Comparative effects of bisoprolol and acebutolol in smokers with airway obstruction

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1 The effects of single oral doses of 10 mg bisoprolol and 400 mg acebutolol on respiratory function were studied in nine smokers with airway obstruction in a double-blind, placebo-controlled experiment.

2 The effects of the drugs were assessed by measuring specific airway conductance (sGaw) for 3 h after their administration and by studying their interaction with the bronchodilator response to inhaled salbutamol.

3 sGaw did not change for 3 h after bisoprolol or acebutolol administration. The bronchodilator response to inhaled salbutamol was not affected by bisoprolol but significantly reduced by acebutolol ($P < 0.05$ vs placebo).

4 Under these conditions, bisoprolol behaves like a selective β_1 -adrenoceptor antagonist but acebutolol exhibits less β_1 -adrenoceptor selectivity.

Keywords bisoprolol acebutolol airway obstruction β_1 -adrenoceptor selectivity

Introduction

β -adrenoceptor blockade is an established treatment for hypertension and angina pectoris; coexisting chronic obstructive pulmonary disease due to cigarette smoking is common in such cases. Patients with chronic airway obstruction usually display some deterioration in pulmonary function in response to β -adrenoceptor antagonists, even the most β_1 -adrenoceptor selective (Perks *et al.*, 1978; Sinclair, 1979; Dorow & Tönnemann, 1984). Bisoprolol, a new β -adrenoceptor antagonist without intrinsic sympathomimetic activity, has been demonstrated to be highly β_1 -adrenoceptor selective in animals and normal volunteers (Schliep & Harting, 1984; Leopold *et al.*, 1986). However, the relevance of this finding to clinical situations needs further assessment. Only a few studies have so far been devoted to investigating the β_1 -adrenoceptor selectivity of bisoprolol in patients with pulmonary disease (Dorow *et al.*, 1986; Lammers *et al.*, 1984; Chatterjee, 1986).

The aim of this study was to assess the β_1 -adrenoceptor selectivity of bisoprolol in relation

to that of acebutolol, a β_1 -adrenoceptor antagonist with intrinsic sympathomimetic activity, by investigating the effects of each drug on airway function in smokers with chronic airflow limitation.

Methods

Subjects

Nine volunteers, aged 31–52 years, with non-asthmatic obstructive lung disease, were recruited for the study. Selection criteria included: (i) a history of cigarette smoking of at least 15 pack-years, (ii) airflow limitation with a forced expiratory flow at 50% of vital capacity of less than 70% of the predicted value, as measured from a maximum expiratory flow-volume curve (Quanjer *et al.*, 1983), (iii) an increase of at least 20% in specific airway conductance (sGaw) following two inhalations of 100 μ g salbutamol each. Exclusion criteria included any history

Table 1 Characteristics of patients

Subject	Age (years)	Sex	Height (cm)	Weight (kg)	Smoking history (pack-years)	FEF ₅₀		FEV ₁
						actual (l s ⁻¹)	predicted values (%)	predicted values (%)
1	39	F	165	62	20	2.1	49	70
2	31	M	176	70	15	2.7	51	80
3	41	M	174	70	20	3.4	69	89
4	33	F	171	64	18	2.1	47	70
5	33	F	157	48	22	2.5	61	90
6	52	M	167	60	30	2.6	59	75
7	39	M	183	74	20	3.2	59	85
8	33	M	175	65	17	2.5	47	70
9	37	F	166	58	15	2.9	67	90
Mean	38		170	63	20	2.7	57	80
Range	31–52		157–183	48–74	15–30	2.1–3.4	47–67	70–90

FEF₅₀: forced expiratory flow at 50% of vital capacity.

FEV₁: forced expiratory volume in one second.

suggestive of asthma. Details of the nine subjects are shown in Tables 1 and 2. None was taking regular medication.

The study was approved by the local Ethics Committee and written informed consent was obtained from each subject before participation.

Cardiovascular and respiratory measurements

All measurements were performed with the subject seated. Specific airway conductance (sGaw) was measured with a flow pressure-compensated body plethysmograph according to the method of Dubois *et al.* (1956) modified by Lorino *et al.* (1985). For the measurements, the subjects panted at a frequency of about 2 cycles s⁻¹ at a thoracic gas volume close to their functional residual capacity. After each manoeuvre, sGaw was calculated and displayed on the visual unit of an Apple IIE microcomputer connected to the plethysmograph. Each determination was the mean of four measurements.

Heart rate (HR), and systolic and diastolic blood pressure (BP) were measured in triplicate with an automatic blood pressure recorder (Mira TM300, Lyon, France).

Protocol

The subjects attended the laboratory on three occasions, separated by intervals of 1 week. They refrained from drinking beverages containing caffeine 12 h before each day of attendance. All studies started at 11.30 h.

