Comparison of the haemodynamic effects of bucindolol, propranolol and pindolol in healthy volunteers

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1 The effects of single oral doses of bucindolol (50, 100, 200 and 400 mg), pindolol (10 mg), propranolol (160 mg) and placebo on arterial pressure and heart rate in the supine and standing positions and exercise heart rate were compared in 12 healthy male volunteers.

2 Supine heart rate was significantly greater after all four doses of bucindolol and pindolol in comparison to propranolol. Bucindolol had no significant effect on standing heart rate which was significantly reduced by pindolol and propranolol. Bucindolol, pindolol and propranolol significantly reduced an exercise tachycardia for at least 24 h after drug administration.

3 Supine systolic pressure was not affected by any treatment but supine diastolic pressure was significantly reduced by bucindolol (200 and 400 mg) and by pindolol. All doses of bucindolol, propranolol and pindolol significantly reduced standing systolic blood pressure. There was a significant linear trend for reductions in standing systolic blood pressure and increasing doses of bucindolol. Standing diastolic blood pressure was significantly reduced by bucindolol 200 and 400 mg.

4 Faintness and light headedness occurred in 6 of 12 subjects after 200 mg bucindolol and in 8 of 10 subjects after 400 mg bucindolol.

5 After bucindolol, analysis of plasma samples demonstrated the presence of bucindolol, 5-hydroxy and 6-hydroxy bucindolol and indolyl-*t*-butylamine.

6 These observations indicate that in man, bucindolol is a β -adrenoceptor blocking drug with hypotensive activity and probably partial agonist activity. It is unlikely that the hypotensive effects result from blockade of β -adrenoceptors or from the drug's partial agonist activity.

Keywords bucindolol propranolol pindolol β -adrenoceptor blockade

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Introduction

Bucindolol (MJ 13105-1, Mead Johnson, USA) is a new non-selective β -adrenoceptor antagonist which has additional properties of partial agonist activity (PAA), direct vasodilatation and weak α -adrenoceptor antagonism in experimental animals (Deitchman *et al.*, 1980; Oates *et al.*, 1981; Rimele *et al.*, 1984). The aim of the present study was to evaluate in man, the heart rate and blood pressure responses to the oral administration of bucindolol and to compare these responses with placebo, and two non-selective β -adrenoceptor antagonists, pindolol which has PAA (Barrett & Carter, 1970) and propranolol which is devoid of PAA (Black *et al.*, 1964).

Methods

Observations were made on 12 healthy male volunteers who had given informed consent to the procedures. Their mean ($\pm$ s.e. mean) age was 21.5 ± 0.5 years and mean weight was 72.4 ± 2.5 kg. The protocol of the study had been approved by the Ethics Committee of the The Queen's University of Belfast. Bucindolol 50 mg, 100 mg, 200 mg, and 400 mg, pindolol 10 mg propranolol 160 mg and placebo were administered double-blind in random order at weekly intervals. The only constraint on the randomization procedure was that no subject received bucindolol 400 mg without having received at least one smaller dose of bucindolol previously.

Heart rate was measured from limb Lead II of an electrocardiogram as the shortest time between six consecutive R waves. Arterial blood pressure was measured by auscultation (phase IV diastolic) with a Hawksley random zero sphygmomanometer. Heart rate and blood pressure were recorded after the subjects had been supine for 15 min and after standing upright

for 3 min. Each subject then completed 3 min of a standard exercise step test (46 cm step, 32 steps min^{-1}). Heart rate was recorded immediately at the end of exercise. Observations in the supine, standing and exercise phase were carried out prior to dosing and at 1, 2, 4, 6, 8 and 24 h after oral drug administration. Blood samples were obtained through an indwelling catheter or by venepuncture on completion of every exercise test and at 12 h. The samples were centrifuged, plasma separated and stored at -20°C . Bucindolol and its metabolites, 5-OH bucindolol, 6-OH bucindolol and indolyl-*t*-butylamine, were measured by high pressure liquid chromatography with fluorescence detection (Meredith *et al.*, 1985). Any adverse effects described by the subjects were recorded.

Statistics

Results were expressed as the mean $\pm$ s.e. mean. The results of blood pressure and heart rate were analysed with SPSS using analysis of variance and Duncan's Multiple Range Test. To determine whether there was a linear relationship between the various cardiovascular parameters and doses of bucindolol, a multi-variate analysis of variance (MANOVA) was employed. A *P* value of less than 0.05 was regarded as significant.

Results

All 12 subjects received placebo, propranolol and pindolol and bucindolol 50, 100 and 200 mg but only 10 subjects had 400 mg bucindolol because of adverse effects to 200 mg.

