance with linear contrast shows atenolol to be less effective than propranolol and sotalol ($P < 0.05$), which have equivalent action ($P > 0.1$).

asked, complained of side effects during any of the periods of medication, six of the nine patients commented that, during the period in which they had been taking atenolol, the drug appeared to be having no effect, and two patients said that they felt more alert while taking atenolol than during the other three treatment periods. When asked which drug they thought controlled their tremor best, four favoured propranolol, four sotalol, and only one patient chose atenolol.

Table 3 Changes in patients' subjective tremor scores during treatment with placebo, propranolol, sotalol, and atenolol

Patient	Placebo	Propranolol	Sotalol	Atenolol
1	7	8.5	7	10
2	10	9	4	9.5
3	0	0	0	0
4	2.5	3.5	3.5	3
5	7	3	3	4.5
6	9.5	5	7	10
7	10	6	8.5	9
8	4	2	0.5	1
9	6	3	4	6.5
Mean score =	6.2	4.4	4.2	5.9
± 1 SEM	1.17	0.99	0.97	1.32

(Maximum tremor score=10)

Tremor is subjectively reduced compared with placebo during treatment with sotalol ($P < 0.05$). Atenolol is no better than placebo ($P > 0.1$) and is less effective than sotalol ($P < 0.05$). Propranolol is just not different from placebo ($P < 0.1$) and atenolol ($P < 0.1$). Analysis of variance with linear contrast shows that the response to propranolol and sotalol are similar ($P > 0.1$), but atenolol is less effective than these two drugs ($P < 0.02$).

Discussion

There have been few studies on the effect of different β -adrenoreceptor antagonists on essential tremor. Teravainen *et al.* (1977) compared the effects of propranolol and pindolol in essential tremor and found that propranolol produced a greater beneficial effect than pindolol. It was suggested from the above study that the membrane

stabilising property of propranolol might be responsible for the difference between the effects of the two drugs, since pindolol has no membrane stabilising activity of clinical importance (Gibson, 1974). The difference between the effects of the two drugs, however, might also be explained on the basis of the intrinsic sympathomimetic action of pindolol (Gibson, 1974) since, in the study of Teravainen *et al.*, pindolol produced an increase in tremor amplitude compared with placebo.

In the present study, no difference was detected between the effects of propranolol and sotalol on either subjective or objective tremor. Since sotalol has no clinical membrane stabilising activity (Stanton *et al.*, 1965), it is likely that the beneficial effect of propranolol in essential tremor is unrelated to a membrane stabilising action. Other clinical studies have confirmed that sotalol reduces essential tremor (Rangel-Guerra, 1974; Rinne and Kaitaniemi, 1974). Further evidence that the membrane stabilising action of propranolol is unimportant in clinical practice comes from the *in vitro* studies of Coltart and Meldrum (1970) who showed that the membrane stabilising effect of propranolol occurs at a minimum blood propranolol concentration of 10 ng/l (38.6 μ mol/l) which is approximately 100 times greater than the level associated with near maximum inhibition of exercise-induced tachycardia (Coltart and Shand, 1970). It is, therefore, reasonable to conclude that the mechanism of action of propranolol in essential tremor is related to its β -adrenoreceptor antagonistic properties.

While the site of the β -adrenoreceptors responsible for the action of propranolol in essential tremor remains undetermined, there is strong evidence that peripheral structures are important in determining the amplitude of physiological tremor. Marsden *et al.* (1967) have shown that, in man, the β -adrenoreceptors associated with physiological hand and finger tremor are situated in the forearm, since the enhanced tremor which is produced by an infusion of isoprenaline into the brachial artery is blocked immediately by the intra-arterial injection of propranolol. It has been shown that adrenaline reduces the tension and degree of fusion of incomplete tetanic contractions of slow-contracting skeletal muscle in cat (Bowman and Zaimis, 1958) and man (Marsden and Meadows, 1970), and it has been suggested that this effect is responsible, at least in part, for the enhancement of physiological tremor which occurs during adrenaline infusion. Subsequently Bowman and Nott (1970) showed that the reduction in the tension and degree of fusion of incomplete tetanic contractions of the cat soleus

muscle which is produced by sympathomimetic drugs is blocked by propranolol and butoxamine (a β_2 -adrenoreceptor antagonist) but not by practolol, which blocks predominantly β_1 -adrenoreceptors (Dunlop and Shanks, 1968; Barrett *et al.*, 1973). A direct action of adrenaline on extrafusal muscle fibres may not, however, be the only mechanism by which physiological tremor is enhanced. There is indirect evidence that adrenaline also acts on muscle spindles in man such as to increase spindle firing (Hodgson *et al.*, 1969), an action that may well contribute to the increased tremor produced by the drug.

Young *et al.* (1975) have argued against the importance of peripheral β -adrenoreceptors in essential tremor because they found that intra-arterial or intravenous propranolol blocked the augmentation of essential tremor produced by isoprenaline, but had no effect on the amplitude of the underlying tremor; however, long-term oral propranolol reduced the amplitude of essential tremor. In contrast, McAllister *et al.* (1977) showed that propranolol given in larger doses intravenously did reduce the amplitude of unstimulated essential tremor, suggesting that the negative results of Young *et al.* were caused by low plasma propranolol concentrations.

In the present study, atenolol produced less reduction in tremor than either propranolol or sotalol, despite producing the same reduction in supine and standing pulse rate as these drugs. Objective assessment of tremor showed that atenolol produced an effect between that of placebo and that of propranolol or sotalol, and the difference between the effects of the latter drugs and atenolol just reached statistical significance. The patient's subjective assessment of tremor indicated that sotalol was superior to atenolol, which was the least favoured of all three drugs. These findings suggest that atenolol may be less effective in relieving essential tremor than propranolol or sotalol in doses which have an equipotent cardiac chronotropic (β_1 -adrenoreceptor) effect. Several studies have shown that atenolol produces greater blockade of β_1 - (cardioreceptors) than β_2 -adrenoreceptors *in vitro* (Barrett *et al.*, 1973; Conway *et al.*, 1976; Coleman and Somerville, 1977) and *in vivo* in animals and man (Singh *et al.*, 1975; Vilsvik and Schaanning, 1976; Decalmer *et al.*, 1978). The present findings, therefore, suggest that β_2 -adrenoreceptor antagonism may be the mechanism of the therapeutic action of β -adrenoreceptor antagonists in essential tremor. Whether this effect is mediated via peripheral or central nervous system receptors is uncertain but

animal experiments have shown that, unlike propranolol, both sotalol (Garvey and Ram, 1975) and atenolol (Day *et al.*, 1977) do not achieve significant concentrations in the central nervous system after chronic oral administration. Since sotalol produced a similar effect on tremor to propranolol in the present study, it may be suggested that it is the peripheral effect of these drugs which is of greater importance in reducing the amplitude of essential tremor.

In conclusion, the present study of a small number of patients with essential tremor has shown that the reduction in tremor produced by propranolol is not the result of a membrane stabilising action since β -adrenoceptor antagonists with (propranolol) and without (sotalol) this property were equally effective in reducing tremor amplitude. Evidence has also been provided that the beneficial effect of β -adrenoceptor antagonists in this condition is the result of a peripheral β_2 -adrenoceptor action on either muscle fibres or spindles, or both.

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