

Beta-adrenoreceptor mechanisms in essential tremor; a double-blind placebo controlled trial of metoprolol, sotalol and atenolol

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SUMMARY In order to elucidate the mode of action of beta-adrenoreceptor antagonists in essential tremor, the efficacy of chronic oral administration of metoprolol, atenolol and sotalol was compared in a randomised, double-blind placebo controlled trial in twenty-four patients. Only sotalol proved superior to placebo on both subjective and "objective" assessments. Metoprolol and sotalol produced comparable degrees of beta-adrenoreceptor antagonism as judged by the blockade of standing tachycardia. Atenolol, in the dose used, produced a trend towards a greater cardiac chronotropic effect. These findings provide no support for the concept that central or peripheral beta₁-adrenoreceptor mechanisms are important in essential tremor. The beneficial effect of beta-adrenoreceptor antagonists may be mediated predominantly through peripheral beta₂-adrenoreceptor mechanisms.

Essential tremor is a common disorder which has been regarded as a form of exaggerated physiological tremor.¹ While physiological tremor, and the tremor of anxiety and thyrotoxicosis, appear to be mediated via peripheral beta₂-adrenoreceptor mechanisms,² the mode of action of beta-adrenoreceptor antagonists in essential tremor remains contentious. Evidence from some clinical trials has supported the notion that the beneficial effects of such drugs are mediated mainly via peripheral beta₂-adrenoreceptor mechanisms.^{3,4} However, studies utilising local intra-arterial, or intravenous, injection of propranolol have implicated central mechanisms.⁵ In addition, recent reports have suggested that the cardio-selective beta-adrenoreceptor antagonist metoprolol may be effective in reducing the amplitude of essential tremor.⁶⁻⁹ Indeed, Ljung¹⁰ has proposed that central beta₁-adrenoreceptor mechanisms may be important in this condition. Unfortunately, many of these studies were not adequately controlled. Some were single-blind or open studies, without placebo refer-

ence, and often the dose of metoprolol may have been in excess of that preferentially acting on beta₁ adrenoreceptors. We have, therefore, carried out a double-blind placebo-controlled trial comparing metoprolol with atenolol and sotalol in patients with essential tremor. Atenolol, like metoprolol, is a relatively selective beta₁-adrenoreceptor antagonist but, unlike metoprolol, it has difficulty entering the CNS.¹¹ Sotalol, a non-selective antagonist acting mainly peripherally,¹² and propranolol, which acts both centrally and peripherally, are equipotent in reducing the severity of essential tremor.³ A preliminary report of this study has appeared elsewhere.¹³

Patients and methods

Twenty-four patients with classical essential tremor gave their informed consent to participate in the trial. Eighteen were male and six female; the average age was 54 years (range 25-71). A family history of essential tremor was obtained in eight patients. All patients had had tremor for more than one year, the range being 1.5 to 30 years. Diagnosis, established after full neurological and general examination, was based upon the presence of a postural tremor, with or without a degree of action tremor and titubation, in the absence of rest tremor of Parkinsonian type or other signs of extra-pyramidal or cerebellar dysfunction. All patients had normal serum electrolytes, liver function tests, random blood glucose and thyroxine levels.

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Patients with a history of diabetes mellitus, bronchial asthma or heart disease were excluded. All therapy was discontinued for two weeks prior to entry to the trial (the "run-in" period).

Protocol

The trial was double-blind and placebo controlled; it was conducted at three centres. Each patient was studied at least once, without any medication, during the two week "run-in" period, following which they were randomly allocated to treatment or placebo periods, each of which lasted two weeks. Patients were asked to take their tablets at 10 a.m. and 10 p.m.; compliance was checked by counting tablets at the end of each period.