Supine heart rate did not significantly alter after placebo administration (Table 1). Bucindolol 50 and 200 mg had no significant effects on resting heart rate compared to placebo. One

Table 1 Effect of placebo, bucindolol, propranolol and pindolol on heart rate (beats min^{-1}) in the supine position. Results are the mean ($\pm$ s.e. mean) of observations in 12 subjects (bucindolol 400 mg in 10 subjects)

Time from treatment (h)	Bucindolol					Propranolol 160 mg	Pindolol 10 mg
	Placebo	50 mg	100 mg	200 mg	400 mg		
0	73 $\pm$ 3.2	73 $\pm$ 3.4	72 $\pm$ 2.6	71 $\pm$ 2.7	73 $\pm$ 3.2	68 $\pm$ 2.3	72 $\pm$ 2.4
1	70 $\pm$ 3.2	72 $\pm$ 2.6	79 $\pm$ 2.7*†	76 $\pm$ 2.4†	80 $\pm$ 2.0*†	67 $\pm$ 1.9	73 $\pm$ 2.3†
2	73 $\pm$ 3.0	73 $\pm$ 1.5	73 $\pm$ 2.2	77 $\pm$ 1.7†	76 $\pm$ 2.2†	67 $\pm$ 2.3	75 $\pm$ 3.0
4	67 $\pm$ 4.0	72 $\pm$ 3.1†	72 $\pm$ 2.6†	73 $\pm$ 2.1†	77 $\pm$ 2.6*†	63 $\pm$ 2.0	69 $\pm$ 2.3
6	73 $\pm$ 3.7	72 $\pm$ 2.2	76 $\pm$ 2.8	73 $\pm$ 3.0	74 $\pm$ 3.8	69 $\pm$ 2.4	71 $\pm$ 3.2
8	73 $\pm$ 4.6	75 $\pm$ 3.5	73 $\pm$ 2.4	73 $\pm$ 1.3	72 $\pm$ 3.6	64 $\pm$ 2.7	71 $\pm$ 3.6
24	70 $\pm$ 3.3	69 $\pm$ 2.7	72 $\pm$ 2.1	69 $\pm$ 2.4	73 $\pm$ 2.3	65 $\pm$ 2.4	74 $\pm$ 2.6

**P* < 0.05 compared with placebo. †*P* < 0.05 compared with propranolol

hour after bucindolol 100 mg the mean supine heart rate was significantly ($P < 0.05$) increased compared to placebo. At 1 h and 4 h after bucindolol 400 mg supine heart rate was significantly raised compared to placebo. The mean heart rate values after propranolol were all less than placebo, but the decrease did not reach significance. There was little change in supine heart rate after pindolol. Supine heart rate was significantly greater after all four doses of bucindolol and pindolol in comparison to propranolol (Table 1).

Standing heart rate did not alter significantly after placebo (Table 2). The 3 min period of standing was not completed by all subjects after 200 mg and 400 mg bucindolol as some subjects became light headed and had to sit down. These subjects are omitted from Table 2 but in a small number of subjects (200 mg—one subject; 400 mg—two subjects) observations were made after 2.5 min standing and these are included. No dose of bucindolol had any significant effect on standing heart rate compared to placebo. This contrasts with propranolol, where from 1 to 24 h there were significant reductions in standing heart rate. From 1 to 4 h after pindolol there

were significant reductions in standing heart rate compared to placebo.

There were no changes in exercise heart rate after placebo (Table 3). All subjects did not complete the 3 min period of exercise and these have been omitted from the results as indicated in Table 3. In a small number of subjects a 2.5 min period of exercise was completed and these results are included in Table 3. Propranolol, pindolol and all doses of bucindolol significantly reduced exercise heart rate compared to placebo at all observation times. The absolute reductions in exercise heart rate after bucindolol 100, 200 and 400 mg were almost identical. The decrease in heart rate after each drug was also calculated as a percentage of the pre-drug exercise heart rate. The maximum inhibition of exercise heart rate and time of its occurrence was 18.17 ± 2.36 (2 h), 22.5 ± 2.1 (4 h), 22.4 ± 2.9 (8 h) and 22.8 ± 2.2 (8 h) % after 50, 100, 200 and 400 mg bucindolol, respectively, and 25.8 ± 7.1 (4 h) after propranolol and 21.8 ± 5.3 (4 h) % after pindolol. Employing MANOVA it was determined that at 2 h there was no significant ($P = 0.742$) linear trend for reductions in exercise heart rate and increasing doses of bucindolol.

