Bopindolol: a new long acting β -receptor antagonist; its effects on haemodynamics, and on the renin response to tilting

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- 1 Oral administration of single doses of bopindolol (1–4mg) caused significant reductions in the rises of systolic blood pressure and heart rate produced by exercise; only the reduction in the rise of heart rate was significantly dose-related.
- 2 Resting heart rate was reduced by bopindolol. There were small effects on resting blood pressure.
- 3 Bopindolol caused a significant attenuation of the rise in plasma renin activity produced by passive head-up tilting to 75–85 degrees.
- 4 Bopindolol produced a dose-related attenuation of the increase in pulse rate evoked by passive tilting.
- 5 All effects 1–4 were maintained for at least 24 h.
- 6 There was no measurable effect on plasma potassium concentration, peak flow rate or forced expiratory volume (FEV_1).

Keywords bopindolol haemodynamics renin response β -adrenoceptor antagonist

Introduction

Bopindolol (LT 31.200 Sandoz Ltd) is a new pro-drug β -receptor antagonist (Berthold *et al.*, 1981). Previous studies have suggested that it is a non-selective antagonist with a long duration of action of at least 24 h, suggesting that less frequent administration may be necessary than with most other β -adrenoceptor blockers (Aellig, 1982). We report a detailed study of its haemodynamic effects during exercise and passive tilting in six healthy young men. Measurements were also made of plasma renin activity before and during passive tilting, since the latter is known to stimulate renin release by a β -adrenergic mechanism (Davies & Slater, 1976; Cunningham *et al.*, 1981). Measurements were continued for 24 h after a single oral dose of the drug, in order to assess its duration of action. Pharmacokinetic data have been reported elsewhere (Beveridge *et al.*, 1981).

Methods

Six healthy male volunteers aged between 18 and 26 years were studied. They weighed between 80.5 and 56.0 kg with a mean of 69.8 kg. Physical examination and electrocardiograms were performed before testing. A single, oral dose of placebo or bopindolol 1 mg, 2 mg or 4 mg was given on each occasion and each dose was separated by at least 2 weeks. All treatments were single-blind to the subjects and the order of administration randomized. Each subject received every treatment. After an early light breakfast an intravenous cannula was inserted. No smoking, tea or coffee were allowed on the day of study. Peak flow rates were recorded in duplicate with a Wright peak flow meter and the ratio FEV_1/FVC recorded on a standard Vitalograph. Plasma was taken for measurement of plasma potassium concentration, and stored at

-20 °C. The subject then rested supine for 15 min after which time the pulse rate was recorded and blood pressure measured by standard mercury sphygmomanometry. Phase IV sounds were taken to represent the diastolic blood pressure, because the fifth phase often falls to zero under the conditions of tilting and severe exercise. Each subject then exercised on a bicycle ergometer for 2 min at each of three loads—400, 800, and 1200 kpm. A direct-reading pulsemeter attached to the thumb or continuous ECG monitoring was used to record pulse rate every 15 s during this 6 min of exercise. Peak pulse rates of between 150 and 180 beats/min were achieved during the highest exercise load without drug but subjects experienced faintness with circulatory instability on several occasions at this workload. Blood pressure was recorded at the end of each 2 min of exercise. After 1 h's rest, pulse rate and blood pressure were again measured, plasma was taken for measurement of renin activity and passive head-up tilting commenced. The subject was passively tilted on a tilting table to an angle of 85° to the horizontal. This position was maintained for 25 min, after which measurements of pulse rate, blood pressure and plasma renin activity were repeated. The above protocol was then repeated at 1 h, 5 h and 24 h after the time of drug ingestion except for the tilt routine which was omitted at 5 h. Blood for plasma renin activity was taken into chilled Vacutainers at 1.5–2 h, and at 24 h, kept on ice and centrifuged at 4 °C within 30 min. Plasma was stored at -20 °C. Plasma renin activity was measured by radioimmunoassay (Sealey *et al.*, 1972). All renin measurements were performed blind.

