Metoprolol and propranolol in essential tremor: a double-blind, controlled study

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SUMMARY Single oral doses of propranolol (120 mg), metoprolol (150 mg) and placebo were given in a randomised, double-blind fashion to 23 patients with essential tremor. Both β blockers were significantly more effective than placebo in reducing the magnitude of tremor. The decrease in tremor produced by metoprolol (47, sem 9%, $n = 23$) was not significantly different from that observed after propranolol (55, sem 5%, $n = 23$). Tachycardia on standing was antagonised by both drugs to a similar extent. These findings suggest that metoprolol may represent a valuable alternative to propranolol in the treatment of essential tremor. The data is consistent with the hypothesis that the tremorolytic effect of β blockers in these patients may be unrelated to peripheral β -2 adreno-receptor blockade, being possibly mediated by other central or peripheral modes of action of these drugs. However, it cannot be excluded that at the dose used, metoprolol had lost its relative cardio-selectivity and that the reduction in tremor was mediated by competitive antagonism at β -2 receptor sites in skeletal muscle.

Essential tremor, with its familial and senile varieties, is a tremor of posture and action mostly involving the upper limbs which usually develops in adult life in the absence of other demonstrable neurological abnormalities.^{1,2} The frequency of the tremor is usually quoted as ranging from 5-9 Hz³ and, as with all tremulous disorders, its amplitude is exacerbated by anxiety and stress. In spite of being classified as benign, in some patients the tremor may be severe enough to disrupt occupational and social activities. Alcohol can be effective in reducing the amplitude of this tremor,⁴ but this therapy is impracticable because of the risk of addiction and other medical problems.

To date, the drug which has been proven to be of greatest therapeutic benefit is propranolol.⁵⁻⁸ The mechanism by which propranolol exerts its therapeutic effect in essential tremor is incompletely understood. Many authors accept that the reduction in tremor is mediated predominantly by blockade of peripheral beta adrenergic receptors^{6,9} but other sites of action have also been postulated.^{10,11} In a recent double-blind study, atenolol, a cardio-selective

β blocking drug, which therefore has preferential action on β -1 receptors, was found to be less effective than either propranolol or sotalol, two non-selective β blockers, on reducing the severity of tremor.¹² This data was interpreted as evidence that the therapeutic effect of β blockers on essential tremor is mediated by the action on peripheral β -2 receptors. This conclusion has recently been challenged following reports that metoprolol, another cardio-selective drug, can be highly effective in reducing tremor in some patients.¹³⁻¹⁷ Unfortunately, most of these later reports are based on uncontrolled clinical observations and do not provide a reliable estimate of the relative efficacy of metoprolol in the treatment of essential tremor.

In the present paper we report the results of a double-blind, placebo controlled study on the comparative effect of a single oral dose of metoprolol and propranolol in patients with essential tremor.

Methods

Patients

Twenty-three patients with essential tremor (15 male and 8 female), aged between 19 and 72 years (mean age 49.2 years), who were attending the Out Patient Clinics at the National Hospital for Nervous Diseases, Queen Square, gave their informed consent to participate in the study. The diagnosis was established on the basis of the

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clinical history and detailed general and neurological examination accompanied by ancillary laboratory investigations. All patients had been symptomatic for at least one year (range 1 to 38 years) prior to the study. In eleven patients there was a family history of tremor affecting hands and head. Serum triiodothyronine and thyroxin were within normal limits in all cases. Fourteen patients were not receiving any drug therapy for tremor at the time of study. One patient was taking lorazepam (1 mg three times daily) and this was continued unaltered throughout the study. Eight patients on chronic β blocking therapy (propranolol, range 20-240 mg daily) agreed to have their treatment discontinued gradually and remained drug free for at least one week prior to and until the completion of the study. Patients with a history of excessive alcohol consumption, congestive cardiac failure, heart block, diabetes mellitus and asthma were excluded.

