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Atenolol, sustained-release oxprenolol, and long-acting propranolol in hypertension

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Summary and conclusions

The effect of once-daily atenolol, sustained-release oxprenolol (a new formulation of oxprenolol presented as a compressed tablet in a waxed matrix), and long-acting propranolol (a new formulation presented as spheroids in a capsule) was studied in a double-blind crossover trial in 23 carefully selected hypertensive outpatients. After a run-in period with matching placebo each patient received atenolol (100 mg/day), sustained-release oxprenolol (160 mg/day), long-acting propranolol (160 mg/day), and placebo according to a randomised sequence.

After four weeks' treatment with sustained-release oxprenolol blood pressure in the two to four hours before the next dose was not significantly lower than after placebo. The effectiveness of atenolol and of the new formulation of propranolol in reducing blood pressure was confirmed.

These results suggest that the present formulation of sustained-release oxprenolol should be reconsidered.

Introduction

We have compared conventional fixed doses of three beta-adrenoceptor antagonists that are claimed to be suitable for once-daily use in hypertension—namely, atenolol, sustained-release oxprenolol (a compressed tablet in a waxed matrix), and long-acting propranolol (a spheroid formulation).

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Patients and methods

Our procedure for selecting patients with mild hypertension has been described.[1 2] Patients were excluded if their lying diastolic pressure fell below 90 mm Hg after a four-week outpatient run-in period with placebo. Suitable patients were then allocated in a randomised order to four treatment periods (double-blind, within-patient) of four weeks each.

Twenty-three patients were studied (12 men; average age 40·9 years, range 21-59). The drugs were taken once daily at 1800, the doses (atenolol 100 mg, sustained-release oxprenolol 160 mg, long-acting propranolol 160 mg, or matching placebo) being considered to be approximately equivalent in effect.

Blood pressures were recorded with Hawksley random-zero sphygmomanometers (diastolic pressure phase 4) under standard conditions.[1 2] The means of two blood-pressure readings and heart rates were recorded after five minutes' lying and two minutes' standing. A single measurement of heart rate and blood pressure was taken immediately after a two-step exercise test designed to produce a target untreated heart rate of 140/min.[1 2] Measurements were made between 1400 and 1630 (20-22 hours after dosing), at the same time of day on each occasion for each patient. Patients were seen fortnightly. A questionnaire on symptoms was completed by a different observer from the one recording blood pressure.[1 2] Compliance with drug taking, assessed by tablet counts, was satisfactory throughout (> 90%).

Data on blood pressure, heart rate, and weight were analysed separately by analysis of variance after two and four weeks with each treatment. If the overall comparison between treatments, as assessed by the F test, was significant at the 5% level then pairs of adjusted means were compared using a t test. The standard deviation used in the t test was based on the residual mean square from the analysis of variance.

Results

Table I lists the mean blood pressures, pulse rates, and weights during the run-in and treatment periods, and table II the levels of statistical significance.

After four weeks' treatment systolic and diastolic blood pressures measured lying, standing, and after exercise were significantly lower after atenolol and long-acting propranolol than after placebo, but the same was not true for sustained-release oxprenolol. Atenolol was significantly superior to sustained-release oxprenolol after four weeks' treatment in lowering systolic and diastolic blood pressures and heart rates in each position. Long-acting propranolol was also superior to

TABLE I—*Mean blood pressures, pulse rates, and weights (±SEM) of 23 patients during run-in and treatment periods*

	Initial	Run-in		Atenolol		Slow oxprenolol		Long-acting propranolol		Placebo	
		2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks
Blood pressure (mm Hg):											
Lying											
Systolic	162·5±3·8	159·3±4·2	155·3±3·0	138·8±4·8	139·5±4·4	144·0±4·0	149·8±5·1	140·0±3·5	141·7±4·5	151·8±4·2	153·6±4·4
Diastolic	104·5±2·2	102·8±2·1	99·9±2·2	88·0±2·9	89·8±2·8	95·3±2·1	96·3±2·8	89·3±2·5	89·7±2·3	102·6±2·6	98·0±2·2
Standing											
Systolic	161·0±4·6	156·4±5·0	155·0±3·9	140·4±5·2	138·5±4·8	143·4±4·0	148·4±4·8	135·0±4·1	139·8±4·6	150·7±3·9	151·8±4·6
Diastolic	112·4±2·1	109·1±2·0	109·4±2·2	95·5±2·6	98·6±2·6	104·7±2·5	106·5±3·1	98·9±2·5	98·7±2·4	110·3±2·7	107·8±2·6
After exercise											
Systolic	185·7±5·0	184·5±6·1	185·7±6·4	161·6±4·6	164·8±4·9	171·2±4·5	178·9±5·9	154·3±4·8	157·3±4·7	184·4±5·6	183·6±6·3
Diastolic	106·5±3·2	104·7±2·4	103·7±2·9	92·9±3·7	93·6±2·6	97·2±2·9	100·9±2·8	96·4±3·0	94·8±2·8	101·2±2·6	100·6±3·7
Pulse rate (beats/min):											
Lying	79·1±2·2	78·8±2·8	79·3±2·7	67·7±2·5	67·8±2·6	77·5±2·5	73·7±2·1	69·2±1·8	69·4±2·3	76·9±2·3	77·5±2·2
Standing	88·6±2·5	87·0±2·9	86·8±2·5	72·6±2·4	75·9±2·9	84·6±2·2	82·9±1·8	75·3±2·4	75·1±2·7	85·9±2·2	81·8±2·7
After exercise	136·3±3·6	131·1±4·2*	137·1±2·9*	108·4±3·2	114·9±4·4	133·3±4·5	130·8±3·9	112·5±3·5	114·1±4·5	138·5±4·4	141·3±4·4
Weight (kg)	71·8±1·7	71·2±1·8	71·8±1·8	71·5±1·8	71·7±1·8	72·0±1·8	71·5±1·8	72·0±1·7	72·0±1·7	71·4±1·7	71·2±1·8

