Assessment of β -adrenoceptor selectivity of a new β -adrenoceptor antagonist, bisoprolol, in man

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1 Bisoprolol is a new β -adrenoceptor antagonist which has shown β -adrenoceptor selectivity in studies in isolated tissues.

2 Bronchial and cardiac β -adrenoceptor blockade were assessed in eight normal subjects before and after oral ingestion of placebo, bisoprolol 20 and 40 mg, metoprolol 200 mg and propranolol 80 mg in random order.

3 Bronchial β -adrenoceptor blockade was assessed as the displacement of the bronchodilator dose-response curve to inhaled isoprenaline after each β -adrenoceptor blocking drug compared to placebo and expressed as the dose ratio. Bronchodilatation was measured as change in specific airway conductance (sGaw) in the body plethysmograph. Cardiac β -adrenoceptor blockade was assessed as the percentage reduction in exercise heart rate during the fifth minute of exercise at 70% of the subject's maximum work rate.

4 Bisoprolol 20 and 40 mg caused a 24 and 25% reduction in exercise heart rate respectively, compared to 26% with metoprolol 200 mg and 20% with propranolol 80 mg. The dose ratios for the airway dose-response curves for the four β -adrenoceptor blocking drugs were 1.04 and 3.4 for bisoprolol 20 and 40 mg, 1.4 for metoprolol 200 mg and 30 for propranolol 80 mg.

6 Both doses of bisoprolol produced considerably less bronchial β -adrenoceptor blockade than propranolol 80 mg despite causing a greater reduction in exercise heart rate. Bisoprolol 20 mg caused a similar amount of bronchial β -adrenoceptor blockade and a similar reduction in exercise heart rate as metoprolol 200 mg, confirming that it is cardio-selective in man.

Keywords bisoprolol β -adrenoceptor antagonist selectivity

Introduction

Bisoprolol is a new β -adrenoceptor antagonist with little local anaesthetic activity and no intrinsic sympathomimetic activity. It is well absorbed after oral administration and ten times more potent on exercise tachycardia than metoprolol (Leopold *et al.*, 1982). Studies in isolated tissues suggest that bisoprolol is a potent β_1 -adrenoceptor antagonist with considerably less affinity for β_2 -adrenoceptors (Manalan *et al.*, 1981). The present study was carried out to determine

whether bisoprolol, in doses which cause a marked reduction in resting heart rate, blood pressure and exercise tachycardia (Leopold *et al.*, 1982; Dorow *et al.*, 1984), was β_1 -selective in man. We measured bronchial β -adrenoceptor blockade and the reduction in exercise heart rate on separate occasions in eight normal subjects after oral bisoprolol 20 and 40 mg, propranolol 80 mg, metoprolol 200 mg and placebo. Bronchial β -adrenoceptor blockade was assessed by measuring the displacement of the airway dose-response curve to inhaled isoprenaline after each β -adrenoceptor

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antagonist compared to placebo, using a similar technique to that used in previous studies using inhaled salbutamol (Gribbin *et al.*, 1979, 1981; Mackay *et al.*, 1981).

Methods

The study was carried out on eight normal, healthy non-asthmatic subjects. All agreed to participate after a full explanation of the procedure and purpose of the study which was approved by the Southampton Ethical Committee. Airway resistance (Raw) and thoracic gas volume (VTG) were measured in a pressure compensated body plethysmograph (Fenyves and Gut, Basle) and the results displayed on an oscilloscope. This was on-line to a microprocessor (Apple II) which calculated a mean value for Raw, VTG and specific airway conductance (sGaw), the reciprocal of airway resistance corrected for lung volume, over at least 10 panting breaths (Shah *et al.*, 1980). All studies were carried out with the subject fasting. Heart rate was measured by palpation of the radial pulse for the airway studies, and from a continuous electrocardiogram during the exercise study. Subjects attended on 10 occasions, five for assessment of bronchial β -adrenoceptor blockade and five for exercise studies. The order of the five drugs was randomised for 10 subjects for both the airway and exercise studies. Two were omitted because the airway studies failed to fulfil the criteria laid down below.

Airway isoprenaline dose-response studies

Subjects attended on five occasions. After sitting quietly for 10 min baseline sGaw was measured three times at 2 min intervals. Further measurements were made if the three values differed by more than 10%. Subjects then took either oral bisoprolol 20 mg and 40 mg, propranolol 80 mg, metoprolol 200 mg and placebo at least 4 days apart. Ninety min later heart rate (HR) was measured and three further measurements of sGaw were made at 2 min intervals. The subject then inhaled increasing doses of isoprenaline from specially prepared metered aerosols delivering 10, 20, 80 and 400 μ g per inhalation. HR was measured at 1.5 min and sGaw at 2.5 and 4 min after each inhalation, and followed by the next dose of isoprenaline at 5 min. At least eight doses of isoprenaline were given to achieve cumulative doses increasing from 10 μ g to 780 μ g after placebo, metoprolol and bisoprolol and from 10 to 7,450 μ g after propranolol. Studies were only considered satisfactory if sGaw had increased by 40% and there were at

least three points on the steep part of the dose-response curve. If after eight doses this was not the case, a further two doses of isoprenaline were taken. The study would have been discontinued if HR exceeded 110 beats/min.