The protocol was approved by the District Ethics Committee.

The results were analysed by two-way repeated measures analysis of variance, testing the *F* values against the interaction terms instead of the residual error so as to compensate for the reduction in variance attributable to repetitions of measurements within subjects.

Results

Haemodynamic responses

Results are given in Table 1. Bopindolol significantly reduced resting pulse rate; this effect was dose-related and maintained for at least 5 h at the higher doses. Resting blood pressure showed very small but statistically significant dose-related falls in systolic and diastolic values. The tachycardia and increased systolic blood pressure produced by exercise were both attenuated by

bopindolol for 24 h but although there was a greater effect with 2 mg than with 1 mg there was no difference in magnitude between the responses to 2 mg and 4 mg of the drug. Though there was statistically significant variation amongst the changes in diastolic values, no consistent pattern was noted. Bopindolol attenuated the increase in pulse rate evoked by tilting over 24 h; other cardiovascular measures were not affected.

Renin responses

Bopindolol significantly reduced the mean rise in plasma renin activity occurring on passive tilting (Table 2 and Fig 1). The effect was statistically significant despite the inclusion of one subject who maintained a very low plasma renin activity both at rest and after tilting. Of the 72 measured paired differences between plasma renin values obtained with the subjects tilted and untilted there were six missing values. These were interpolated from the whole matrix of data using a MANOVA programme (SPSS Version 7, 1977). The full matrix was then analysed by standard 2-way repeated measures analysis of variance, which yielded significant results for dose ($F = 3.31$; $df\ 15, 3$; $P = 0.05$) and for times ($F = 9.1$; $df\ 10, 2$; $P = 0.006$) but not for dose by time interaction ($F = 0.4$). Partitioning sums of squares showed that only the first time intervals yielded a significant result compared with the pre-dose results. Though there appeared to be an effect at 24 h, this did not reach significance; placebo and small number effects cannot be discriminated from those attributable to drug action.

Peak flow rate and FEV_1/FVC

These were not affected by bopindolol.

Plasma potassium

This was not affected by bopindolol.

Discussion

The β -receptor antagonist efficacy of bopindolol has been confirmed by its significant effect on the rise in systolic blood pressure and heart rate induced by exercise. This effect was well maintained for the twenty four hours of this study. There was no increase in the degree of β -adrenoceptor blockade produced by 4 mg compared with 2 mg of bopindolol and it would seem that 2 mg provided maximal β -adrenoceptor blockade in these subjects. The effect on plasma renin response to tilting followed a similar pattern, was consistently produced in each subject and, like the haemodynamic changes, was

