COMPARISON OF ONCE AND TWICE DAILY ADMINISTRATION OF ACEBUTOLOL IN HYPERTENSION

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- 1 Thirteen hypertensive patients completed a double-blind comparison of placebo, acebutolol 200 mg twice daily and acebutolol 400 mg once daily, administered for 4 weeks in random order.
- 2 Blood pressure and heart rate were significantly reduced by both acebutolol treatments. The mean reduction of resting pressure 12 h after 200 mg twice daily (12/7 mmHg) was similar to that 24 h after 400 mg once daily (13/9 mmHg).
- 3 Compared to placebo, reductions in exercise heart rate and systolic pressure at 12 h after 200 mg twice daily and 24 h after 400 mg once daily were significant and similar.
- 4 β -adrenoceptor antagonism was also assessed by inhibition of the heart rate response to sublingual glyceryl trinitrate taken in the standing position. Both acebutolol treatments reduced the response; the reduction after twice daily treatment (mean 25 beats/min) was significantly greater than after once daily treatment (mean 19 beats/min).
- 5 There was no difference in blood pressure control between acebutolol administered once and twice daily in a total daily dose of 400 mg.

Introduction

Several β -adrenoceptor antagonists have been shown to lower blood pressure when administered once daily (Wilson, Morgan & Morgan, 1976; Gordon, 1976; Jeffers, Webster, Petrie & Barker, 1977; Wilcox & Mitchell, 1977; Frithz, Danielson, Henningsen, Malmberg, Nordström-Ohrberg & Schroder, 1978; Wilcox, 1978; Martin, Phillips & Smith, 1978; Waite, 1978). Most of these studies demonstrated the efficacy of once daily administration but did not specifically compare, in double-blind manner, the effects of once daily treatment with more frequent administration. We report a double-blind comparison of placebo and once and twice daily administration of acebutolol in a total daily dose of 400 g in hypertensive patients. β -adrenoceptor antagonism was assessed from inhibition of tachycardia during exercise and sublingual glyceryl trinitrate (GTN) taken in the upright position (Fitzgerald, 1970).

Methods

Seventeen patients with essential hypertension and average outpatient blood pressure (BP) greater than 150/100 mmHg entered the trial. Patients with target organ damage or asthma were excluded. Previous

hypotensive therapy was discontinued at least 4 weeks prior to entry and no patient received sedative or other drugs which could influence BP.

Each patient received three treatments administered double-blind for 4 weeks in random order:

(i) Placebo	2 capsules morning and evening
(ii) Acebutolol 400 mg once daily	2 capsules acebutolol 200 mg in the morning
2 capsules placebo in the evening
(iii) Acebutolol 200 mg twice daily	2 capsules acebutolol 100 mg in the morning and evening.

Morning and evening doses were taken from separate containers between 0.700 h and 09.00 h and 19.00 h and 21.00 h respectively. Compliance was checked by capsule contents.

Resting blood pressure and heart rate

Patients attended at two weekly intervals between 08.00 h and 10.00 h having taken no capsules on that day; therefore, observations were made at least 12 or 24 h after the last dose of active treatment. After

resting for 5 min in a quiet room, supine BP was recorded three times by the same observer (RDSW) using a Hawksley random zero sphygmomanometer and a standard 13 cm cuff. Muffling (phase 4) was taken as diastolic blood pressure (DBP). Heart rate (HR) was counted by radial palpation over 30 s and the response noted to the standard question, 'Has the treatment upset you in any way?'.

Serum drug levels

On the second visit during each 4 week period, venous blood was obtained for measurement in serum of pharmacologically active material (acebutolol plus its acetyl metabolite, M&B 16,942) using a colorimetric method (Cuthbert & Collins, 1975) at May & Baker Limited. The reproducibility of this is $\pm 5\%$.

Degree of β -adrenoceptor antagonism

At the end of each treatment period, submaximal upright bicycle exercise was performed at constant load, determined from a previous multistage test to exhaustion as the load which caused 85% of maximum heart rate (HR). After 15 min rest, subjects stood upright for 2 min and a fresh tablet of GTN 0.5 mg was placed sublingually, without chewing, for 4 min. HR was recorded each minute during the tests from the electrocardiogram recorded on a Mingograf 34 recorder, averaged over 15 s and the maximum value during exercise and after GTN used for analysis. Systolic blood pressure (SBP) during exercise was measured with a standard mercury sphygmomanometer as the level at which the Phase I sounds became audible throughout most of the respiratory cycle.

Consent

All patients gave informed consent to the trial which was approved by the hospital Ethics Committee.

Statistics

All results are expressed as mean $\pm$ 1 s.e. mean. The significance of differences between mean values was tested using Student's *t*-test (two tailed) for paired observations. For resting BP and HR, the mean values of all the observations during each treatment period were compared.

Results

Thirteen of the seventeen patients completed the trial. The following reasons accounted for the withdrawal of one patient each: poor compliance; inability to

record BP due to difficulty in hearing the Korotkoff sounds; agoraphobia requiring drug treatment; development of dizziness and tinnitus due to labyrinthitis. The last patient completed the two active treatment periods and average BP was 193/122 mmHg during once daily treatment and 204/123 mmHg during twice daily treatment.

Personal details of patients completing the trial and side effects are recorded in Table 1. Symptoms reported before treatment or during placebo were omitted.

Resting HR and BP (Figures 1 and 2)

Resting BP on placebo was $\frac{169 \pm 3}{112 \pm 3}$ mmHg.