Exercise study

Subjects attended the laboratory on five further occasions. They rested on an electrically braked bicycle (Elema Schonander) for 5 min before carrying out a steady state exercise study for 5 min at 70% of their previously determined maximum exercise work rate. Heart rate was measured during the fifth minute of rest and fifth minute of exercise. The subject then ingested, in random order, one of the five drugs under study, and returned 2 h later to repeat the exercise test in an identical manner.

Analysis of results

The mean of three sGaw and VTG readings before each drug were compared to the mean of three readings 1.5 h after each drug by Wilcoxon's paired rank test. A regression of Δ sGaw on log cumulative isoprenaline dose was calculated by the method of least mean squares and subjected to an algorithm which selected the points which best fitted the regression of response on log dose. This process was repeated until r exceeded 0.98 or only four points remained; an analysis of covariance was then performed on the slopes. Maximum Δ sGaw was taken as the mean of the two highest Δ sGaw values from all dose-response studies for each subject. Dose ratios were calculated from the dose of isoprenaline causing a 50% maximum increase in sGaw after each β -adrenoceptor antagonist compared to placebo. Geometric mean dose ratios were compared by Student's t -test. Heart rate was measured over 1 min and mean values for placebo and each drug, before and during exercise, were compared by paired Student's t -test.

Results

The only side-effect after active β -adrenoceptor blocking drug or placebo was increased tiredness in two subjects after metoprolol. Mild tremor occurred on occasions following inhaled isoprenaline. Heart rate never exceeded 100 beats min^{-1} .

Airway dose-response studies

Mean resting values for sGaw and VTG before

Table 1 Mean resting sGaw and VTG values, pre- and post-drug.

Treatment	sGaw ($\text{s}^{-1} \text{kPa}^{-1}$)			VTG (l)		
	Pre-drug	Post-drug	P value	Pre-drug	Post-drug	P value
Placebo	1.65	1.79	NS	4.36	4.53	NS
Bisoprolol 20 mg	1.72	1.69	NS	4.81	4.65	NS
Bisoprolol 40 mg	1.71	1.79	NS	4.94	4.65	NS
Metoprolol 200 mg	1.60	1.65	NS	5.02	4.88	NS
Propranolol 80 mg	1.73	1.79	NS	4.57	4.38	NS

Table 2 Analysis of variance of dose-response curves.

	<i>F</i> parallel	P value	<i>F</i> coincidence	P value
Placebo vs bisoprolol 20 mg	1.15	NS	0.17	NS
Placebo vs bisoprolol 40 mg	1.29	NS	13.76	$P < 0.01$
Placebo vs metoprolol 200 mg	1.33	NS	2.24	NS
Placebo vs propranolol 80 mg	2.93	NS	41.05	$P < 0.01$
Bisoprolol 20 mg vs bisoprolol 40 mg	0.05	NS	6.43	$P < 0.05$

and after the β -adrenoceptor antagonists and placebo are shown in Table 1. There were no differences in pre-drug resting sGaw or VTG values and no significant change in sGaw or VTG after any drug or placebo.

Mean sGaw values ranged from 0.9 to $2.6 \text{ s}^{-1} \text{kPa}^{-1}$ in the eight subjects (Table 3). None of the drugs caused a significant change in the slope of the isoprenaline dose-response curve compared to placebo (Table 2).

Analysis of the dose-response curves showed that the curves for bisoprolol 20 mg and metoprolol 200 mg were not significantly displaced from placebo (Table 2), whilst the curves for bisoprolol 40 mg and propranolol 80 mg were significantly displaced to the right ($P < 0.01$).

Following β -adrenoceptor antagonists the geometric mean isoprenaline dose ratios were 1.05 and 3.4 for bisoprolol 20 and 40 mg, 1.4 for metoprolol 200 mg and 30.2 for propranolol 80 mg (Table 3).

Exercise heart rate

Mean values for heart rate at rest and during exercise, and the percentage reduction in heart rate at rest and during exercise for each drug are shown in Table 4 and Figure 1. The mean reduction in resting heart rate after placebo was 14%, metoprolol 22%, propranolol 17% and bisoprolol 20 and 40 mg, 21 and 20% respectively. The mean reduction in exercise heart rate after

Table 3 Mean sGaw values and dose ratios for the eight subjects

Subject	Mean resting sGaw (s ⁻¹ kPa ⁻¹)	Maximum ΔsGaw	Dose ratio				
			Bisop 20	Bisop 40	Met 200	Prop 80	
1	1.93	1.62	0.7	10.7	0.8	4.2	
2	0.94	1.53	1.5	7.4	2.7	426.6	
3	1.37	0.96	2.5	5.0	0.9	14.8	
4	1.55	1.14	1.1	16.6	1.5	60.3	
5	1.23	2.19	1.3	0.4	4.0	58.9	
6	2.62	1.30	1.9	4.8	2.3	10.9	
7	1.83	1.19	0.3	1.2	0.6	109.7	
8	2.34	1.46	0.8	1.1	1.0	5.8	
			1.1	3.4	1.4	30.2	Geometric mean
			1.3	5.4	1.8	53.1	Geometric mean + s.e. mean - s.e. mean
			0.8	2.2	1.1	17.2	

