*Br. J. clin. Pharmaç.* (1987), **23**, 383–389

# Effects of β-adrenoceptor blockade on heart rate and physiological tremor in diabetics with autonomic neuropathy A comparative study of epanolol, atenolol and pindolol

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**1** Eight diabetics with autonomic neuropathy were given single oral doses of epanolol (200 mg), atenolol (50 mg), pindolol (5 mg) and placebo in a double-blind randomised order at weekly intervals. Supine resting heart rate, physiological tremor and blood glucose were measured before, 2 and 4 h after dosing, and ambulatory heart rate monitored for 24 h.

**2** Supine resting heart rate was significantly lowered by atenolol both at 2 and 4 h, and increased on pindolol at 4 h. Heart rate was unaffected by epanolol compared with placebo.

**3** Heart rate during the 'waking' period (14.00–23.00 h) was lower than placebo after epanolol and atenolol but unaffected by pindolol. During the 'sleeping' period (23.00 h–08.00 h) heart rate was significantly increased by pindolol, lowered with atenolol and unaffected on epanolol.

**4** Pindolol significantly increased physiological tremor at 4 h. No differences were seen between epanolol, atenolol and placebo.

**5** Plasma glucose was significantly increased by pindolol 2 h after dosing.

**6** These results suggest that pindolol probably produces its partial agonist activity at both $\beta_1$- and $\beta_2$-adrenoceptors, while the partial agonist activity of epanolol is $\beta_1$-selective.

**7** Despite abnormal cardiovascular reflex tests in these diabetics, the heart rate responses obtained in this study after β-adrenoceptor blockade were surprisingly normal, and suggest that the concept of 'cardiac denervation' in diabetes requires modification.

**Keywords** diabetic autonomic neuropathy β-adrenoceptor blockers partial agonist activity heart rate physiological tremor

## Introduction

Some β-adrenoceptor blocking agents are known to be partial agonists at the β-adrenoceptors, for example practolol and pindolol. It is, however, unclear, especially in man, whether the stimulant effect of a non-selective β-adrenoceptor blocking drug with partial agonism is at the $\beta_1$-adrenoceptor, $\beta_2$-adrenoceptor, or both, or whether a $\beta_1$-selective partial agonist produces stimulation only at the $\beta_1$-adrenoceptor. To answer this a study measuring both $\beta_1$- and $\beta_2$-adrenoceptor function is required in which a non-selective and a $\beta_1$-selective adrenoceptor blocking agent, both with partial agonist activity (PAA), are compared in the same subjects.

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The demonstration of partial agonism of β-adrenoceptor blocking drugs at the $\beta_1$-adrenoceptor in animal models requires that the heart is surgically denervated and the animal depleted of catecholamines (Barrett & Carter, 1970). This situation may be analogous in man to diabetic patients with severe autonomic neuropathy (Watkins and Edmonds, 1983). Certainly in autonomic failure from other causes an increase in heart rate has been noted when β-adrenoceptor blocking agents with partial agonism were given (Man in 't Veld *et al.*, 1982). If β-adrenoceptor blocking drugs with PAA are given to such diabetics, increases in heart rate might occur due to $\beta_1$-adrenoceptor stimulation. Increase in physiological tremor induced by sympathomimetic amines is thought to be due to $\beta_2$-adrenoceptor stimulation (Arnold & McDevitt, 1984).

Diabetics with extensive autonomic neuropathy may therefore provide a model in man for investigating β-adrenoceptor blocking drugs with PAA. The aim of this study was to determine the effects of three different β-adrenoceptor drugs: epanolol ($\beta_1$-selective with PAA (Pringle *et al.*, 1986)), atenolol ($\beta_1$-selective with no PAA) and pindolol (non-selective with PAA) on heart rate and physiological tremor in diabetics with autonomic neuropathy. Their selectivity or otherwise has been established in man (Harry, 1977; Aellig, 1982; Norris *et al.*, 1984; Pringle *et al.*, 1986). In animals, atenolol has been shown to have no PAA, while epanolol and pindolol do (Harry *et al.*, 1974; Bilski *et al.*, 1979; Smith *et al.*, 1983). Pindolol stimulated the heart rate of catecholamine depleted rats (a $\beta_1$ effect) to a maximum of 120 beats $min^{-1}$ (Bilski *et al.*, 1979) whereas epanolol stimulated it only to 80 beats $min^{-1}$ (Data for clinical investigators on epanolol-ICI document), and therefore pindolol has more PAA than epanolol.