Table 2 Effect of placebo, bucindolol, propranolol and pindolol on heart rate (beats min^{-1}) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in 12 subjects (bucindolol 400 mg in 10 subjects)

Time from treatment (h)	Placebo	50 mg	Bucindolol				Propranolol 160 mg	Pindolol 10 mg
			100 mg	200 mg	400 mg			
0	97 $\pm$ 3.9	95 $\pm$ 4.1	98 $\pm$ 4.5	95 $\pm$ 3.3	95 $\pm$ 3.8	90 $\pm$ 2.8	95 $\pm$ 3.3	
1	97 $\pm$ 4.9	91 $\pm$ 4.9	95 $\pm$ 2.5	94 $\pm$ 3.0	94 $\pm$ 3.6‡	80 $\pm$ 3.0*	84 $\pm$ 1.8*	
2	99 $\pm$ 5.4	93 $\pm$ 2.8	89 $\pm$ 3.3	99 $\pm$ 2.0†	87 $\pm$ 5.0††	80 $\pm$ 3.0*	86 $\pm$ 3.0*	
4	94 $\pm$ 5.1	87 $\pm$ 3.2	86 $\pm$ 3.3	93 $\pm$ 1.6	97 $\pm$ 2.2	77 $\pm$ 3.0*	83 $\pm$ 2.1*	
6	97 $\pm$ 5.4	89 $\pm$ 2.7	92 $\pm$ 2.7	91 $\pm$ 3.3	97 $\pm$ 3.5	81 $\pm$ 3.0*	89 $\pm$ 3.4	
8	98 $\pm$ 5.6	92 $\pm$ 2.3	90 $\pm$ 2.6	89 $\pm$ 2.8	88 $\pm$ 3.2	82 $\pm$ 3.2*	89 $\pm$ 4.6	
24	93 $\pm$ 3.7	89 $\pm$ 3.0	90 $\pm$ 3.0	86 $\pm$ 3.2	90 $\pm$ 3.4	81 $\pm$ 2.4*	91 $\pm$ 3.2	

* $P < 0.05$ compared with placebo

‡Mean of five subjects, †mean of 11 subjects, †† mean of nine subjects

Table 3 Effect of placebo, bucindolol, propranolol and pindolol on exercise heart rate (beats min^{-1}). Results are the mean ($\pm$ s.e. mean) of observations in 12 subjects (bucindolol 400 mg in 10 subjects)

Time from treatment (h)	Placebo	50 mg	Bucindolol			Propranolol 160 mg	Pindolol 10 mg
			100 mg	200 mg	400 mg		
0	162 $\pm$ 3.6	159 $\pm$ 2.6	163 $\pm$ 3.9	160 $\pm$ 2.6	161 $\pm$ 2.6	159 $\pm$ 4.4	155 $\pm$ 3.5
1	158 $\pm$ 4.0	134 $\pm$ 4.1*	135 $\pm$ 4.4*‡	128 $\pm$ 3.7*†	132 $\pm$ 2.5*††	123 $\pm$ 4.2*	121 $\pm$ 2.9*
2	163 $\pm$ 5.4	130 $\pm$ 2.0*	126 $\pm$ 2.4*	131 $\pm$ 4.0*‡	126 $\pm$ 1.9*‡‡	118 $\pm$ 3.4*	122 $\pm$ 2.4*
4	158 $\pm$ 4.8	132 $\pm$ 2.2*	126 $\pm$ 2.2*	124 $\pm$ 2.8*	129 $\pm$ 2.5*	116 $\pm$ 2.6*	122 $\pm$ 1.4*
6	158 $\pm$ 4.2	124 $\pm$ 8.4*	131 $\pm$ 2.6*	124 $\pm$ 2.4*	130 $\pm$ 2.6*	124 $\pm$ 2.3*	127 $\pm$ 2.0*
8	161 $\pm$ 4.7	137 $\pm$ 2.6*	132 $\pm$ 2.7*	124 $\pm$ 1.9*	125 $\pm$ 3.0*	128 $\pm$ 2.9*	128 $\pm$ 2.4*
24	157 $\pm$ 3.7	148 $\pm$ 3.3*	145 $\pm$ 2.9*	135 $\pm$ 2.3*	134 $\pm$ 2.0*	147 $\pm$ 2.4*	149 $\pm$ 2.7*

* $P < 0.05$ compared with placebo

††Mean of six subjects, †mean of 10 subjects, ‡‡mean of seven subjects, ‡mean of 11 subjects

The inhibition of an exercise heart rate by bucindolol persisted for 24 h for each dose examined. After 100 mg the percentage inhibition of an exercise heart rate had fallen from a maximum inhibition of 22.5% at 2 h to 11.0% at 24 h. After bucindolol 200 and 400 mg the percentage inhibition fell by about one-quarter at 24 h, from 22.4% to 16.5% and 22.8% to 16.7%, respectively.