After subjects had been sitting quietly for 10 min, base-line HR, and systolic and diastolic BP and sGaw were measured. Subjects were then given 10 mg bisoprolol, 400 mg acebutolol or

Table 2 Salbutamol test: specific airway conductance (sGaw) before and 10 min after inhalation of 200 µg salbutamol

Subject	sGaw* baseline values	sGaw* after 200 µg salbutamol	% increase with salbutamol
1	1.01	1.54	52
2	0.86	1.37	59
3	0.70	1.09	56
4	0.63	1.18	54
5	1.43	1.78	24
6	1.95	2.35	21
7	1.05	1.50	56
8	1.01	1.58	56
9	0.82	1.56	90
Mean	1.05	1.55	52
Range	0.63–1.95	1.09–2.35	21–90

* expressed in kPa⁻¹ s⁻¹.

placebo orally in a double-blind and randomized manner according to a Latin square design. A light meal was provided 30 min after drug administration. HR, BP and sGaw were again measured 1, 2 and 3 h after drug intake. Subjects then inhaled 100, 200, 400 and 800 µg salbutamol administered at 15 min intervals as cumulative doses with a commercially available metered dose aerosol delivering 100 µg per puff. sGaw was measured 10 min after inhalation of each dose.

Analysis of results

Statistical analysis was performed using BMDP statistical software (Dixon *et al.*, 1985).

Baseline values of the parameters measured on the 3 study days were compared by analysis

of variance for Latin square design testing for two factors, the order of drug administration and the drug itself. Values of the parameters measured over the 3 h observation period were computed by analysis of variance for repeated measures models testing for the drug and time factors and their interaction. In cases of significant time-drug interaction, the main effects of each factor were respectively considered at each level of the other factor. When drug effects were significant, Tukey's test (if distribution was normal) or Duncan's Multiple Range Test (if data were not normally distributed) was used for pairwise comparison of the effects of medication.

Statistical analysis of the dose-response curves with salbutamol was performed using an analysis of variance for repeated measures models as described above. The parameter used for analysis was the increase in sGaw (Δ sGaw = the value after inhalation of each dose of salbutamol minus the value 3 h after drug ingestion). Since no interaction was found and a significant medication effect was, Tukey's test was used for pairwise comparison of the treatment effect after testing that data were normally distributed. *P* values of less than 0.05 were considered statistically significant.

Results

No significant differences were found between the baseline values of the HR, systolic and diastolic BP, or sGaw measured on the 3 study days (Table 3).

The effects of placebo, acebutolol and bisoprolol on HR and BP are shown in Table 3.

Comparisons of the changes in these parameters did reveal significant differences between the effects of placebo, bisoprolol and acebutolol. Both the latter significantly reduced BP and HR compared with placebo. Three hours after drug administration, the declines in HR and BP after bisoprolol or acebutolol did not differ significantly.

There were no significant changes in sGaw, 1, 2 and 3 h after administration of placebo, bisoprolol or acebutolol (Figure 1), but significant differences were observed between the increases in sGaw induced by salbutamol after administration of placebo, bisoprolol or acebutolol (Figure 2, Table 4). Treatment with acebutolol *vs* placebo inhibited the increase in sGaw in response to salbutamol (*P* < 0.05). However, the effect of bisoprolol on this increase was not significantly different from that of placebo.

Discussion

Only a few clinical studies have so far assessed the bronchopulmonary effects of bisoprolol, a new β_1 -adrenoceptor antagonist reported to be highly β_1 -selective in animal studies. In normal subjects, Tattersfield *et al.* (1984) found that 20 or 40 mg bisoprolol did not change sGaw and did not shift the airway dose-response curve resulting from β_2 -adrenoceptor agonist inhalation. In asthmatic patients, Lammers *et al.* (1984) showed that 10 mg bisoprolol significantly reduced the peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV₁) but that 20 mg did not. However, in the latter study, the bronchodilator response to inhaled terbuta-

Table 3 Systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) before and 1, 2 and 3 h after ingestion of placebo, 10 mg bisoprolol or 400 mg acebutolol

		Baseline values	Time after administration (h)		
			1	2	3
Placebo	SBP	115 $\pm$ 3	116 $\pm$ 3	113 $\pm$ 3	116 $\pm$ 2
	DBP	70 $\pm$ 2	66 $\pm$ 1	67 $\pm$ 2	68 $\pm$ 2
	HR	74 $\pm$ 3	72 $\pm$ 4	71 $\pm$ 3	74 $\pm$ 4
Bisoprolol	SBP	116 $\pm$ 1	110 $\pm$ 3	102 $\pm$ 2**	103 $\pm$ 2**
	DBP	70 $\pm$ 2	66 $\pm$ 2	58 $\pm$ 3**	60 $\pm$ 2**
	HR	77 $\pm$ 4	62 $\pm$ 3**	60 $\pm$ 3**	61 $\pm$ 3**
Acebutolol	SBP	117 $\pm$ 2	110 $\pm$ 2	106 $\pm$ 3*	105 $\pm$ 2**
	DBP	69 $\pm$ 2	67 $\pm$ 2	65 $\pm$ 2	61 $\pm$ 2*
	HR	70 $\pm$ 4	63 $\pm$ 4**	64 $\pm$ 3**	64 $\pm$ 3**

* *P* < 0.05, ** *P* < 0.01 compared with baseline values.

