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The Cardioselective and Hypotensive Effects of Bisoprolol in Hypertensive Asthmatics

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Summary: The cardioselectivity and hypotensive properties of the β_1-specific β-blocker bisoprolol were investigated using a single-dose comparison of 10 and 20 mg bisoprolol, 100 mg atenolol, and placebo in 12 hypertensive asthmatic patients. The study was of a randomised four-way crossover design with 1 week's washout between each treatment. β_1-Selectivity was determined by using lung function parameters — vital capacity (VC), airway resistance (AWR), peak expiratory flow rate (PEFR), forced expiratory volume (FEV_1) — at baseline and at predetermined intervals following each medication and salbutamol challenge. Potency of β-blockade was determined using heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP). 100 mg atenolol and 10 and 20 mg bisoprolol reduced HR, SBP, and DBP 2 h postmedication. All active treatments produced only small nonsignificant reductions in PEFR, FEV_1, and VC, compared with baseline, without any significant differences between the four groups. Bisoprolol at both dose levels had only a minor nonsignificant influence on AWR. 100 mg atenolol significantly increased AWR, compared with placebo. Following all treatments, salbutamol did not affect cardiovascular parameters, but significantly reduced AWR and increased PEFR, FEV_1, and VC without any significant differences between groups. Bisoprolol, at both dose levels tested, was found to possess a strong β_1-adrenoceptor–blocking activity without affecting bronchial β_2-adrenoceptors. An equipotent β_1-adrenoceptor–blocking dose of atenolol (100 mg), compared with 10 and 20 mg bisoprolol, was found to increase airway resistance in the population of asthmatic patients studied. Bisoprolol has been shown to exhibit a greater β_1-selectivity than atenolol. **Key Words:** Bisoprolol — Atenolol — β_1-Selectivity — Asthmatics — Hypertension

Bisoprolol is a new cardioselective β_1-adrenergic blocking agent with no partial agonist or membrane stabilising activity.

Studies using isolated tissue preparations (1) and animals (2) suggest that bisoprolol is a potent β_1-adrenoceptor antagonist with considerably less affinity for β_2-adrenoceptors.

Subsequent clinical studies with normal volunteers (4–7), in patients with coronary heart disease and chronic obstructive bronchitis (8,9), and in patients with asthma (10) have confirmed the efficacy and β_1-selectivity of bisoprolol in humans. Furthermore, the results of the studies have indicated that bisoprolol exhibits a higher β_1-selectivity than atenolol when assessed by using the respiratory tract (9) or the peripheral vascular system (5,11).

The present study was designed to investigate the degree of cardioselectivity of bisoprolol (at two dose levels) in comparison with atenolol in patients with coexistent bronchial asthma and hypertension.

PATIENTS AND METHODS

Twelve patients (11 male and one female) with mild to moderate hypertension (120/90–160/115 mm Hg) and bronchial asthma were admitted to this study. Their mean age was 60 years (range, 50–71 years). The patients were screened for inclusion in the study based on whether they had an FEV_1/vital capacity ratio of $\leq 30\%$, which improved by at least 15% on salbutamol inhalation (Table 1).

All patients gave written informed consent for participation in the study, and the study protocol was approved by the Hospital Ethical Committee.

Patients were excluded from the study if pregnancy, renal failure, overt heart failure, or second or third degree heart block were present. Patients were withdrawn during the study if there was onset of unacceptable side effects, heart failure, or second or third degree heart block, and FEV_1 of < 1 L. Before inclusion in the study, current antihypertensive therapy was excluded, and the use of a bronchodilator within the previous 12 h also was prohibited.

All patients, on fulfilling the inclusion criteria, were randomised to a double-blind (double-dummy technique)

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TABLE 1. *Reversibility of bronchial obstruction after salbutamol inhalation*

	Salbutamol		Change
	Before	After	(Δ%)
FEV_1 (l)	1.74 ± 0.13	2.14 ± 0.15	+22.8 ± 4.6
VC (l)	3.20 ± 0.16	3.60 ± 0.18	+14.2 ± 3.7
PEFR (l/min)	302 ± 23	355 ± 26	+21.4 ± 3.9

FEV_1, forced expiratory volume in 1 s; VC, vital capacity; PEFR, peak expiratory flow rate.
Means ± SEM, n = 12.

four-way crossover study, in which they received either a single dose of 100 mg atenolol, 20 mg bisoprolol, 10 mg bisoprolol, or placebo.

Following a light breakfast, patients reported to the hospital between 8.00 a.m. and 9.00 a.m., where they rested for 30 min before baseline assessments were carried out. Baseline data were obtained for blood pressure standing (2 min), heart rate (HR), respiratory function, forced expiratory volume in 1 s (FEV_1), vital capacity (VC), peak expiratory flow rate (PEFR), and airway resistance (AWR). Following baseline assessments, each patient received a single dose of either 100 mg atenolol, 20 mg bisoprolol, 10 mg bisoprolol, or placebo. The assessments (previously outlined) were then carried out 30, 60, and 120 min postdosing. Two hours postdosing, and after an interval of 5 min, two puffs of the β_2-stimulant bronchodilator salbutamol (2 × 100 μg) were given, the respiratory function tests (RFTs) were repeated, and the HR and BP recorded. RFTs, HR, and BP were again recorded 5, 15, 30, 60, and 120 min following salbumatol challenge.