Seventeen patients received metoprolol 50 mg twice daily, sotalol 80 mg twice daily, atenolol 50 mg twice daily or placebo (ascorbic acid 50 mg twice daily) in randomised order. A further seven patients received metoprolol 100 mg twice daily and sotalol, atenolol and placebo as before. Assessments were carried out by the same observers as near as possible at the same time of day (11 a.m.–1 p.m.) in the same environment. Heart rate and blood pressure were recorded lying and standing after patients had rested recumbent for 10 minutes. Patients were then asked to rate their tremor on a 100 mm scale, to give a subjective score (worst = 0, best = 100). They were then asked to write name and address and to draw standard spiral and sinusoidal lines. Handwriting, spiral and sinusoidal drawings were later scored "blind" by the observer and by another "blind" assessor on a 0–5 scale (0 = no tremor; 5 = severe tremor, such as to render writing illegible and drawings unrecognisable). The tremor score for each test (observer and assessor) was added to give a total "objective" tremor score for each two-week period, giving a maximum total tremor score of 30. In addition, each patient was asked to complete the Gibson Maze^{14,15} as fast as possible. All contacts between the patients' tracing and the printed diagrams were counted to give a contact score. Mazes were not completed during the "run-in" period in ten patients and mean "run-in" scores are not included in the analysis. Tremor scores were analysed using the Wilcoxon signed

rank test for paired samples. Rise in heart rate, and diastolic blood pressure, on standing were analysed using the Kruskal-Wallis test for one-way analysis of variance by ranks, and the Mann-Whitney U test. A probability level of 5% was accepted as significant.

Results

CHANGES IN PULSE AND BLOOD PRESSURE

All drugs caused a decrease in standing tachycardia compared with placebo (fig 1), although these differences were not statistically significant (Kruskal-Wallis one-way analysis of variance by ranks). Diastolic blood pressure was decreased in all treatment groups when compared with placebo (fig 2) but the differences only reached statistical significance ($p < 0.05$; Kruskal-Wallis one-way analysis of variance by ranks) when the results of the whole group of 24 patients were considered. Statistical analysis using the Mann-Whitney U test revealed statistically significant differences between placebo and metoprolol ($p < 0.01$), atenolol ($p < 0.023$), and sotalol ($p < 0.006$), but not between any of the three drugs. Changes in pulse and blood pressure were therefore comparable for the three drugs, although atenolol produced a trend towards a greater depression of standing tachycardia than metoprolol or sotalol.

TREMOR SCORES

A Subjective scores (table 1: fig. 3)

Analysis of scores of the first seventeen patients revealed that only sotalol was beneficial when compared with placebo ($p < 0.01$). There were no statistically significant differences between the three drugs. Considering all patients, sotalol still obtained a higher rating than placebo ($p < 0.01$), but atenolol and metoprolol also proved better than placebo (p

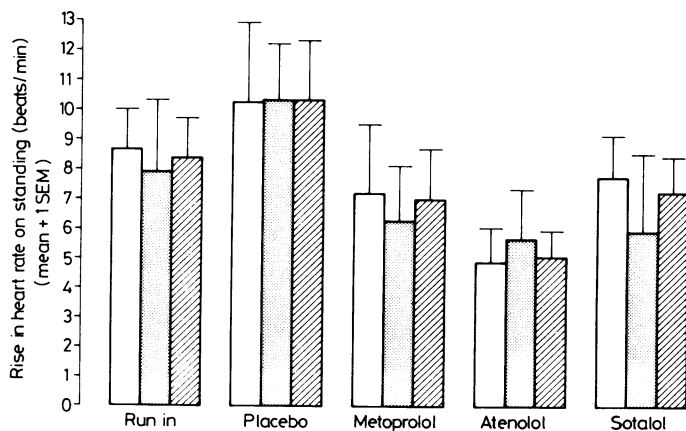


Fig 1 Rise in heart rate on standing (beats per minute, Mean + 1 SEM) for 17 patients (open columns) taking metoprolol 50 mg twice daily, 7 patients (stippled columns) on metoprolol 100 mg twice daily, and all 24 patients (hatched columns), during the run-in period and the phase on placebo, metoprolol, atenolol (50 mg twice daily) and sotalol (80 mg twice daily). No significant differences between drugs (see text).