Supine systolic and diastolic blood pressure were not significantly influenced by placebo administration. Bucindolol (50, 100, 200, 400 mg), propranolol (160 mg) and pindolol (10 mg) had no significant effect on supine systolic blood pressure compared to placebo. Supine diastolic blood pressure was reduced significantly at 2 h by bucindolol 200 and 400 mg compared to placebo. From 4 h to 24 h no dose of bucindolol had any significant effect on supine diastolic blood pressure. Mean supine diastolic blood pressure was reduced from 2 to 8 h by pindolol but the reduction was only significant at 8 h.

There was no significant change in standing systolic blood pressure after placebo (Table 4).

At 2 h all doses of bucindolol, propranolol and pindolol significantly reduced standing systolic blood pressure compared to placebo; pressure was lower after 200 and 400 mg bucindolol than after propranolol and pindolol. Employing MANOVA it was shown that at 2 h there was a significant ($P < 0.001$) linear trend for reductions in standing systolic blood pressure and increasing doses of bucindolol. Bucindolol, 200 and 400 mg significantly reduced standing systolic blood pressure at 1 h and 4 h compared to placebo, while pindolol also decreased standing systolic pressure significantly at 4 h.

There was no significant change on standing diastolic blood pressure after placebo (Table 5). At 1 and 2 h after bucindolol 50 and 100 mg mean standing diastolic pressures were less than placebo values but the difference did not reach significance. At 1 and 2 h bucindolol 200 and 400 mg significantly reduced diastolic standing blood pressure compared to placebo. With MANOVA it was demonstrated that at 2 h there was a significant ($P < 0.01$) linear trend for reductions in standing diastolic blood pressure and increas-

Table 4 Effect of placebo, bucindolol, propranolol and pindolol on systolic blood pressure (mm Hg) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in 12 subjects (bucindolol 400 mg in 10 subjects)

Time from treatment (h)	Placebo	50 mg	100 mg	Bucindolol 200 mg	400 mg	Propranolol 160 mg	Pindolol 10 mg
0	112 $\pm$ 3.7	117 $\pm$ 4.3	109 $\pm$ 2.8	113 $\pm$ 4.5	113 $\pm$ 3.2	115 $\pm$ 3.3	111 $\pm$ 2.6
1	109 $\pm$ 2.5	107 $\pm$ 3.2	104 $\pm$ 3.6	96 $\pm$ 3.8*	93 $\pm$ 5.1*‡	105 $\pm$ 5.0	99 $\pm$ 3.7
2	112 $\pm$ 3.3	99 $\pm$ 2.6*	101 $\pm$ 2.4*	93 $\pm$ 2.9*†	84 $\pm$ 4.5*††	99 $\pm$ 3.6*	102 $\pm$ 3.4*
4	109 $\pm$ 3.3	106 $\pm$ 4.1	100 $\pm$ 2.3	99 $\pm$ 2.7*	91 $\pm$ 3.7*	101 $\pm$ 3.2	99 $\pm$ 3.8*
6	105 $\pm$ 3.8	104 $\pm$ 3.1	100 $\pm$ 4.7	102 $\pm$ 2.5	98 $\pm$ 3.8	104 $\pm$ 3.3	100 $\pm$ 2.9
8	111 $\pm$ 2.7	105 $\pm$ 2.7	104 $\pm$ 4.0	106 $\pm$ 2.6	105 $\pm$ 3.4	102 $\pm$ 3.2	111 $\pm$ 3.8
24	112 $\pm$ 3.0	114 $\pm$ 3.9	110 $\pm$ 3.0	110 $\pm$ 2.8	117 $\pm$ 3.8	109 $\pm$ 4.9	114 $\pm$ 3.6

* $P < 0.05$ compared with placebo

‡Mean of five subjects, †mean of 11 subjects, ††mean of seven subjects

Table 5 Effect of placebo, bucindolol, propranolol and pindolol on diastolic blood pressure (mm Hg) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in 12 subjects (bucindolol 400 mg in 10 subjects)