## Methods

### *Subjects*

Eight diabetic men (six taking insulin and two on oral hypoglycaemic agents) aged 34–58 (mean 48.5) years and mean duration of diabetes 6–28 (mean 17) years with symptomatic autonomic neuropathy and markedly abnormal cardiovascular reflex function with both parasympathetic and sympathetic involvement (Table 1) were studied (Ewing & Clarke, 1982). No subject had an abnormal 12-lead electrocardiograph (ECG) or evidence of airways obstruction. The insulin or tablet regimes were not changed in any patient during the study. The local hospital ethics committee granted approval for the study and all subjects gave their informed written consent.

### *Methods of assessment*

(a) *Heart rate* This was recorded in two ways:

(i) For 24 h after each drug, using a standard ambulatory ECG technique ('Tracker' — Reynolds Medical Co Ltd).

(ii) For the last 5 min of a 10 min period of supine rest before, 2 and 4 h after each drug. Heart rate was averaged over each 5 min period using a BBC microcomputer.

(b) *Physiological tremor* This was measured with an accelerometer (Vibro-Meter Corp, Boston,

**Table 1** Age, duration of diabetes and cardiovascular reflex test results in the eight diabetics studied

| | *Age (years)* | *Duration (years)* | *Valsalva ratio* | *30:15 ratio* | *Heart rate variation (beats $min^{-1}$)* | *Systolic BP fall on standing (mmHg)* | *Diastolic BP rise during sustained handgrip (mmHg)* |
|---|---|---|---|---|---|---|---|
| 1 | 34 | 17 | 1.04 | 0.97 | 5 | 78 | 26 |
| 2 | 51 | 28 | 1.00 | 1.00 | 3 | 50 | 28 |
| 3 | 51 | 18 | 1.01 | 1.03 | 2 | 26 | 26 |
| 4 | 52 | 22 | 1.06 | 1.00 | 1 | 22 | 14 |
| 5 | 51 | 11 | 1.41 | 1.00 | 8 | 30 | 21 |
| 6 | 58 | 12 | 1.07 | 0.97 | 17 | 70 | 14 |
| 7 | 50 | 6 | 1.80 | 0.93 | 3 | 36 | 15 |
| 8 | 44 | 24 | 1.14 | 0.97 | 0 | 26 | 19 |
| Normal values | | | ⩾ 1.21 | ⩾ 1.04 | ⩾ 15 | ⩽ 10 | ⩾ 16 |

USA—sensitivity in the vertical plane 10.05 mV $g^{-1}$) attached to the outstretched index finger of the right hand with the arm supported at the elbow. Measurements were made for a 2 min period at baseline, 2 and 4 h after each drug. The output from the transducer was recorded onto magnetic tape via the vibration module of an Instrumentation Cassette Recorder (Type DA 1442 Data Acquisition Ltd, Stockport, UK). The magnetic tape signal was subjected to a fast Fourier Transformation using a PDP11 computer and a power spectrum in the frequency 0–30 Hz obtained.

(c) *Plasma glucose* This was measured at baseline, 2 and 4 h after each drug using a standard glucose oxidase technique.

*Drugs used*

The drugs used were epanolol (200 mg), atenolol (50 mg), pindolol (5 mg) and placebo, and the doses chosen were the 'unit doses' used in clinical practice. At these doses each drug has a 24 h duration of action in man (Aellig, 1976; Harry, 1977; Floras *et al.*, 1982; Pringle *et al.*, 1986). The drugs were given as single oral doses in a double-blind randomised order with at least 1 week between dosing. Each patient received each drug and was therefore studied on four occasions.

*Procedures*

On each study day, the subjects were fitted with an ambulatory ECG tape recorder in the late morning following which they were given their midday meal. Baseline measurements of resting heart rate, physiological tremor and blood glucose were made between 12.00 and 13.00 h. The patients then received their single randomised dose of drug. Two and four hours after taking the tablets further measurements of heart rate, tremor and blood glucose were made. The patients were then allowed home to their usual daily activities while ambulatory monitoring was continued until lunchtime the following day.