*Only 22 observations.

TABLE II—*Significance levels (p values) of each drug compared with placebo and two other drugs*

	Atenolol *v* placebo		Long-acting propranolol *v* placebo		Slow oxprenolol *v* placebo		Atenolol *v* slow oxprenolol		Atenolol *v* long-acting propranolol		Long-acting propranolol *v* slow oxprenolol	
	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks
Lying												
Systolic blood pressure	<0·001	<0·001	<0·001	<0·001	<0·05	NS	NS	<0·01	NS	NS	NS	<0·01
Diastolic blood pressure	<0·001	<0·001	<0·001	<0·001	<0·01	NS	<0·05	<0·01	NS	NS	<0·05	<0·01
Pulse rate	<0·001	<0·001	<0·01	<0·01	NS	NS	<0·001	<0·05	NS	NS	<0·001	NS
Standing												
Systolic blood pressure	<0·01	<0·001	<0·001	<0·001	<0·05	NS	NS	<0·01	NS	NS	<0·05	<0·05
Diastolic blood pressure	<0·001	<0·001	<0·001	<0·001	<0·05	NS	<0·001	<0·01	NS	NS	<0·01	<0·01
Pulse rate	<0·001	<0·001	<0·001	<0·001	NS	NS	<0·01	<0·05	NS	NS	<0·001	<0·05
After exercise												
Systolic blood pressure	<0·001	<0·001	<0·001	<0·001	<0·01	NS	<0·05	<0·01	NS	NS	<0·001	<0·001
Diastolic blood pressure	<0·01	<0·05	NS	<0·05	NS	NS	NS	<0·01	NS	NS	NS	<0·05
Pulse rate	<0·001	<0·001	<0·001	<0·001	NS	<0·05	<0·001	<0·01	NS	NS	<0·001	<0·01

sustained-release oxprenolol after four weeks, except for the effect on lying heart rates. There were no significant differences between atenolol and long-acting propranolol for the above measurements. Fourteen patients (61%) achieved a supine diastolic blood pressure of 90 mm Hg or less after four weeks' treatment with atenolol and long-acting propranolol compared with seven patients (30%) after treatment with sustained-release oxprenolol. All treatments were well tolerated.

Discussion

Four weeks' treatment with sustained-release oxprenolol taken once daily does not produce satisfactory control of blood pressure in the two to four hours before the next dose is due. Our findings confirm the small loss of control of blood pressure that occurs towards the end of the 24 hours when the next dose is due,[3] and the return to control values of exercise systolic blood pressure responses 24 hours after sustained-release oxprenolol noted in volunteers.[4] Contrasting evidence from two smaller studies (six patients in each; some patients also taking diuretics) does not seriously challenge our findings. In the first of these the reduction in blood pressure compared with the placebo reading 24 hours after dosing was only 7/4 mm Hg, readings during treatment with placebo were below 140/90 mm Hg, there were no exercise measurements, and there was no run-in period with placebo.[5] The second study was carried out on patients already controlled with sustained-release oxprenolol and conducted during 3-24 hours after dosing.[6] During this interval there was a progressive rise in post-exercise heart rate (from 87 to 102 beats/min) and an increase in blood pressure that did not reach statistical significance: standing blood pressure rose by 12/10 to 140/105 mm Hg. We reported continued reduction of blood pressure and exercise-induced tachycardia for at least 48 hours after withdrawing long-term atenolol.[7]

If the observations in our carefully controlled study are confirmed we conclude that the release characteristics of this formulation of sustained-release oxprenolol should be reconsidered. Our findings confirm the effectiveness of atenolol (100 mg once daily) and the long-acting propranolol formulation (160 mg once daily) and show them to be superior to sustained-release oxprenolol (160 mg once daily) in lowering blood pressure over 24 hours.

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