Time from treatment (h)	Placebo	50 mg	100 mg	Bucindolol 200 mg	400 mg	Propranolol 160 mg	Pindolol 10 mg
0	82 $\pm$ 3.6	87 $\pm$ 3.4	81 $\pm$ 3.2	83 $\pm$ 3.7	81 $\pm$ 2.4	81 $\pm$ 3.0	83 $\pm$ 2.1
1	84 $\pm$ 2.7	78 $\pm$ 4.6	78 $\pm$ 3.0	71 $\pm$ 4.2*	68 $\pm$ 7.3*†	78 $\pm$ 5.6	77 $\pm$ 3.1
2	84 $\pm$ 3.1	77 $\pm$ 2.7	77 $\pm$ 2.0	70 $\pm$ 4.0*†	58 $\pm$ 7.8*††	77 $\pm$ 2.5	77 $\pm$ 2.7
4	83 $\pm$ 2.9	83 $\pm$ 2.6	76 $\pm$ 2.7	77 $\pm$ 2.8	69 $\pm$ 4.0*	79 $\pm$ 2.7	76 $\pm$ 4.2
6	79 $\pm$ 3.1	77 $\pm$ 2.2	72 $\pm$ 4.1	79 $\pm$ 2.7	75 $\pm$ 3.3	73 $\pm$ 3.9	78 $\pm$ 2.3
8	86 $\pm$ 2.4	81 $\pm$ 3.0	81 $\pm$ 3.9	80 $\pm$ 2.6	79 $\pm$ 2.5	81 $\pm$ 3.7	81 $\pm$ 2.7
24	83 $\pm$ 2.1	87 $\pm$ 2.9	81 $\pm$ 3.6	83 $\pm$ 2.5	84 $\pm$ 3.6	77 $\pm$ 3.5	81 $\pm$ 2.8

* $P < 0.05$ compared with placebo

‡Mean of five subjects, †mean of 11 subjects, ††mean of seven subjects

ing doses of bucindolol. At 4 h bucindolol 400 mg significantly reduced pressure compared to placebo. While mean values after propranolol and pindolol were less than after placebo none of these reached significance.

Adverse reactions

There were no adverse reactions reported by any subject after placebo. One subject felt faint on standing upright 1 h after bucindolol 50 mg. After 100 mg of bucindolol one subject had nausea on standing at 1 h and did not exercise at this time; one subject was unable to continue exercise because of tiredness at 2 h. Six subjects complained of feeling faint or light-headed and were unable to complete the exercise from 1 to 2 h after bucindolol 200 mg. One subject had a syncopal episode while standing at 1 h after 200 mg; the following week the same subject again received 200 mg bucindolol, complained of feeling light-headed at 1 h but had no syncopal episode, and was able to complete all observations from 2 h onwards. Five subjects complained of feeling tired and sleepy for varying periods between 1 and 6 h after 200 mg. One subject felt so tired that he refused to take any higher dose of the drug but the following week received 200 mg of bucindolol and did not complain of undue fatigue. One subject had marked facial flushing.

Only 10 subjects received bucindolol 400 mg because of the unwillingness of one subject to take a larger dose of bucindolol after receiving 200 mg, and as another subject had a syncopal episode after 200 mg he was not given 400 mg. Two subjects out of 10 reported no adverse effects after 400 mg of bucindolol. The other eight subjects had either a feeling of faintness or light-headedness when standing upright at 1 or 2 h. One subject had a syncopal episode at 2 h after bucindolol 400 mg.

Most of the subjects were obviously vasodilated with facial flushing and suffusion of their conjunctivae. One subject complained of feeling tired and sleepy for 1–2 h after taking bucindolol 400 mg and three subjects had nausea for 1–3 h.

After propranolol one subject had nausea for 1–2 h and one subject felt faint after standing for 3 min at 1 h post-dosing. The same subject stopped exercising at 2 min at 1 and 2 h after propranolol as he complained of his legs feeling excessively tired. Two subjects complained of feeling tired and sleepy 1–4 h after propranolol. Three subjects felt drowsy and sleepy for 1–6 h after pindolol. One subject felt light-headed at 6 h after pindolol. This did not prevent him from performing any of the procedures.

Plasma concentrations

The plasma concentrations of bucindolol and its metabolites, 5-OH bucindolol, 6-OH bucindolol and indolyl-*t*-butylamine measured after bucindolol 50, 100, 200 and 400 mg are shown in Table 6. The number of subjects at each time interval after each dose where bucindolol or its metabolites was identified is indicated.

After 50 mg bucindolol, parent drug was only present in samples from four subjects but 5-OH bucindolol was identified in all subjects but only at 2 h. Bucindolol and the three metabolites were identified after 100 mg; only 5-OH bucindolol occurred in all 12 subjects and just for the first 4 h. After the 200 mg dose, bucindolol, 5-OH bucindolol and indolyl-*t*-butylamine were present in the majority of subjects for 12 h; 10 of the 12 subjects had 5-OH bucindolol present at 24 h. 6-OH-bucindolol was present in less than half the subjects. After 400 mg, bucindolol, 5-OH bucindolol and indolyl-*t*-butylamine were present for 12 h in the majority of the volunteers. A lesser number of the subjects had 6-OH bucindolol present over the first 8 h. The peak plasma concentrations of bucindolol and its metabolites and their time of occurrence are shown in Table 7. The peak plasma concentrations of bucindolol increased to a greater extent than would be expected from the increases in doses.

