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ATENOLOL ONCE-DAILY IN HYPERTENSION

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1 The effect of atenolol, a cardioselective β-adrenoceptor antagonist, was studied in a double-blind crossover trial in twenty-one carefully selected hypertensive outpatients. Each patient received atenolol (50 mg/day, 100 mg/day, 200 mg/day) and placebo according to a randomized sequence in a once-daily dose. Wash-out periods on a matching placebo were included between the treatment periods.

2 The effect on lying, standing and post-exercise blood pressure of atenolol 50 mg once-daily was not significantly different from atenolol 100 or 200 mg once-daily. The reduction in lying and standing blood pressure was approximately 23/16 and 22/18 mm Hg from levels at the end of a run-in period on matching placebo of 167/108 and 162/112 mm Hg respectively.

3 The study shows that atenolol is an effective hypotensive agent in a once-daily dose.

Introduction

Atenolol is a cardioselective β-adrenoceptor antagonist which is devoid of significant membrane stabilizing and partial agonist activity (Barrett, Carter, Fitzgerald, Hull & Lecount, 1973). It has a plasma half-life in man of 6–9 h (Conway, Fitzgerald, McAinsh, Rowlands & Simpson, 1976) and, when administered two or three times daily, is effective in the treatment of hypertension (Petrie, Galloway, Webster, Simpson & Lewis, 1975; Hansson, Åberg, Karlberg & Westerlund, 1975). Douglas-Jones & Cruickshank (1976) reported the use of atenolol once-daily but the design of the study was criticised because placebo periods were not included and no post-exercise readings were taken (Muir, 1976; Besterman, 1976). We report a controlled assessment of once-daily atenolol in patients with mild hypertension.

Methods

Selection of patients

The procedure that was followed has been described previously (Petrie *et al.*, 1975; Galloway, Beattie & Petrie, 1974; Petrie, Galloway, Jeffers, Millar, Smith, Wood, Lewis & Simpson, 1976).

Conduct of trial

After discharge from hospital the patients were seen at the hypertension clinic within 2 weeks. The protocol excluded patients from further participation in the trial if the lying diastolic pressure fell below 90 mm Hg after a 4-week outpatient run-in period on a matching placebo. A double-blind cross-over method was used to assess the effects on lying, standing and post-exercise blood pressure of the following four treatments each provided by identical-looking tablets and given once-daily at 18.00 h for a 4-week period: (a) atenolol (50 mg); (b) atenolol (100 mg); (c) atenolol (200 mg); (d) placebo. The order of administration was determined by a random code and each patient received all four treatments. Wash-out periods on matching placebo were included between the treatment periods. Two-week supplies of drugs were given to each patient in pre-packed containers.

The patients were seen every 2 weeks and the blood pressure of each patient was recorded using Hawksley random-zero sphygmomanometers under standard conditions at the same time of day (14.00–17.00 h–20–23 h after most recent tablet; diastolic pressure—phase 4) by the same observers. The mean of two or three blood pressure readings after 3–5 min lying and 2–3 min standing was recorded. A single reading was taken after performance of the predetermined exercise load specified for each patient. Between observer comparisons of the blood pressure readings were made at intervals throughout the trial.

The observer not recording the blood pressure completed the questionnaire on symptoms in another room. Separate forms were completed for every patient at each of seventeen visits over the 8-month trial. Questions covered volunteered information and

Table I Mean blood pressure, pulse rate and weight (± s.e. mean) during run-in period, treatment periods and wash-out periods