SBP fell by 7% on once daily treatment to 157 ± 4 mmHg ($P < 0.001$) and to 156 ± 3 mmHg on twice daily treatment ($P < 0.001$). DBP fell by 6% to 105 ± 3 mmHg on once daily treatment ($P < 0.005$) and to 103 ± 2 mmHg on twice daily treatment. Differences between active treatments were not significant.

Compared to placebo, SBP fell by more than 10 mmHg in ten patients, nine on once daily treatment and eight on twice daily treatment. When SBP was compared in these patients the mean values of 156 ± 4 mmHg on once daily treatment and 154 ± 3 mmHg on twice daily treatment were not significantly different.

The reduction in resting HR (Figure 2) from 79 ± 3 to 68 ± 2 beats/min on once daily treatment ($P < 0.005$) was significantly less ($P < 0.02$) than that observed on twice daily treatment (64 ± 2 beats/min).

Exercise HR and SBP (Figure 2)

Maximum exercise HR during placebo was 137 ± 5 beats/min and decreased by 18% to 110 ± 3 beats/min on once daily treatment ($P < 0.001$) and to 109 ± 2 beats/min on twice daily treatment ($P < 0.001$); the difference between treatments was not significant.

Maximum exercise SBP was 233 ± 9 mmHg on placebo and decreased by 11% to 206 ± 5 mmHg on once daily treatment ($P < 0.005$) and to 202 ± 5 mmHg on twice daily treatment ($P < 0.005$); the difference between treatments was not significant.

GTN test

This was performed in twelve patients; 6 of 36 tests were terminated because of faintness (3 tests in patient 1). Maximum HR on placebo was 106 ± 4 beats/min and decreased to 87 ± 3 beats/min on once daily treatment ($P < 0.001$) and to 81 ± 3 beats/min on twice daily treatment ($P < 0.001$). The difference between active treatments was significant ($P < 0.05$).

Table 1 Personal details of patients completing the trial

Patient number	Sex	Age (years)	Weight (kg)	Average outpatient pressure (mmHg)	Exercise (Watts)	Side effects during once daily treatment	Side effects during twice daily treatment
1	F	41	57	220/115	65		
2	M	48	67	179/118	95		Insomnia, dreams, depression
3	F	35	63	163/100	35		
4	F	55	60	197/116	75		Raynaud's phenomenon, bronchospasm, headache
5	F	48	71	172/130	60		
6	F	37	48	180/105	75	Headache	Headache
7	F	53	96	182/112	90	Tiredness	
8	M	58	85	164/109	100	Sweating	Indigestion
9	M	52	74	190/120	80		
10	F	40	56	174/112	70	Tiredness	
11	M	45	91	153/110	115	Tiredness	
12	F	57	51	170/110	60		
13	M	58	100	163/107	110	Tiredness	
Mean $\pm$ s.e. mean		48	71	177 $\pm$ 5	79		
		$\pm$ 2	$\pm$ 5	113 $\pm$ 2	$\pm$ 6

Figure 1 Mean resting systolic and diastolic blood pressure (mmHg) ($\pm$ 1 s.e. mean) during treatment with placebo, acebutolol 400 mg once daily (400 OD) and acebutolol 200 mg twice daily (200 BD). (* P < 0.001; ** P < 0.005).

Figure 2 Mean systolic blood pressure during exercise and heart rate during exercise (●—●) and at rest (○—○) during treatment with placebo, acebutolol 400 mg once daily (400 OD) and acebutolol 200 mg twice daily (200 BD). (* P < 0.005; ** P < 0.001).

Serum drug levels

Values in patient 8 were excluded from analysis because high levels detected during the placebo period, in the absence of clinical evidence of β -adrenoceptor antagonism, suggested that the sample was incorrectly labelled. In twelve patients, there was

no significant difference ($P=0.1$) between levels on once daily treatment (0.35 ± 0.04 mg/l) and twice daily treatment (0.42 ± 0.04 mg/l).

Compliance

According to capsule counts, 93% of prescribed capsules were taken.

Discussion

Observations were made 12 to 24 h after the last dose of active treatment when the drug would be expected to be having the least effect on once or twice daily treatment. The fall in BP at rest and on exercise was statistically significant during both treatment periods and no difference was observed between treatments. Resting HR was significantly lower on twice daily than on once daily treatment. After exclusion of three patients in whom SBP at rest fell by less than 10 mmHg during either active treatment period, differences between treatments remained small and insignificant.

The modest reduction of resting BP of 6–8% was similar to that observed by Wilcox (1978) using identical treatment. We conclude that acebutolol is equally effective in reducing resting blood pressure when administered as 400 mg once daily or 200 mg twice daily; it is likely that the optimal effect occurs with higher doses in some patients (Martin *et al.*, 1978) and we suggest that titration of dose against effect is advisable.

Side effects of tiredness during once daily treatment and insomnia and dreaming during twice daily treatment may be related to high serum drug levels during the day or night respectively and

adjustment of the time of the dose may reduce these side effects (Wilson *et al.*, 1976).

Inhibition of the response to exercise and GTN indicated persisting antagonism to endogenously released catecholamines. Since differences in serum drug levels at 12 and 24 h were small and insignificant, differences in exercise HR would not be expected (Watson & Littler, 1979). Although the heart rate response to GTN is claimed to be independent of vagal effects (Fitzgerald, 1970) our own unpublished observations indicate both vagal and sympathetic components. This test detected β -adrenoceptor antagonism at 12 and 24 h after the last dose and a small but significant difference was observed between these times. Therefore, the GTN test appears to be at least as effective as bicycle exercise in detecting low levels of β -adrenoceptor antagonism in middle-aged hypertensives. The test is simple to perform in the outpatient department; however, its usefulness may be limited by the common occurrence of syncope.

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