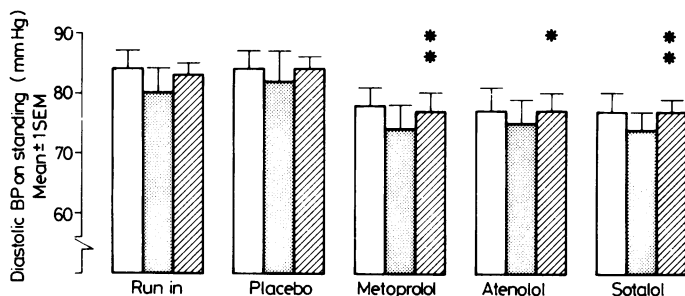


Fig 2 Fall in diastolic blood pressure on standing (MM Hg, + 1 SEM) for 17 patients (open columns) taking metoprolol 50 mg twice daily, 7 patients (stippled columns) on metoprolol 100 mg twice daily, and all 24 patients (hatched columns) during the run-in period and the phase on placebo, metoprolol, atenolol (50 mg twice daily) and sotalol (80 mg twice daily). * $p < 0.05$ ** $p < 0.01$ (Mann-Whitney U test) compared with placebo.

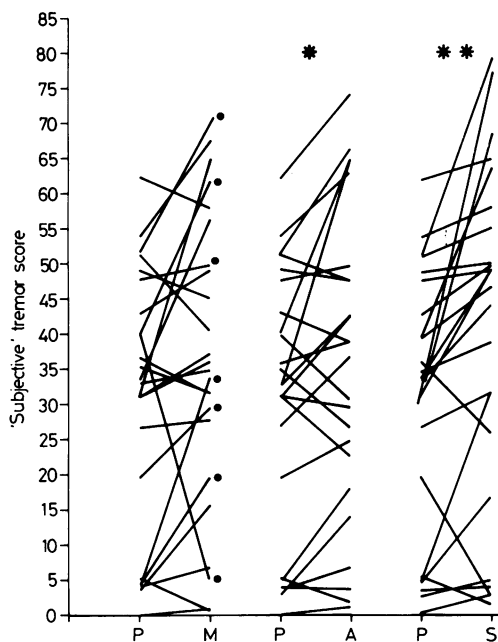


Fig 3 Individual subjective tremor scores. P = placebo, M = metoprolol, A = atenolol (50 mg twice daily), S = sotalol (80 mg twice daily). * indicates metoprolol 100 mg twice daily (seven patients); remainder took 50 mg twice daily. * $p < 0.05$; ** $p < 0.01$ (Wilcoxon signed rank test) for all patients compared with placebo.

< 0.05). Once again, there were no statistically significant differences between the drugs.

B "Objective" scores (table 2: fig. 4)

In the first seventeen patients all drugs reduced tremor scores but the difference between drug scores and placebo scores was only statistically significant for sotalol ($p < 0.01$) and atenolol ($p < 0.05$). When all patients were considered, atenolol and sotalol proved better than placebo ($p < 0.05$ and $p < 0.012$, respectively). In the first seventeen patients sotalol proved more effective than metoprolol ($p < 0.05$), but there was no difference between sotalol and atenolol, or between metoprolol and atenolol. When scores of all patients were analysed together, sotalol again proved better than metoprolol ($p < 0.05$), but not atenolol. Tremor scores were lower for all these drugs when compared with scores for the "run-in" period ($p < 0.01$ in each case). There were no statistically significant differences between "run-in" and placebo scores, although the latter were always lower than the former.

Analysis of scores from the Gibson Maze Test (table 3) revealed that mean scores were lowest for sotalol but that the difference did not reach statistical significance, either for the first seventeen patients or for the complete series. In two patients the tracings were so grossly erratic that they could not be scored.

No patients experienced troublesome, unwanted effects with any of the drugs. Compliance, as judged by tablet counting, was excellent.

Table 1 Subjective tremor scores derived from analogue scale

	"Run-in"	Placebo	Metoprolol	Atenolol	Sotalol
17 patients*	34(4.3)	31(4.6)	36(5.1)	35(5.3)	40(5.8)§
7 patients†	39(9.8)	30(7.6)	39(8.6)	38(9.4)	41(9.3)
All patients	35(4.1)	31(4)	37(4.3)‡	36(4.5)†	40(5)§

*Metoprolol 50 mg twice daily.

†Metoprolol 100 mg twice daily.

‡ $p < 0.05$; § $p < 0.01$ (Wilcoxon signed rank test) compared with placebo.