		Run-in															
		Visit 1	*Visit 2*	*Visit 3*	*A*		*B*		*C*		*D*		*Wash-out 1*		*Wash-out 2*		*Wash-out 3*	
					2 wks	*4 wks*	*2 wks*	*4wks*	*2 wks*	*4 wks*	*2 wks*	*4 wks*	*2 wks*	*4 wks*	*2 wks*	*4 wks*	*2 wks*	*4 wks*
								Blood pressure (mm Hg)										
Lying	Mean	163.2	161.3	166.9	143.0	144.4	144.3	143.6	138.5	151.2	160.4	160.6	155.0	164.0	161.6	163.2	156.0	162.8
systolic	s.e.	2.6	2.6	2.6	3.5	2.7	3.4	2.7	3.5	2.7	3.4	2.6	2.6	2.6	2.6	2.6	2.6	2.6
Lying	Mean	104.9	106.8	107.7	91.3	93.8	93.3	92.1	89.0	98.2	105.9	104.1	102.5	105.7	105.2	106.9	102.6	104.1
diastolic	s.e.	1.6	1.6	1.6	2.2	2.2	2.1	2.2	2.2	2.2	2.1	2.1	1.6	1.6	1.6	1.6	1.6	1.6
Standing	Mean	160.8	157.8	161.7	139.6	141.2	140.6	140.2	135.6	145.1	156.4	155.5	155.8	160.0	155.9	158.7	151.3	157.8
systolic	s.e.	2.9	2.9	2.9	2.8	3.0	2.8	3.0	2.8	3.0	2.8	2.9	2.9	2.9	2.9	2.9	2.9	2.9
Standing	Mean	110.2	110.0	111.5	97.8	97.4	98.9	94.4	95.7	99.1	109.3	108.9	109.3	110.5	108.8	109.6	106.0	110.6
diastolic	s.e.	1.8	1.8	1.8	1.7	2.0	1.7	2.0	1.7	2.0	1.7	1.9	1.8	1.8	1.8	1.8	1.8	1.8
Post-exercise	Mean	181.4	169.3	175.6	149.7	153.2	146.1	152.0	145.4	159.0	173.3	170.4	172.0	175.0	167.8	174.3	165.2	175.3
systolic	s.e.	3.5	3.5	3.5	2.8	3.9	2.7	3.8	2.8	3.9	2.7	3.7	3.5	3.5	3.5	3.5	3.5	3.5
Post-exercise	Mean	107.3	107.2	105.6	96.1	97.0	94.6	96.0	95.0	98.4	110.1	109.6	107.7	108.7	105.4	108.4	106.5	110.4
diastolic	s.e.	1.7	1.7	1.7	2.1	2.1	2.0	2.1	2.1	2.1	2.0	2.0	1.7	1.7	1.7	1.7	1.7	1.7
								Pulse rate (beats/min)										
Lying	Mean	82.3	83.9	84.2	73.6	71.2	69.7	66.1	66.7	68.1	80.1	82.8	85.3	83.8	80.9	85.6	82.1	82.9
	s.e.	2.0	2.0	2.0	1.3	1.7	1.3	1.7	1.3	1.7	1.3	1.7	2.0	2.0	2.0	2.0	2.0	2.0
Standing	Mean	91.4	95.3	92.6	79.2	76.1	72.8	69.1	67.5	70.6	89.4	93.9	95.7	93.9	88.8	94.0	93.0	97.7
	s.e.	2.8	2.8	2.8	1.7	1.8	1.7	1.8	1.7	1.8	1.7	1.8	2.8	2.8	2.8	2.8	2.8	2.8
Post-exercise	Mean	119.4	124.2	113.1	96.7	95.9	90.8	90.7	83.6	92.1	115.6	120.7	118.9	114.6	113.2	117.8	116.7	118.9
	s.e.	2.8	2.8	2.8	2.2	2.8	2.1	2.8	2.2	2.8	2.1	2.7	2.8	2.8	2.8	2.8	2.9	2.8
								Weight (kg)										
	Mean	71.2	71.0	71.2	71.0	70.6	70.4	70.3	71.2	71.2	70.9	70.6	70.5	71.2	71.0	71.0	70.8	70.1
	s.e.	0.4	0.4	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.4	0.4	0.4	0.4	0.4	0.4

A atenolol 50 mg/day; B atenolol 100 mg/day; C atenolol 200 mg/day; D placebo.