Protocol

The study was double-blind and placebo controlled. Each patient was studied on three different occasions, separated by an interval of at least one week. Tests were performed in the morning, approximately three hours after a light breakfast. The patients were instructed to abstain from smoking and from taking alcohol or caffeinated beverages for at least 12 hours before testing. After 15 minutes rest, piezo-resistive linear accelerometers (Endevco 7625-10) were attached with adhesive tape, their sensitive axes orientated in the vertical plane, to the dorsal surface of each hand in the second interspace 1 cm proximal to the metacarpophalangeal joints. These devices weighed 6 gm and had a frequency response extending from a steady state acceleration to 300 Hz with a sensitivity of 50 mv/g. (g = acceleration of gravity). Hand tremor was assessed with the patient seated, fully relaxed and looking directly ahead. The forearms were supported up to the wrist, and the hands were unsupported and outstretched horizontally in pronated posture during the recording. Three separate tremor recordings of about one minute duration were obtained at five minute intervals and to minimise the possible effects of fatigue the hands were allowed to rest freely between recordings. The patient's position was monitored throughout the recordings by closed circuit video. Accelerometric signals were amplified and recorded simultaneously on paper and magnetic tape for subsequent analysis. Measurements of pulse rate and blood pressure were obtained after a ten minute period of rest in the supine position and repeated after 1, 2 and 3 minutes of standing. At this stage the patients were given a single oral dose of propranolol hydrochloride (Inderal), metoprolol tartrate (Betaloc) or placebo together with 50 ml of plain water. The selected dose of propranolol was 120 mg as this dose had previously been shown to be superior to placebo in reducing essential tremor when given on a daily basis.⁷ The dose of metoprolol given was 150 mg which, on the basis of available data, produces a degree of cardiac β blockade equivalent to that produced by 120 mg propranolol.¹⁸ The order of treatment was randomised.

Recording of tremor, measurement of supine and

standing heart rate and blood pressure were repeated at 1.5 hours after drug administration at a time when the serum level of both β blockers was expected to be approaching the maximum. All measurements were performed by the same investigator (SC).

Tremor analysis

Analysis was performed off line using a Hewlett Packard 5420A signal analyser.¹⁹ For each condition (that is before or after treatment) the programme averaged 150 auto-spectra each derived from overlapping 10-24 second samples of tremor. Fifty samples were taken from the beginning of each of the three separate recordings and approximately 45 seconds of tremor recording contributed to the analysis of each condition. The advantage of "overlap" analysis is that it compensates for the reduced contribution of the beginning and end of the data sample which results from the application of a window. The spectra, averaged thus, were displayed for measurement in the form of "auto-spectra"

Fig 1 Computer print out of averaged (#A) 150 auto-spectra derived from overlapping 10-24 samples of tremor before (A) and after (B) metoprolol (150 mg) in a patient included in the study. On the vertical axis tremor magnitude scaled in root mean squared acceleration as $g \times 10^{-3}$ ($g = 981 \text{ cm/sec}^2$) and on the horizontal axis tremor frequency (Hz). X gives value of frequency of dominant peak and Y value of its magnitude (arrow).

in which the root mean squared (rms) magnitude of the frequency components was plotted as a function of frequency. For a simple characterisation of the tremor, measurements were taken of the frequency (Hz) of the dominant peak and of its amplitude scaled in rms acceleration, the unit of acceleration being taken as $1g$ ($g = 981 \text{ cm/sec}^2$). As it was found that the dominant tremor frequency did not vary significantly before and after treatment, the amplitude of acceleration is proportional to the amplitude of hand displacement, that is, amplitude of displacement = $(\text{acceleration} \times 981) / 4 \times \pi^2 \times \text{frequency}^2$ cm rms.

In each patient only the data obtained from the more affected hand was used for computation of results. It was interesting to note that in three patients the more involved hand differed from one session to another. An example of computer "print out" of tremor analysis before and after a single oral dose of metoprolol is illustrated in fig 1.

Statistical analysis

Values of tremor magnitude were compared by using the Wilcoxon's test for paired differences. Statistical analysis of heart rate and blood pressure values were performed by using the Student's t test for paired data. For testing the correlation between the reduction of tremor magnitude and the inhibition of standing tachycardia, Spearman rank correlation coefficient was used.