Scores 0 = severe tremor at its worst, 100 = no tremor.

Means (± 1 SEM) are shown.

Table 2 "Objective" tremor scores (handwriting + spiral + sinusoidal)

	"Run-in"	Placebo	Metoprolol	Atenolol	Sotalol
17 patients*	11.2(1.5)	10.4(1.6)	9.0(1.1)	7.9(1.2)§	7.1(1.5)¶§
7 patients†	15.0(3.0)	12.7(3.3)	14.0(3.4)	12.3(3.0)	13.0(3.7)
All patients	2.3(1.4)	11.0(1.5)	10.5(1.3)	9.2(1.2)‡	8.8(1.6)¶§
% improvement (all patients) compared with placebo	—	—	4.5	16.0	20.0

*Metoprolol 50 mg twice daily.

†Metoprolol 100 mg twice daily.

‡p < 0.05; § p < 0.01 (Wilcoxon signed rank test) compared with placebo.

¶p < 0.05 (Wilcoxon signed rank test) compared with metoprolol.

Scores 0 = no tremor, 30 = maximum tremor score.

Means (± 1 SEM) are shown.

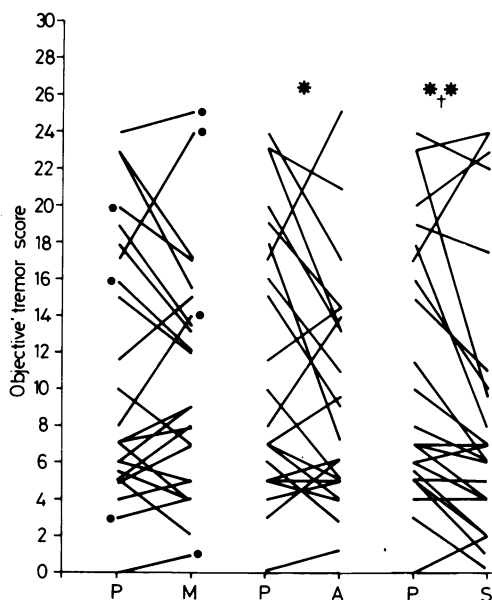


Fig 4 Individual "objective" tremor scores. A rise in score indicates greater tremor. P = placebo, M = metoprolol, A = atenolol, S = sotalol. * indicates metoprolol 100 mg twice daily (seven patients); remainder took 50 mg twice daily. † p < 0.05; ** p < 0.01 (Wilcoxon signed rank test) for all patients compared with placebo: ‡ p < 0.05 sotalol compared with metoprolol.

Table 3 Scores derived from Gibson Maze Test

	Placebo	Metoprolol	Atenolol	Sotalol
17 patients*	18(5.1)	14(5.4)	13(3.2)	10(2.6)
5 patients†	23(4.2)	20(3.1)	21(2.4)	21(3.0)
All patients	19(4.1)	15(2.3)	15(2.3)	13(2.3)

*Metoprolol 50 mg twice daily.

†Metoprolol 100 mg twice daily; two patients' traces not scored. The number of points of contact between the patients' tracing and the Maze diagram is shown (as means ± SEM). A high score indicates much tremor.

Discussion

Many patients with essential tremor benefit from treatment with beta-adrenoreceptor antagonists such as propranolol, but the mechanism by which this effect is mediated remains uncertain. Previous clinical evidence from our own studies supported involvement of peripheral beta₂-adrenoreceptor mechanisms. Thus, propranolol and sotalol were equally effective in reducing tremor.³ Propranolol is non-selective and enters the CNS with relative ease; sotalol also is non-selective, but achieves only low CNS concentrations after oral administration.¹² The cardio-selective beta₁-adrenoreceptor antagonist atenolol was less effective in controlling tremor than both propranolol and sotalol in doses with an equivalent cardiac chronotropic effect.³ Similarly, in another study atenolol was less effective than timolol which, like sotalol, is non-selective and relatively hydrophilic so probably acts mainly via peripheral adrenoreceptor mechanisms.⁴ However, some evidence has thrown doubt upon this interpretation. Whereas physiological or isoprenaline-induced hand tremor can be blocked by intra-arterial injection of propranolol, underlying essential tremor is not affected, although it may be reduced by intravenous injection of propranolol.^{5,16} These observations led the authors to suggest that the effect of propranolol might be mediated by a central action, or possibly by way of a metabolite, since chronic oral administration appeared to be more effective than both intra-arterial and intravenous administration.⁵ Further doubt concerning the role of peripheral beta₂-adrenoreceptor mechanisms in essential tremor arose from reports that metoprolol, a cardio-selective adrenoreceptor antagonist which enters the brain with relative ease, was beneficial.⁶⁻⁹ These observations led Ljung¹⁰ to suggest that central beta₁-adrenoreceptor mechanisms might be important in essential tremor.