*Statistical analysis*

(a) *Missing data* There was a technical fault in part of the 24 h ECG recording of patient 1 after placebo, and this data has not been used in the analysis. The tremor recording 4 h after atenolol on patient 8 was also technically unsatisfactory. The only glucose results obtained from patient 3 were at baseline and 2 h after pindolol. No blood glucose results were obtained on patient 4 after atenolol. All other data obtained from all the subjects was used in the statistical analysis of the results.

(b) *Analysis* The 24 h heart rate measurements were analysed over three periods: a first waking period of 14.00–23.00 h; a second period of 23.00 h–08.00 h, when the subjects were assumed to be asleep; and 08.00 h–13.00 h the following morning. Mean hourly heart rates and mean heart rate (mean of the mean hourly heart rates) within each of the three periods have been used in the analysis. The physiological tremor data was transformed into natural logarithms for statistical analysis as its distribution was non-normal and the transformed data was displayed as power spectra over the range 0–30 Hz (Figures 2 and 3). To give an overall measure of tremor for each patient, the log transformed readings were summed over the frequency range 0–30 Hz ('area under the curve') and this measurement was used in the analysis. These results and the resting heart rate and glucose measurements were subjected to an analysis of variance technique. Overall treatment significance was assessed by an $F$ test after which, if significant differences were found ($P < 0.05$), pairs of treatments were compared using a two sided Student's $t$-test with the residual mean square estimating the standard error. The level of significance for the $t$-tests was $P < 0.05$, calculated from the least square estimates of the means. Values given in the tables are crude means ± s.e. mean.

## Results

*Heart rate*

Mean supine resting heart rates at baseline, and 2 and 4 h after each drug are shown in Table 2. Atenolol lowered heart rate significantly, whereas at 4 h the heart rate after pindolol was higher than placebo, epanolol and atenolol. The heart rate following epanolol was similar to placebo but significantly higher than atenolol at 2 and 4 h. The 24 h mean heart rates are shown in Table 3 and Figure 1. During the 'waking' hours (14.00–23.00 h), the mean heart rates on epanolol and atenolol were less than placebo or pindolol with atenolol lower than epanolol. By contrast during the sleeping hours 23.00–08.00 h the heart rate on pindolol was significantly higher than placebo, epanolol and atenolol, while the heart rate on atenolol was lower than on epanolol or placebo.

**Table 2** Group mean resting supine heart rates (beats $min^{-1}$) at baseline, 2 and 4 h after taking each of the drugs or placebo (mean ± s.e. mean) ($n$ = 8)

| | *Baseline* | *2 h* | *4 h* |
|---|---|---|---|
| Placebo | 83.5 ± 4.8 | 80.0 ± 3.8 | 77.0 ± 3.3 |
| Epanolol | 83.3 ± 4.1 | 76.4 ± 3.9 | 74.4 ± 3.1 |
| Atenolol | 84.6 ± 3.6 | 68.8 ± 2.2 | 67.5 ± 2.2 |
| Pindolol | 84.0 ± 3.6 | 80.0 ± 2.4 | 80.9 ± 2.6 |
| *Significance values* | | | |
| Placebo *vs* epanolol | | NS | NS |
| Placebo *vs* atenolol | | $P < 0.01$ | $P < 0.001$ |
| Placebo *vs* pindolol | | NS | $P < 0.05$ |
| Epanolol *vs* atenolol | | $P < 0.05$ | $P < 0.01$ |
| Epanolol *vs* pindolol | | NS | $P < 0.01$ |
| Atenolol *vs* pindolol | | $P < 0.001$ | $P < 0.001$ |

**Table 3** Group mean heart rates (beats $min^{-1}$) during the 24 h ECG recordings after taking each of the drugs or placebo (mean ± s.e. mean) ($n$ = 8 except where indicated)