Discussion

β -adrenoceptor antagonists with PAA decrease resting heart rate less than drugs without this property (McDevitt, 1979; Lysbo Svendsen *et al.*, 1979). Bucindolol which produced approximately the same degree of inhibition of an exercise tachycardia as pindolol and propranolol had no effect on standing heart rate which was reduced by pindolol and propranolol; supine resting heart rates after pindolol and bucindolol were significantly higher than after propranolol. These effects on supine and standing heart rate suggest that bucindolol has PAA. In hypertensive patients bucindolol did not decrease supine heart rate (Gill & Beevers, 1984). Bucindolol has direct vasodilator properties (Deitchman & Snyder, 1981; Oates *et al.*, 1981) and in the present study reduced supine and standing blood pressure to a greater extent than propranolol and pindolol. The resultant reflex tachycardia in response to the fall in blood pressure makes it difficult to separate the reflex effects from possible PAA on resting heart rate. However the absence of an effect of bucindolol on supine and standing heart rate does suggest the presence of PAA in bucindolol.

Table 6 Mean ($\pm$ s.e. mean) plasma concentration of bucindolol, 5-OH bucindolol, 6-OH bucindolol and indolyl-*t*-butylamine (ng ml⁻¹) after the oral administration of bucindolol (50 and 100 mg in 12 subjects, 200 and 400 mg in 10 subjects). The number of subjects in which bucindolol and its metabolites were measured for each dose and time is given in brackets

Drug	Plasma concentrations	Time (h)					
		1	2	4	6	8	24
Bucindolol 50 mg	Bucindolol	11.7 $\pm$ 4.7 (4)	10.6 $\pm$ 3.1 (4)	10.8 $\pm$ 4.0 (2)	8.6 $\pm$ (1)	5.2 $\pm$ (1)	
	5-OH bucindolol	3.8 $\pm$ 0.9 (11)	2.5 $\pm$ 0.4 (12)	1.2 $\pm$ 0.3 (11)	0.8 $\pm$ 0.1 (8)	0.7 $\pm$ 0.1 (4)	0.3 $\pm$ (1)
	Bucindolol	32.3 $\pm$ 11.3 (8)	21.3 $\pm$ 8.9 (10)	25.5 $\pm$ 15.1 (6)	20.5 $\pm$ 10.8 (4)	16.8 $\pm$ 9.4 (3)	4.3 (1)
	5-OH bucindolol	8.9 $\pm$ 2.3 (12)	6.7 $\pm$ 1.2 (12)	2.9 $\pm$ 1.0 (12)	1.3 $\pm$ 0.4 (11)	1.0 $\pm$ 0.3 (10)	1.3 $\pm$ 0.8 (3)
Bucindolol 100 mg	6-OH bucindolol	7.6 $\pm$ 0.9 (3)	5.7 $\pm$ 0.7 (2)				
	Indolyl- <i>t</i> -butyl-amine	0.6 $\pm$ 0.1 (3)	0.6 $\pm$ 0.02 (4)	0.7 $\pm$ 0.2 (2)	0.6 (1)	0.6 (1)	
	Bucindolol	82.6 $\pm$ 18.7 (11)	84.3 $\pm$ 27.8 (12)	42.3 $\pm$ 15.1 (11)	25.1 $\pm$ 8.5 (12)	18.1 $\pm$ 6.1 (9)	9.1 (1)
	5-OH bucindolol	23.0 $\pm$ 4.1 (12)	20.4 $\pm$ 4.5 (12)	6.8 $\pm$ 1.6 (12)	3.3 $\pm$ 0.7 (12)	2.3 $\pm$ 0.6 (12)	0.7 $\pm$ 0.1 (10)
Bucindolol 200 mg	6-OH bucindolol	18.6 $\pm$ 4.8 (4)	13.1 $\pm$ 2.3 (5)	7.9 $\pm$ 1.2 (4)	7.1 $\pm$ 1.1 (2)	5.0 (1)	
	Indolyl- <i>t</i> -butyl-amine	1.3 $\pm$ 0.2 (9)	1.3 $\pm$ 0.3 (12)	1.1 $\pm$ 0.1 (11)	0.8 $\pm$ 0.1 (10)	0.7 $\pm$ 0.1 (10)	0.6 $\pm$ 0.1 (3)
	Bucindolol	346.2 $\pm$ 96.3 (10)	301.2 $\pm$ 52.7 (10)	181.9 $\pm$ 52.8 (9)	112.9 $\pm$ 33.5 (10)	71.6 $\pm$ 24.6 (10)	29.2 $\pm$ 13.5 (10)
	5-OH bucindolol	39.2 $\pm$ 7.6 (10)	45.7 $\pm$ 5.1 (10)	22.2 $\pm$ 3.3 (9)	10.2 $\pm$ 1.8 (10)	5.9 $\pm$ 1.0 (10)	11.3 $\pm$ 4.9 (4)
Bucindolol 400 mg	6-OH bucindolol	28.0 $\pm$ 4.6 (6)	23.7 $\pm$ 6.0 (7)	16.8 $\pm$ 4.1 (4)	9.9 $\pm$ 2.4 (5)	5.9 $\pm$ 0.3 (4)	1.9 $\pm$ 0.3 (10)
	Indolyl- <i>t</i> -butyl-amine	2.7 $\pm$ 0.5 (8)	3.1 $\pm$ 0.4 (10)	3.0 $\pm$ 0.3 (9)	2.2 $\pm$ 0.2 (10)	1.7 $\pm$ 0.2 (10)	0.9 $\pm$ 0.1 (10)
							0.7 (1)