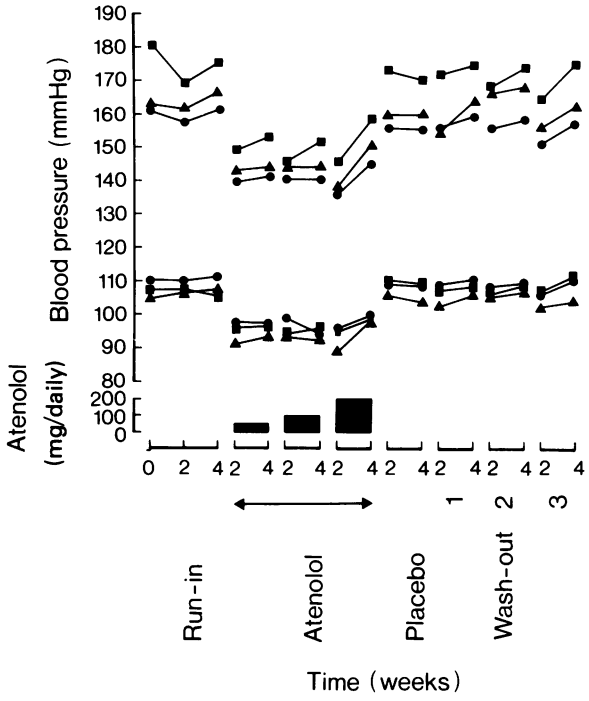

Figure 1 Run-in, treatment and wash-out period means of blood pressure on atenolol 50, 100, 200 mg once-daily and placebo.
▲ lying, ● standing, ■ post-exercise.

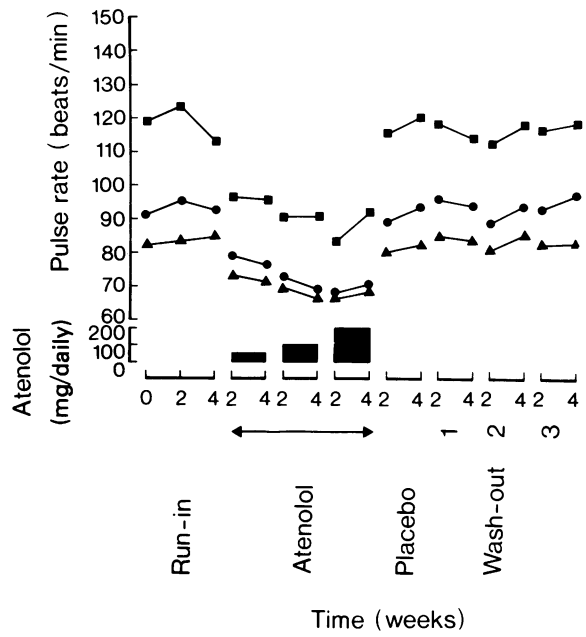

Figure 2 Run-in, treatment and wash-out period means of pulse rate.
▲ lying, ● standing; ■ post-exercise.

included specific items about general well being, dizziness, headache, energy, tiredness, mood, sleep, dreams, and bowel habit. A blood sample was taken at the end of each 4-week treatment period for biochemical and haematological tests.

In order to analyse readings of blood pressure, heart rate and weight the statistical technique of analysis of covariance was used with the immediately preceding non-active treatment visit as covariate. This was used to see if and to what extent the covariate influenced the active treatments. This analysis also allowed the overall statistical significance of patient effects, treatment effects and sequence effects to be tested.

Student's *t*-tests were used to test between individual treatments using adjusted means (adjusted for patients, sequence and covariate). Standard errors were based on the residual mean square from the analysis of covariance.

Results

The trial was analysed on information from twenty-one patients (eight male) aged 31–62 years (mean 53 years) with a mean initial weight of 70.7 kg (54–104 kg). Two of these patients did not complete the final treatment period because of withdrawal from the study. One patient developed sore eyes, not related to atenolol therapy (Wright, personal communication). The other patient complained of abdominal symptoms which proved to be due to a carcinoma of colon.

The run-in and treatment and wash-out period means (± s.e. mean) of blood pressure, pulse and weight are shown in Table 1. The effects on blood pressure and pulse are also shown in Figures 1 and 2. The mean lying and standing blood pressures at the end of the run-in period on placebo were 167/108 and 162/112 mm Hg. Analysis of variance on the non-treatment periods showed no sequence effects. The reduction in mean lying and standing blood pressure during the effective treatment periods was approximately 23/16 and 22/18 mm Hg respectively. The comparison of treatments is shown in Table 2. Analysis of the response of individual patients showed that a reduction of lying systolic blood pressure of 20 mm Hg or more by treatment with 50, 100 and 200 mg atenolol once-daily was achieved in twelve, fourteen and thirteen individuals respectively. Similarly, a reduction in lying diastolic pressure of 10 mm Hg or more was achieved in fifteen, fifteen and thirteen individuals respectively.