In the present double-blind trial we compared metoprolol, atenolol and sotalol with placebo. We

used a low dose of metoprolol (50 mg twice daily) in seventeen patients in order to avoid loss of cardio-selectivity. A further seven patients received a higher dose of metoprolol (100 mg twice daily). Blockade of standing tachycardia and reduction in standing diastolic blood pressure were similar with all three drugs, although atenolol had a tendency to a greater effect upon standing tachycardia, and sotalol had a greater effect upon blood pressure than the other drugs. As it turns out, these comparative effects of the different beta-blockers on the rise in pulse rate on standing, and diastolic blood pressure on standing, add to the interpretation of their significance of their actions in essential tremor. Atenolol had more effect on pulse and blood pressure than sotalol, but had less effect on essential tremor. So beta₂-antagonism appears to be important for tremor relief. For reasons already mentioned, the adrenoreceptors involved are likely to be peripheral, although with chronic treatment it is possible that even hydrophilic beta-adrenoreceptors such as atenolol and sotalol may enter the CNS in significant amounts.¹⁷ However, despite its powerful beta₂-antagonist actions and its central effects, metoprolol proved no better than placebo in doses of 50 mg or 100 mg twice daily, although it has been shown to have greater effects upon pulmonary beta₂-adrenoreceptors (at a dose of 100 mg twice daily) than atenolol (100 mg daily).¹⁸ This raises the possibility that atenolol exerts its beneficial effect at least partly via peripheral beta₁-adrenoreceptor mechanisms.

Recent studies support our findings. Larsen and Teravainen¹⁹ compared oral atenolol (100 mg daily), metoprolol (150 mg daily) and propranolol (240 mg daily) with placebo in a double-blind cross-over study in twenty-four patients with essential tremor. Propranolol was most, and metoprolol least effective in reducing the amount of tremor, although all drugs produced statistically significant decreases in the amount of tremor when compared with placebo. Calzetti *et al*²⁰ have also compared metoprolol with propranolol. In an *acute* experiment, they gave single oral doses of metoprolol (150 mg), propranolol (120 mg) or placebo to essential tremor patients, and assessed the amount of tremor before and 1.5 hr after treatment. Both drugs produced an equivalent reduction in tremor, and both were superior to placebo. However, in a *chronic* cross-over study using two oral dosage regimes (150 mg and 300 mg daily for metoprolol and 120 mg and 240 mg daily for propranolol) only propranolol produced a statistically significant reduction in tremor when compared with placebo. In both acute and chronic experiments, the degree of blockade of standing tachycardia was the same for both beta-

antagonists. Development of tolerance to metoprolol and the difficulties of obtaining accurate assessment of tremor, which may fluctuate considerably in severity from moment to moment, were suggested as explanations for these discrepancies. Alternatively, the dose of metoprolol given acutely (150 mg) may have led to blockade of beta₂-receptors.

Our study thus provides no support for the notion that central beta₁-adrenoreceptors mechanisms are responsible for the beneficial actions of beta-antagonists on essential tremor. They point to peripheral beta₂-adrenoreceptor antagonism as the main therapeutic action. We cannot exclude the contribution of a central effect, or of a peripheral beta₂-antagonist action, but neither appears critical. Further work is necessary to clarify the discrepancy between the effects of intra-arterial and oral beta-adrenoreceptor antagonists upon tremor, and between acute and chronic administration of such agents. For asthmatic patients with essential tremor warranting treatment, metoprolol may be at once more hazardous, and less effective, than atenolol.

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