Results

TREMOR

The frequency of the dominant peak of the hand tremor of the patients included in the study ranged from 4.3 to 8.5 Hz. In any single patient the frequency was similar in all pre-drug recordings and did not change significantly after the administration of the β blockers. Prior to drug administration the peak magnitude of tremor ranged from 3.2 to $920 g \times 10^{-3}$ and showed considerable variation between and within patients on different occasions of recording. However, *within* any single pre-drug recording session there was little fluctuation in tremor magnitude.

After the administration of placebo, the magnitude of tremor decreased in 14 patients, increased in three patients and remained unchanged in six (that is, showed a change of less than 15%). Following the administration of propranolol, the tremor decreased in 20 patients and remained substantially unchanged in two (one patient who had received metoprolol and placebo was lost to follow-up and his response to propranolol could not be studied). Administration of metoprolol was associated with a reduction in tremor magnitude in 20 patients and an increase in three patients (fig 2). On average the magnitude of tremor decreased by $22 \pm 7.3\%$ (sem) after placebo (NS), by $55 \pm 5.0\%$ (sem) after propranolol ($p < 0.01$) and by $47 \pm 9.7\%$ (sem)

Fig. 2 Effect of placebo, propranolol (120 mg) and metoprolol (150 mg) on postural hand tremor in the patients included in this study.

Fig 3 Percentage change in tremor magnitude after administration of placebo, propranolol (120 mg) and metoprolol (150 mg) in the patients studied. Histograms represent the mean change $\pm$ sem (* $p < 0.01$ compared with placebo).

after metoprolol ($p < 0.01$) (fig. 3). The reduction in tremor magnitude produced by both propranolol and metoprolol was significantly greater than that observed after the administration of placebo ($p < 0.01$) irrespective of whether the results were calculated as absolute or as percentage change values. The decrease in tremor magnitude produced by propranolol, on the other hand, was not significantly different from that observed after metoprolol. There was suggestive evidence that the response might be influenced by the base-line amplitude and frequency of the tremor. All the patients with a tremor peak frequency below 8 Hz improved after propranolol, whereas of the three patients whose peak frequency exceeded 8 Hz, two failed to respond. The peak frequencies of tremor in the three patients who did not improve after metoprolol were 7.7 Hz, 7.5 Hz and 6.4 Hz respectively.

HEART RATE AND BLOOD PRESSURE

There was no significant difference in the pulse rate recorded at 1, 2 and 3 minutes after standing in each subject and therefore the mean of the three values was taken for further calculations.^{20 21} Pre-drug values of supine and standing pulse rate and systolic blood pressure did not differ significantly between treatments.

Propranolol and metoprolol diminished the normal increase in pulse rate on standing ($p < 0.01$) whereas placebo had no effect (fig 4). The reduction in standing tachycardia produced by metoprolol was similar to that observed after propranolol. There was no significant correlation between reduction in tremor magnitude and the inhibition of

Fig 4 Increase in pulse rate on standing before and after administration of placebo, propranolol (120 mg) and metoprolol (150 mg). Bars represent the mean $\pm$ sem (* $p < 0.01$ as compared with pre-drug values and placebo).

Fig 5 Effect of placebo, propranolol (120 mg) and metoprolol (150 mg) on lying (L) and standing (S) systolic blood pressure. Bars represent the mean $\pm$ sem (* $p < 0.05$ as compared with pre-drug values and placebo).

standing tachycardia following the administration of the two β blocking drugs: (propranolol: $r_s = 0.073$; metoprolol: $r_s = 0.01$). Metoprolol and propranolol reduced the systolic blood pressure significantly as compared with base line and placebo, in the supine and standing positions ($p < 0.05$) (fig 5).

Discussion

The present study provides the first clear demonstration that a single oral dose of either propranolol or metoprolol is significantly better than placebo in reducing the magnitude of essential tremor. Both β blockers reduced the tremor magnitude to approximately 50% of the base-line value. A moderate (but statistically non-significant) improvement in tremor, however, was also seen after the administration of placebo, an observation that emphasises the importance of using a controlled designed trial if a reliable estimate of drug efficacy is to be obtained. The rapid improvement in tremor after a single oral dose of β blocker is in agreement with the results previously obtained by Morgan *et al*⁸ who found that single oral doses of propranolol were effective in reducing the amplitude of tremor in four out of five patients. McAllister *et al*⁶ also found a rapid reduction in tremor amplitude following intravenous administration of propranolol in six patients. Young *et al*¹⁰ on the other hand, found intravenous propranolol ineffective and oral propranolol fully effective only after a latent period of 24-48 hours. It is possible that differences in dosage and experimental design were responsible for the apparent discrepancy between our results and those reported by the latter authors.