The results show that atenolol 50 mg once-daily

Table 2 Comparison of treatments (*P* values) after 2 and 4 weeks of treatment

Comparison of treatments	*Weeks*	*Lying*			*Standing*			*Post-exercise*			
		Systolic BP	*Diastolic BP*	*Pulse*	*Systolic BP*	*Diastolic BP*	*Pulse*	*Systolic BP*	*Diastolic BP*	*Pulse*	*Weight*
A *v* B	2	NS	NS	<0.05	NS	NS	<0.05	NS	NS	NS	<0.05
	4	NS	NS	<0.05	NS	NS	<0.01	NS	NS	NS	NS
A *v* C	2	NS	NS	<0.001	NS	NS	<0.001	NS	NS	<0.001	NS
	4	NS	NS	NS	NS	NS	<0.05	NS	NS	NS	NS
B *v* C	2	NS	NS	NS	NS	NS	<0.05	NS	NS	<0.05	<0.01
	4	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	<0.01
A *v* D	2	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS
	4	<0.001	<0.01	<0.001	<0.01	<0.001	<0.01	<0.001	<0.001	<0.001	NS
B *v* D	2	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS
	4	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	NS
C *v* D	2	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS
	4	<0.05	NS	<0.001	<0.05	<0.001	<0.001	<0.05	<0.001	<0.001	NS

A atenolol 50 mg/day; B atenolol 100 mg/day; C atenolol 200 mg/day; D placebo.
BP = Blood pressure.
NS = Not significant.

was not significantly different in effect on lying, standing or post-exercise blood pressure from atenolol 100 mg or 200 mg once-daily. The three atenolol treatments were significantly superior to placebo. The lying and standing pulse rates after 4 weeks treatment were significantly lower for 100 mg than 50 mg atenolol ($P<0.05$ and $P<0.01$ respectively). There were no differences in effect on post-exercise pulse rates between once-daily 50, 100 or 200 mg atenolol. No differences were found between the results of the first and second fortnight of the wash-out periods.

There were no differences between the incidence of side effects for any of the periods.

The mean ($\pm$s.e. mean) whole blood levels of atenolol after 4 weeks therapy with 50, 100 or 200 mg 20–23 h after the last dose were 0.06 ± 0.01, 0.11 ± 0.02 and 0.16 ± 0.02 μg/ml respectively.

Discussion

This study shows that atenolol once-daily is an effective hypotensive agent in the treatment of mild hypertension. Under the conditions of this study there was no difference between the effect on lying, standing or post-exercise blood pressure of 50, 100 or 200 mg of atenolol. A reduction of about 22/17 mm Hg was achieved from an initial level of about 164/110 mm Hg. This reduction is similar to the effect of a twice-daily dosage with atenolol 200–400 mg/day (Petrie *et al.*, 1975).

The design of this study avoids the criticisms (Muir, 1976; Besterman, 1976) of the only other controlled study of the effect of once-daily atenolol in mild hypertension (Douglas-Jones & Cruickshank, 1976). A run-in period and a treatment period and three wash-out periods between treatments on a matching placebo were included in the design. All blood pressure measurements were taken between 20 and 23 h after the last dose of atenolol. In addition the effect on the control of blood pressure and pulse after exercise was assessed, and the results show that the effect of atenolol on blood pressure persists beyond the chemical half-life of 6–9 h (Conway *et al.*, 1976).

The similarity of the hypotensive effect of atenolol 50, 100 and 200 mg/day 20–23 h after the dose was not matched by identical effects on pulse rates. Further studies are required to establish whether the difference shown between the effects of 50 and 100 mg/day on lying and standing pulse rates will extend to the post-exercise readings, if more severe exercise is carried out by the patients. It is also of interest that the duration of the reduction in blood pressure outlasts the duration of the reduction in the pulse rate at the 50 mg dose. This separation of effect is being studied further.

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