Table 4 Mean $\pm$ s.e. mean heart rate values

	Pre-drug		Post-drug		% Reduction	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Placebo	87 $\pm$ 4	157 $\pm$ 5	77 $\pm$ 4	151 $\pm$ 3.6	14 $\pm$ 2	3 $\pm$ 1.3
Bisoprolol 20 mg	84 $\pm$ 3	155 $\pm$ 4	65 $\pm$ 2	118 $\pm$ 3	21 $\pm$ 3	24 $\pm$ 0.7
Bisoprolol 40 mg	80 $\pm$ 4	158 $\pm$ 3	64 $\pm$ 3	119 $\pm$ 3	20 $\pm$ 2	25 $\pm$ 1.5
Metoprolol 200 mg	86 $\pm$ 3	158 $\pm$ 5	67 $\pm$ 2	116 $\pm$ 3	22 $\pm$ 3	26 $\pm$ 1.3
Propranolol 80 mg	83 $\pm$ 3	155 $\pm$ 6	68 $\pm$ 1.5	123 $\pm$ 4	17 $\pm$ 2	20 $\pm$ 1.2

placebo was 3%, compared to metoprolol 26%, propranolol 20% and bisoprolol 20 and 40 mg, 24 and 25% respectively. The fall after each β -adrenoceptor blocking drug was significantly different to placebo ($P < 0.001$). The change after propranolol was less than the reduction after metoprolol ($P < 0.01$) and both doses of bisoprolol ($P < 0.05$).

Discussion

We have shown previously that following oral β -adrenoceptor antagonists the airway dose-response curve to inhaled salbutamol is displaced to the right in a parallel manner, as would be expected with a competitive antagonist (Gribbin *et al.*, 1979). The extent of the displacement has been used to quantify the extent of bronchial β -adrenoceptor blockade. Combining this measure of bronchial β -adrenoceptor blockade with exercise heart rate as a measure of cardiac β -adrenoceptor blockade allows us to assess the cardioselectivity of β -adrenoceptor antagonists in normal subjects without putting patients with asthma at risk. In this study we modified our previous technique by using iso-

prenaline rather than salbutamol. This reduces the length of each airway study from 90 to 30–40 min. Since all the drugs under study caused β_1 -adrenoceptor blockade there were no problems with excessive β_1 -receptor stimulation, despite the large doses of isoprenaline (8000 μ g) needed to overcome the effect of propranolol on the airways. Studies in the department show that the reproducibility of isoprenaline dose-response curves is very similar to that of salbutamol (Harrison, personal communication). The algorithm used to fit the points to a regression line was introduced to try to exclude the occasional rogue points which occur with the body plethysmograph, without introducing observer bias.

The two doses of bisoprolol used in this study caused much less bronchial β -adrenoceptor blockade than 80 mg propranolol. The dose ratio for the isoprenaline airway dose-response curves following propranolol was 30 in these eight subjects compared to 61 in a previous study of salbutamol in six different normal subjects (Gribbin *et al.*, 1979). Theoretically the use of isoprenaline rather than salbutamol should not alter the dose ratio and we believe the difference is due to the relatively small number of subjects

Figure 1 Mean heart values for eight subjects at rest and during exercise before and after placebo (Δ), bisoprolol 20 mg ($\circ$), bisoprolol 40 mg ($\bullet$), metoprolol ($\square$) and propranolol ($\blacksquare$).

and the larger intersubject differences in dose ratio which ranged from 16 to 218 in the first study and from 4 to 427 in the present study. This highlights the importance of comparing different drugs in the same subject. The mean dose ratio after bisoprolol was 1.04 for the 20 mg dose and 3.4 for the 40 mg dose. The dose ratio for the 20 mg dose was clearly close to unity and also very close to the value of 1.4 obtained with metoprolol 200 mg.

Bisoprolol, 20 and 40 mg, caused a 24 and 25% reduction in exercise heart rate in the eight normal subjects in this study compared to a 26% reduction with metoprolol and 20% with 80 mg propranolol. The results with propranolol and metoprolol are similar to those seen in previous studies (Mackay *et al.*, 1981; Oh *et al.*, 1978; Harron *et al.*, 1981). Both doses of bisoprolol

therefore caused a marked reduction in exercise tachycardia with little difference between the two doses. This suggests that the doses of bisoprolol may be relatively high compared to the other drugs and this may cause an underestimate of cardioselectivity. Bisoprolol 20 mg therefore caused a marked reduction in exercise heart rate with minimal bronchial β -adrenoceptor blockade. The results are very similar to those for metoprolol and suggest that bisoprolol is at least as cardioselective as metoprolol. The design of the study does not allow more detailed comparison between the two drugs.

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