Table 7 The time ($t_{\max}$) of the maximum plasma concentration of ($C_{\max}$ ng ml⁻¹) of bucindolol, 5-OH bucindolol, 6-OH bucindolol and indolyl-*t*-butylamine) after bucindolol 50, 100, 200 and 400 mg. Results are derived from Table 6

Dose bucindolol (mg)	Bucindolol $C_{\max}$ (ng ml ⁻¹) $t_{\max}$ (h)	5-OH bucindolol $C_{\max}$ (ng ml ⁻¹) $t_{\max}$ (h)	6-OH bucindolol $C_{\max}$ (ng ml ⁻¹) $t_{\max}$ (h)	Indolyl- <i>t</i> -butylamine $C_{\max}$ (ng ml ⁻¹) $t_{\max}$ (h)
50	11.7 ± 4.7 1	3.8 ± 0.9 1	—	—
100	32.3 ± 11.3 1	8.9 ± 2.3 1	7.6 ± 0.9 1	0.7 ± 0.2 4
200	84.3 ± 27.8 2	23.0 ± 4.1 1	18.6 ± 4.8 1	1.3 ± 0.2 1
400	346.2 ± 96.3 1	45.7 ± 5.1 2	28.0 ± 4.6 1	3.1 ± 0.4 2

dolol and confirms the observations in animals (Deitchman *et al.*, 1980).

In man the degree of β -adrenoceptor antagonism can be determined by the use of a standardized isoprenaline sensitivity test (Cleaveland *et al.*, 1972; George *et al.*, 1972) or by the degree of inhibition of an exercise tachycardia (Brick *et al.*, 1968; Carruthers *et al.*, 1974; Harron *et al.*, 1981). In the present study all doses of bucindolol significantly reduced an exercise tachycardia. The percentage inhibition of an exercise tachycardia after bucindolol 100 mg (22.4%) was not increased by doses of 200 and 400 mg. β -adrenoceptor antagonists without PAA can produce a greater inhibition of an exercise tachycardia; atenolol (200 mg) resulted in a 36% inhibition of an exercise tachycardia, sotalol (400 mg) a 38.5% inhibition, propranolol (480 mg) a 34% inhibition (De Plaen *et al.*, 1976; Harron *et al.*, 1981). In the present study propranolol (160 mg) reduced an exercise tachycardia by 25.8%. Bucindolol has a strikingly flat dose-response curve for inhibition of an exercise tachycardia which was similar to that of practolol, a β -adrenoceptor antagonist with PAA (Brick *et al.*, 1968). It has been suggested that β -adrenoceptor antagonists with PAA demonstrate flattening of the dose-response curve to severe exercise (McDevitt *et al.*, 1977). The flattening of the dose-response curve for inhibition of an exercise heart rate by bucindolol is further evidence that this drug has PAA. The effects of bucindolol on exercise heart rate persisted for 24 h. The degree of inhibition of an exercise tachycardia by bucindolol was dose dependent at 24 h. Following 100 mg the mean exercise heart rate was 145 beats min⁻¹, while after 400 mg the mean exercise heart rate was 134 beats min⁻¹ even though the mean exercise heart rate at 2 h was 126 beats min⁻¹ after both doses.

β -adrenoceptor antagonists are effective hypotensive agents in patients with hypertension (Prichard *et al.*, 1976). The mechanism of their hypotensive action remains unclear. In healthy subjects β -adrenoceptor antagonists have either

little or no effect on blood pressure (Lysbo Svendsen *et al.*, 1979; Gugler *et al.*, 1980) or produce a modest fall in blood pressure (Fitzgerald *et al.*, 1978; Maling *et al.*, 1979). In the present study propranolol and pindolol had mild hypotensive effects on supine and standing systolic and diastolic blood pressure. In contrast bucindolol had greater effects on blood pressure producing significant reductions in supine diastolic pressure and in standing systolic and diastolic pressure. The falls in pressure produced by bucindolol were dose related.