| | *14.00–23.00 h* | *23.00–08.00 h* | *08.00–13.00 h* |
|---|---|---|---|
| Placebo | 89.0 ± 1.3 | 76.6 ± 1.2 ($n$ = 7) | 91.4 ± 1.6 ($n$ = 7) |
| Epanolol | 81.5 ± 1.0 | 76.5 ± 0.9 | 86.0 ± 1.2 |
| Atenolol | 72.9 ± 0.8 | 68.0 ± 0.9 | 78.1 ± 1.2 |
| Pindolol | 85.8 ± 0.9 | 84.4 ± 1.4 | 90.1 ± 1.5 |
| *Significance values* | | | |
| Placebo *vs* epanolol | $P < 0.05$ | NS | $P < 0.05$ |
| Placebo *vs* atenolol | $P < 0.001$ | $P < 0.01$ | $P < 0.001$ |
| Placebo *vs* pindolol | NS | $P < 0.05$ | NS |
| Epanolol *vs* atenolol | $P < 0.05$ | $P < 0.05$ | NS |
| Epanolol *vs* pindolol | $P < 0.05$ | $P < 0.01$ | NS |
| Atenolol *vs* pindolol | $P < 0.001$ | $P < 0.001$ | $P < 0.01$ |

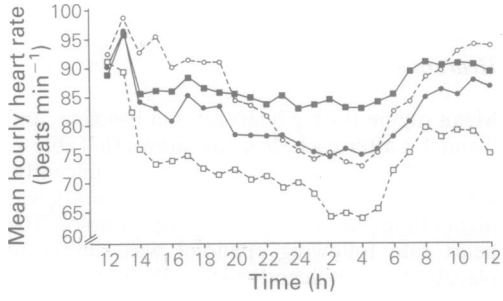


**Figure 1** Group mean hourly heart rates during ambulatory monitoring over the 24 h after dosing with placebo (○), epanolol (●), atenolol (□), and pindolol (■).

*Physiological tremor*

There were no significant changes seen in baseline physiological tremor over the four different study days thus showing that the tremor measurements were reproducible (Table 4, Figure 2). At 4 h post dose pindolol produced a significant increase in physiological tremor when compared with placebo, epanolol and atenolol. There were no differences between the tremor measurements on placebo, epanolol or atenolol (Table 4, Figure 3).

*Plasma glucose* Plasma glucose did not change significantly during the 4 h study period after placebo, epanolol or atenolol (Table 5, Figure 4). However, there was a rise after pindolol, which was significantly different from both epanolol and atenolol.

## Discussion

In our study, despite looking at a group of diabetics in whom there was clear evidence of both

**Table 4** Group mean tremor measurements (log tremor readings summed over frequency) at baseline, 2 and 4 h after taking each of the drugs or placebo (mean ± s.e. mean) ($n$ = 8 except where indicated)

| | *Baseline* | *2 h* | *4 h* |
|---|---|---|---|
| Placebo | 418.7 ± 14.8 | 409.0 ± 16.3 | 395.7 ± 14.8 |
| Epanolol | 419.8 ± 10.3 | 406.0 ± 16.2 | 402.0 ± 16.4 |
| Atenolol | 418.6 ± 13.7 | 402.9 ± 12.9 | 394.0 ± 13.8 ($n$ = 7) |
| Pindolol | 417.1 ± 16.1 | 422.6 ± 17.8 | 425.8 ± 17.6 |
| *Significance values* | | | |
| Placebo *vs* epanolol | | NS | NS |
| Placebo *vs* atenolol | | NS | NS |
| Placebo *vs* pindolol | | NS | $P < 0.01$ |
| Epanolol *vs* atenolol | | NS | NS |
| Epanolol *vs* pindolol | | NS | $P < 0.05$ |
| Atenolol *vs* pindolol | | NS | $P < 0.05$ |

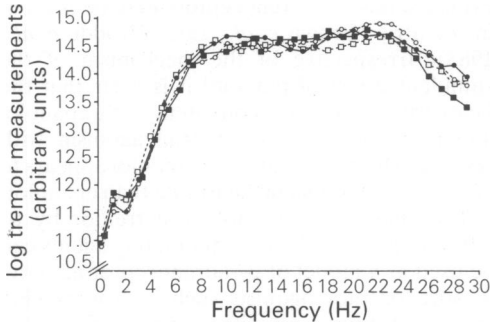


**Figure 2** Group mean log tremor measurements at each frequency (range 0–30 Hz) at baseline before dosing with placebo (○), epanolol (●), atenolol (□), and pindolol (■).