Table 1 Means and analysis of variance for haemodynamic measures

Variable	Dose (mg)	Pre-dose	Time			Analysis of variance for whole table of results
			1-3 h	5 h	24 h	
Mean resting pulse rate (beats/min)	0	70.2	67.7	69.0	70.8	Overall time difference: ($F_{3,9} = 4.08$) $P < 0.05$ Overall dose difference: ($F_{3,9} = 15.0$) $P < 0.01$ Systolic: Dose contrast, ($F_{3,9} = 10.49$) $P < 0.01$ Diastolic: Dose contrast ($F_{3,9} = 9.74$) $P < 0.01$ Times NS Overall time difference: $F_{2,22} = 5.73$; $0.05 > P > 0.01$ Dose $\times$ workload interaction: $F_{11,22} = 16.32$; $P < 0.01$ Dose contrast: $F_{1,22} = 74$; $P < 0.01$ Only baseline values subtracted, only time and workload contrasts attained significance. For times, systolic, $F_{3,9} = 6.33$; $0.05 < P < 0.01$ Diastolic contrast at 1-3 h, $F_{1,22} = 14.22$; $P < 0.01$ With baseline values subtracted, dose contrast $F_{1,3} = 36.1$; $P < 0.01$
	1	67.3	63	68.0	64.4	
	2	62.7	60.8	62.2	64.5	
	4	66.2	58.5	60.0	63.5	
Mean resting blood pressure (mm Hg, systolic/diastolic)	0	109.7/72	115.5/73.7	109/67.8	114.3/70.5	With baseline values subtracted, dose contrast, $F_{1,3} = 42.6$; $P < 0.01$
	1	115/72.5	107.7/71.5	107.7/65.7	110.0/65.2	
	2	101.8/62.8	101.2/64.8	98.8/57.0	102.7/62.3	
	4	108.8/67.2	98.4/59.8	104.2/65	105/60.2	
Mean increase in pulse rate rise on exercise (baseline values subtracted) (800 kpm)	0	—	+3.93	+1.16	+3.83	
	1	—	-16.1	-21.43	-13.1	
	2	—	-20.7	-27.0	-18.2	
	4	—	-21.5	-23.0	-19.67	
Mean changes in systolic and diastolic blood pressure on exercise (800 kpm)	0	61.2/-0.5	53.0/-10.2	56.0/0.5	47.3/-11.7	
	1	43/4.6	16.2/0.6	28.3/0.0	31.5/0.4	
	2	62.3/4.6	15.6/3.83	24.3/10.5	33.3/4.0	
	4	54.5/1.5	3.8/-0.4	14.2/5.2	23.8/9.2	
Mean tilt differences: pulse rate (changes from baseline values in brackets)	0	16.4	30.0 (+13.6)	—	24.17 (+8.77)	
	1	28.2	10.25 (-7.95)	—	18.50 (-9.7)	
	2	28.2	13.33 (-4.87)	—	16.17 (-12.0)	
	4	23.7	8.0 (-15.7)	—	7.83 (-15.87)	
Systolic blood pressure	0	-7.2	-3.3	—	-5.7	
	1	-0.75	-6.3	—	-8.7	
	2	3.0	-5.3	—	-4.3	
	4	2.3	-10.8	—	-9.8	

Table 2 Mean plasma renin activities in six subjects (s.e. values in brackets)

Dose of bopindolol	Predose			2 h			24 h		
	Flat	Tilt	Rise	Flat	Tilt	Rise	Flat	Tilt	Rise
Placebo	0.88 (0.17)	3.14 (0.87)	2.26 (0.77)	1.29 (0.22)	3.360 (0.83)	2.07 (0.81)	0.87 (0.16)	2.68 (0.62)	1.89 (0.53)
1 mg	1.15 (0.44)	3.02 (0.86)	1.87 (0.71)	0.88 (0.16)	1.82 (0.60)	0.94 (0.52)	0.69 (0.35)	1.28 (0.47)	0.56 (0.36)
2 mg	1.22 (0.53)	2.25 (0.33)	1.12 (0.50)	1.09 (0.25)	1.71 (0.35)	0.62 (0.20)	0.46 (0.05)	1.02 (0.14)	0.56 (0.15)
4 mg	0.86 (0.15)	2.98 (0.73)	2.11 (0.67)	1.35 (0.25)	2.32 (0.53)	0.97 (0.40)	0.89 (1.11)	1.80 (0.38)	0.91 (0.32)

well maintained for 24 h. Measures of pulmonary function, and red and white cell indices remained unchanged throughout and no adverse effects were reported by the subjects.

Some subjects fainted when tilted to 85°, or exercised to 1200 kpm as specified by the protocol; others sustained these stresses without difficulty. At 1200 kpm workloads most subjects showed instability of their measured cardiovascular responses. For these reasons the tilt

angle was reduced to 75° for one subject, and the workload at 1200 kpm discontinued prematurely. It seems wise, therefore, to limit such stressful stimuli in subjects taking β -adrenoceptor blocking drugs, and to maintain careful clinical supervision throughout experimental procedures.

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Figure 1 The effects of bopindolol on PRA (plasma renin activity) at various times and doses. (a) represents mean absolute changes in PRA in tilting, (b) the percentage changes of the means. The limits in (a) are for 1 s.e. mean., the other symbols indicate placebo (P), and dose (1, 2, 4 mg).

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