The potency of bucindolol as a hypotensive agent was demonstrated by most subjects being unable to stand upright for the full 3 min at 1 and 2 h after 200 and 400 mg. Due to the subjects' fainting tendency the reduction in standing blood pressure by bucindolol has almost certainly been under-estimated. It is unlikely that the hypotensive effect of bucindolol is due solely to β -adrenoceptor blockade as propranolol and pindolol had much smaller effects on blood pressure but produced equal or greater β -adrenoceptor blockade as measured by inhibition of an exercise tachycardia. This conclusion is supported by the difference in time course of the effects of bucindolol on arterial blood pressure and on an exercise tachycardia. The fall in pressure produced by bucindolol had worn off by 6 h but there was still a significant reduction in an exercise tachycardia at 24 h. The relatively short duration of the hypotensive effect does not appear to be due to the pharmacokinetic properties of bucindolol in view of the duration of β -adrenoceptor antagonism unless it results from the effects of one of the metabolites. However the major metabolite—5-OH bucindolol—was present in most subjects at 12 and 24 h. Of the other two metabolites—6 OH bucindolol—was not present in all subjects after 200 and 400 mg and indolyl-*t*-butylamine was present in very low concentrations.

Labetalol which blocks α - and β -adrenoceptors does not appear to have this separation between β -adrenoceptor blockade and hypo-

tensive effects (Richards *et al.*, 1974). However the affinity characteristics of bucindolol for α - and β -adrenoceptors may be quite different and may account for the differences in the duration of hypotensive and β -adrenoceptor blocking effects. In isolated vascular preparations, bucindolol has non-selective β - and α -adrenoceptor blocking properties (Rimele *et al.*, 1984) as well as a non-specific direct relaxation effect on vascular smooth muscle. *In vitro* radioligand studies have suggested (Hamilton & Reid, 1983) that bucindolol and one of its main metabolites, 5-OH bucindolol, have a relatively high affinity for α_1 - and β -adrenoceptors. Thus bucindolol may be similar to labetalol, a drug which has both α - and β -adrenoceptor antagonist properties.

Eight out of ten subjects had adverse effects 1–2 h after 400 mg bucindolol. These consisted of faintness, light-headedness and occasionally syncope when the subjects stood upright and appeared to result from the hypotensive action of bucindolol. At the time of these effects the subjects had facial flushing and suffusion of their conjunctiva. Similar effects occurred to a smaller extent in a few subjects after 100 and 200 mg bucindolol. The tiredness, fatigue and sleepiness occurring at 1–2 h may also have been related to the fall in blood pressure. The number of adverse effects, especially light-headedness was much less after propranolol and pindolol. The occurrence of postural hypotension with bucindolol may suggest that the fall in pressure arises from interference with α -adrenoceptor function.

Bucindolol was extensively metabolized with the detection and measurement of bucindolol and three metabolites—5-OH bucindolol, 6-OH bucindolol and indolyl-*t*-butylamine—after the administration of 100, 200 and 400 mg bucindolol. While bucindolol was not detected in samples from all subjects after 50 and 100 mg bucindolol, 5-OH bucindolol was present in all subjects although not at all sampling times and was present

in all subjects up to 12 h after 200 mg and 24 h after 400 mg. The plasma concentration of 5-OH bucindolol was always less than that of parent drug. The metabolite, 6-OH bucindolol, was never present in all subjects at one sampling time and except after the 400 mg dose was only present in a small number of subjects. The third metabolite was present in small concentrations and only after the two larger doses was present in most subjects. As the plasma concentration of bucindolol was greater than that of any of its metabolites throughout the 24 h observation period, it is probable that it accounted for the β -adrenoceptor blocking activity of the drug. The profile of the plasma concentrations of the metabolites does not suggest that they were responsible for the hypotensive action of bucindolol. The most noticeable feature of the pharmacokinetics of bucindolol was the disproportionate rise in plasma levels of bucindolol when the dose was increased from 200 to 400 mg when there was approximately a four fold increase in plasma concentration at 1, 2, 4, 6 and 8 h. There were not similar increases in plasma concentrations of metabolites. It is not clear if this represents non-linear kinetics.

The present studies indicate that bucindolol is a β -adrenoceptor blocking drug with a long duration of effect and probably with partial agonist activity. In addition it reduced arterial blood pressure in subjects in the standing position but this effect was of short duration. The higher doses (200 and 400 mg) produced postural hypotension. The mechanism of the hypotensive action of bucindolol is unclear but it does not appear to result from blockade of β -adrenoceptors. Bucindolol was extensively metabolized and there is suggestive evidence that the kinetics are not linearly related to the dose of drug.

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