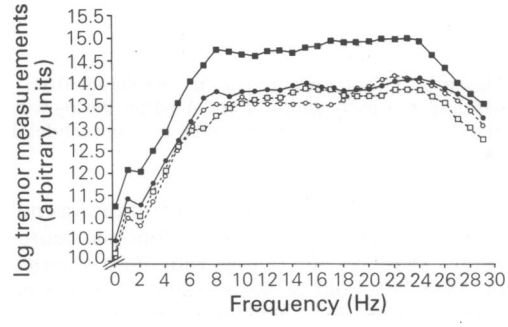


**Figure 3** Group mean log tremor measurements at each frequency (range 0–30 Hz) 4 h after dosing with placebo (○), epanolol (●), atenolol (□), and pindolol (■).

**Table 5** Group mean plasma glucose values (mmol $l^{-1}$) at baseline, 2 and 4 h after taking each of the drugs or placebo (mean ± s.e. mean) (numbers of subjects are indicated in brackets)

| | *Baseline* | *2 h* | *4 h* |
|---|---|---|---|
| Placebo | 11.1 ± 1.5 ($n$ = 7) | 11.6 ± 1.9 ($n$ = 7) | 11.6 ± 1.3 ($n$ = 7) |
| Epanolol | 14.4 ± 3.5 ($n$ = 7) | 14.6 ± 2.5 ($n$ = 7) | 13.3 ± 2.5 ($n$ = 7) |
| Atenolol | 10.1 ± 2.7 ($n$ = 6) | 11.2 ± 2.1 ($n$ = 6) | 10.5 ± 1.7 ($n$ = 6) |
| Pindolol | 11.2 ± 2.3 ($n$ = 8) | 15.1 ± 2.1 ($n$ = 8) | 16.3 ± 2.3 ($n$ = 7) |
| *Significance values* | | | |
| Placebo *vs* epanolol | | NS | NS |
| Placebo *vs* atenolol | | NS | NS |
| Placebo *vs* pindolol | | $P < 0.05$ | NS ($P$ = 0.059) |
| Epanolol *vs* atenolol | | NS | NS |
| Epanolol *vs* pindolol | | $P < 0.05$ | $P < 0.01$ |
| Atenolol *vs* pindolol | | $P < 0.01$ | $P < 0.01$ |

cardiac parasympathetic and sympathetic dysfunction, we were unable to show any direct stimulating effects of β-adrenoceptor blocking drugs with PAA. However, relative changes in heart rate emerged which were most marked during sleep, and which could be considered to be dependent upon the different degrees of PAA in the drugs used. If there had been complete absence of any sympathetic neural influence, as in the animal model, no drop in heart rate after atenolol would have been observed, and an increased heart rate after the drugs with partial agonism would have been seen, most marked on pindolol. From this evidence it might be inferred

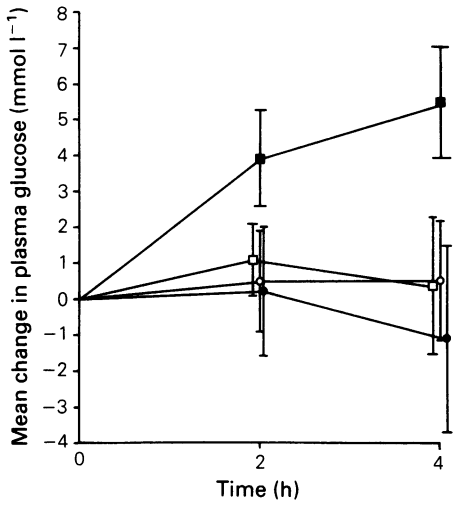


**Figure 4** Group mean (± s.e. mean) change from baseline in plasma glucose 2 and 4 h after dosing with placebo (○), epanolol (●), atenolol (□), and pindolol (■).

that complete sympathetic denervation was not present in our diabetics with autonomic neuropathy. These results contrast with those reported by Man in't Veld & Schalekamp (1981), who studied four patients with autonomic failure (two with amyloidosis, and two with idiopathic orthostatic hypotension) after treatment with pindolol, both acutely by intravenous injection and chronically by oral administration. A rise in heart rate was demonstrated on both occasions. It seems likely that these patients had more complete denervation than the diabetics in our study. Although our diabetics were severely affected with grossly abnormal tests of cardiovascular reflex function, it is apparent that complete denervation does not occur in these diabetics, and that our concepts of denervation in diabetes will have to be modified.