Data are presented as means $\pm$ s.e. mean.

Figure 1 Specific airway conductance (sGaw) before (□) and 1 (▨), 2 (▩) and 3 h (▧) after a single administration of placebo, 10 mg bisoprolol or 400 mg acebutolol to nine smokers with airflow limitation. Data are presented as means $\pm$ s.e. mean.

Figure 2 Dose-response curves following inhalation of salbutamol 3 h after intake of placebo (■), 10 mg bisoprolol (□) or 400 mg acebutolol (Δ). The mean increase in sGaw (Δ sGaw) is plotted against the cumulative doses of salbutamol inhaled. Data are presented as means $\pm$ s.e. mean. Asterisks denote significant differences between two curves (analysis of variance) * P < 0.05, ** P < 0.01.

Table 4 Specific airway conductance (sGaw*) before and 3 h after intake of placebo, 10 mg bisoprolol and 400 mg acebutolol and after cumulative doses of inhaled salbutamol (means $\pm$ s.e. mean)

	Baseline values	Values 3 h after drug administration	Values after inhalation of salbutamol			
			100 μ g	200 μ g	400 μ g	800 μ g
Placebo	1.09 $\pm$ 0.11	1.07 $\pm$ 0.13	1.43 $\pm$ 0.09	1.49 $\pm$ 0.09	1.51 $\pm$ 0.13	1.51 $\pm$ 0.11
Bisoprolol	1.08 $\pm$ 0.11	1.05 $\pm$ 0.13	1.54 $\pm$ 0.12	1.59 $\pm$ 0.11	1.60 $\pm$ 0.09	1.68 $\pm$ 0.11
Acebutolol	1.09 $\pm$ 0.09	1.06 $\pm$ 0.09	1.19 $\pm$ 0.07	1.28 $\pm$ 0.06	1.30 $\pm$ 0.04	1.34 $\pm$ 0.05

* expressed in $\text{kPa}^{-1} \text{s}^{-1}$.

line was not different from that of placebo for either 10 or 20 mg bisoprolol, so that there is no clear explanation for the reduction in PEFR and FEV₁ with 10 mg. In patients with non-asthmatic chronic airway obstruction, Dorow *et al.* (1986) did not find any change in airway resistance after 20 mg bisoprolol whereas 100 mg atenolol significantly increased airway resistance but no airway dose-response curves to a β_2 -adrenoceptor agonist were constructed.

We performed our study in middle-aged smokers with mild airflow limitation, as shown by the abnormal results of small airway function tests, for two reasons: first, younger subjects are more likely to be given β -adrenoceptor blockers than older ones for hypertension and angina pectoris; secondly, airway obstruction, when not accompanied by clear clinical manifestations of chronic bronchitis often remains undetected. Under these conditions, prescription of β -adrenoceptor blockers could therefore be unsafe. One of the criteria for the choice of the patients in this study was that they must exhibit bronchodilator response after β_2 -adrenoceptor agonist inhalation since it has been demonstrated that pulmonary function can only be reduced during β -adrenoceptor blockade in patients with reversible airway obstruction (Perks *et al.*, 1978; Van Herwaarden, 1983). To ensure the clinical relevance of this study, the oral doses of bisoprolol and acebutolol (10 mg and 400 mg respectively), were those recommended in clinical practice for hypertension treatment. Both drugs lowered systolic and diastolic blood pressure and heart rate in degrees which did not differ significantly 3 h after their administration.

Although neither drug affected resting bronchial tone, it has been demonstrated that the most suitable method of assessing the cardio-selectivity of β -adrenoceptor blockers is to construct a curve for the bronchodilator airway dose-response to an inhaled β_2 -adrenoceptor agonist (Tattersfield, 1986). After acebutolol treatment, the bronchodilator effect of salbutamol was significantly reduced, compared with the effect observed after placebo or bisoprolol treatment. This indicates that acebutolol at 400 mg no longer exhibits β_1 -adrenoceptor selectivity, in agreement with the results of previous studies in normal subjects, asthmatic patients and patients with non-asthmatic chronic airway obstruction (Gribbin *et al.*, 1981; Skinner *et al.*, 1975; Whitsett *et al.*, 1982). By contrast, with 10 mg bisoprolol, salbutamol was found to cause the same degree of bronchodilatation as placebo, indicating that at this dose, bisoprolol possesses β_1 -adrenoceptor selectivity. These results confirm the β_1 -adrenoceptor selectivity previously reported for bisoprolol by Dorow & Tönnemann (1984) and Dorow *et al.* (1986) who demonstrated the absence of change in sGaw after administration of up to 20 mg bisoprolol in patients with reversible non-asthmatic chronic airway disease. The bronchodilator airway dose-response curves obtained in our study after salbutamol inhalation further confirm these findings.

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