In a more recent study Jefferson *et al*¹² found that atenolol, a cardio-selective β adrenoceptor blocking drug, was significantly less effective than either propranolol or sotalol in the treatment of tremor. They concluded that the action of β blockers in essential tremor is predominantly mediated by blockade of peripheral β -2 adrenergic receptors, analogous to a mode of action of the same drugs in suppressing isoprenaline-enhanced physiological tremor.^{10 22-24} In the present study metoprolol, another cardio-selective drug, was at least as effective as propranolol in reducing the magnitude of essential tremor. Both drugs were given in doses that are considered to produce approximately equal cardiac β -1 receptor blockade.^{18 25} Even if the inhibition of standing tachycardia is a rather imprecise measure of β -1 blocking activity, the fact that propranolol and metoprolol reduced standing heart rate to virtually the same extent, provides additional evidence that the two drugs had a similar effect on cardiac β receptors in the doses used. Under these circumstances the efficacy of metoprolol in reducing essential tremor may be explained in two ways: either (1) at the dose used, the drug had lost its relative cardio-selectivity and thus its suppressive effect on tremor could then be related to blockade of peripheral β -2 adrenergic receptors, or (2) cardio-selectivity was at least in part maintained, and the reduction in tremor was mediated by an action other than blockade of peripheral β -2 receptors. The first hypothesis cannot be excluded since cardio-selectivity is a dose-dependant phenomenon and β -2 blocking effects are known to appear when metoprolol is given in doses greater than 100 mg.²⁵ Antagonism at β -2 receptor sites in skeletal muscle is known to mediate the suppressive effect of propranolol on isoprenaline enhanced physiological tremor^{10 22-24} and it is reasonable to assume that a similar mode of action may be operative in essential tremor. In this respect, it would be of interest to determine whether lower doses of metoprolol maintain their comparative efficacy in reducing the magnitude of tremor in these patients.

In contrast to the hypotheses discussed above, other authors have suggested that the therapeutic effect of β blockers in essential tremor is unrelated to peripheral β -2 receptor blockade but is mediated by central nervous system mechanisms,^{5 10 11} in analogy with the mode of action of ethanol in the same condition.⁴ The observation that metoprolol readily crosses the blood brain barrier²⁵ may be particularly relevant in this context. However, it is possible that there are other peripheral modes of action of β blocking drugs that are not associated with antagonism of adrenergic receptors. A mode of action unrelated to β -2 adrenoceptor

blockade is suggested by isolated clinical reports that relatively low doses of metoprolol can relieve essential tremor without exacerbating respiratory symptoms in patients with asthma or chronic obstructive airways disease.¹⁴⁻¹⁶ It cannot be excluded, however, that β -2 adrenergic receptors in skeletal muscle are blocked at doses of metoprolol lower than those required to block the same type of receptors in the bronchial muscles.

The experimental design used in this study provides a potentially useful approach to the evaluation of the efficacy of β adrenoceptor blocking drugs in essential tremor. One important aspect that needs to be examined in future studies is whether the effect observed after a single dose can be used to predict the pharmacological response to chronic administration. Several authors have previously commented on the fact that some patients are apparently refractory to chronic propranolol therapy while others respond particularly well.^{12 16} Although so far no reliable predictive criterion of response has been recognised in these patients, the suggestion has been made that patients with higher peak frequencies of tremor may show a comparatively less favourable response.^{26 27} In our study all patients with tremor frequency below 8 Hz improved after propranolol whereas of the three patients with tremor frequencies above 8 Hz, two failed to respond. With metoprolol the differential effect according to tremor frequency was less clear. These observations concerning the relationship between frequency and responsiveness may have important therapeutic and pathophysiological implications and deserves further evaluation.

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