The diurnal variation in heart rate in these diabetics was affected by the β-adrenoceptor blocking agents used in this study in proportion to the amount of partial agonism present. The resting supine heart rate fell during the 4 h after dosage even on placebo, reflecting the normal afternoon heart rate pattern, and both epanolol and atenolol lowered heart rate significantly more than pindolol, with atenolol producing the lowest heart rate. Pindolol, by contrast, lowered heart rate significantly less and at 4h after dosing the heart rate was significantly higher than on placebo. This pattern of heart rate change was also reflected in the 24 h ECG tape recording. At night on pindolol, the drug in this study with most PAA, the heart rate was significantly higher than on placebo. On epanolol, which has less PAA than pindolol, the heart rate was similar to that on placebo, whilst after atenolol, with no PAA, the heart rate was significantly lower.

We have assumed that the heart rate changes after dosing with these drugs are mediated through cardiac $\beta_1$-adrenoceptors. Epanolol and atenolol are $\beta_1$-selective at the doses used and would appear to affect heart rate by this means. It could, however, be argued from animal experiments that pindolol, as well as acting on $\beta_1$-adrenoceptors, might also be directly stimulating cardiac $\beta_2$-adrenoceptors to effect a relative increase in heart rate (Clark *et al.*, 1982). As yet there is no convincing support for this contention in man, although there is suggestive evidence that $\beta_2$-adrenoceptors may be present in the atria (Brown *et al.*, 1983; Brodde *et al.*, 1983). Irrespective of the mechanism of the stimulant effect of pindolol it is clear that the heart rate results are consistent with epanolol and pindolol possessing partial agonism with respect to heart rate and that pindolol appears to have a greater effect on heart rate than epanolol.

The changes in physiological tremor by β-adrenoceptor blocking or stimulating agents can be used as a model of $\beta_2$-adrenoceptor activity. $\beta_2$-adrenoceptor agonists such as isoprenaline increase tremor and differences between $\beta_1$-selective and non-selective β-adrenoceptor blocking drugs can be detected in man (Arnold & McDevitt, 1984). As epanolol and atenolol are both selective $\beta_1$-adrenoceptor blocking drugs at this dosage, it was not surprising that physiological tremor was unchanged after these drugs. By contrast there was a significant increase in tremor values after the non-cardioselective drug pindolol which is known to have PAA. The effect of pindolol on tremor has not, to our knowledge, been previously demonstrated. These observations suggest that of the drugs studied only pindolol has $\beta_2$-adrenoceptor stimulating properties.

The surprising finding that pindolol, in contrast to the two cardioselective β-adrenoceptor blockers, increased blood glucose values also suggests that $\beta_2$-adrenoceptors are stimulated by this drug. Isoprenaline (a $\beta_1$- and $\beta_2$-adrenoceptor agonist), when given intravenously to man, increased blood glucose which was reduced by ICI 118,551 (a $\beta_2$-selective antagonist) and not by atenolol (Arnold *et al.*, 1985). This suggests that sympathomimetic amine-induced increases in glucose are due to stimulation of $\beta_2$-adrenoceptors probably by glycogenolysis in the liver (Koelle, 1975). The rise in glucose after pindolol in our study could therefore be explained by

stimulation of $\beta_2$-adrenoceptors. Whether this effect would be seen in all diabetics, or simply reflects some kind of denervation supersensitivity secondary to autonomic neuropathy, is unclear and further studies may clarify this.

The results presented in this study clearly demonstrate that epanolol and pindolol show evidence of partial agonism with their effects on heart rate. By contrast, stimulation of tremor and blood glucose was seen only with pindolol. Pindolol thus appears to have PAA at both $\beta_1$- and $\beta_2$-adrenoceptors, while epanolol has PAA only at $\beta_1$-adrenoceptors, at least in the doses used in this study. Similar results might be seen in normal subjects and indeed some recent preliminary evidence (McCaffrey *et al.*, 1986) would support this view. Despite the limitations of this study, therefore, we have in a group of diabetics with severe autonomic neuropathy, observed changes in both $\beta_1$- and $\beta_2$-adrenoceptor function which probably reflect the amount and selectivity of partial agonist activity in the drugs used.

We thank Mr Steve Cook, Statistician, Clinical Research Department, ICI (Pharmaceuticals Division), for his help in performing the statistical analysis. Dr D. J. Ewing is a Wellcome Trust Senior Lecturer.

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*(Received 17 May 1986, accepted 11 November 1986)*