All patients remained in the hospital for a further 4 h under observation. The patients returned to the hospital at weekly intervals on the following 3 consecutive weeks and received a single dose of one of the alternative study treatments. The aforementioned measurements were repeated at similar time intervals.

Statistical methods

Within each treatment, differences were tested using paired Student's *t* tests; comparisons were made between values at baseline, 2 h postdose, and 5 and 120 min after salbutamol challenge. Between-group comparisons were also made using paired Student's *t* tests. Comparisons were made at baseline, 2 h postdose, and 5 and 120 min following salbutamol challenge.

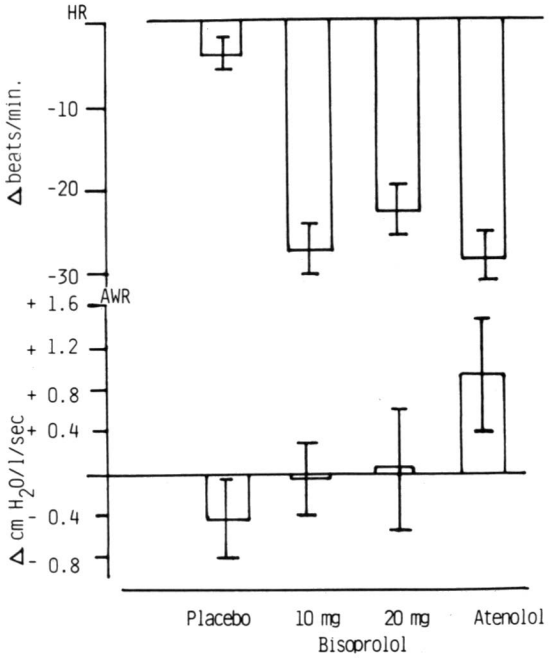

FIG. 1. Changes (Δ) in heart rate (HR) **(upper panel)** and in airway resistance (AWR) **(lower panel)** from baseline values 2 h postmedication of placebo, 10 and 20 mg bisoprolol, and 100 mg atenolol.

RESULTS

All 12 patients completed the study, and none of the courses of assessments had to be discontinued prematurely. None of the patients had any clinical impairment of lung function, and no other side effects were observed.

Results 2 h after dosing

The effects of placebo, atenolol (100 mg), and two dose levels of bisoprolol (10 mg and 20 mg) on the various parameters are shown in Table 2 (SBP, DBP, PEFR, FEV_1, and VC) and Figure 1 (HR and AWR) in the form of mean changes from baseline 2 h postdosing.

HR, SBP and DBP. All treatments reduced HR significantly, with the exception of placebo. All active medications showed a significantly greater reduction in HR compared with placebo ($p < 0.001$), but there was no significant difference in reduction between groups.

TABLE 2. *Changes (Δ) in blood pressure and lung function parameters from baseline values 2-h postmedication*

	SBP (mm Hg)	DBP (mm Hg)	PEFR (l/min)	FEV_1 (l)	VC (l)
Placebo	−8 ± 2	−8 ± 2	+8.5 ± 8.7	+0.02 ± 0.07	−0.09 ± 0.14
Bisoprolol (10 mg)	−20 ± 3	−13 ± 2	−4.5 ± 5.8	−0.08 ± 0.05	+0.19 ± 0.10
Bisoprolol (20 mg)	−21 ± 3	−13 ± 2	−12.8 ± 11.6	−0.11 ± 0.08	−0.09 ± 0.12
Atenolol (100 mg)	−23 ± 4	−12 ± 2	−7.1 ± 9.6	−0.11 ± 0.06	+0.02 ± 0.13

Means ± SEM; n = 12.
SPB/DBP, systolic/diastolic blood pressure; PEFR, peak expiratory flow rate; FEV_1, forced expiratory volume in 1 s; VC, vital capacity.

TABLE 3. *Effects of salbutamol (S) on heart rate (HR) and blood pressure (SBP, DBP) 5 min and 2 h after challenge in 12 patients pretreated 2 h before challenge with placebo (Pl), bisoprolol 10 (B10), bisoprolol 20 (B20), and atenolol 100 mg (A100), respectively*

	HR (beats/min)				SBP (mm Hg)				DBP (mm Hg)			
	Pl	B10	B20	A100	Pl	B10	B20	A100	Pl	B10	B20	A100
Baseline	93.5 ± 5	95 ± 4	89 ± 3	94 ± 3	151 ± 5	155 ± 4	154 ± 5	153 ± 6	95 ± 1	97 ± 1	95 ± 1	95 ± 1
2-h post-medication	89 ± 4	68 ± 3	65 ± 2	66 ± 2	143 ± 6	135 ± 5	133 ± 4	130 ± 4	87 ± 2	84 ± 2	83 ± 2	84 ± 2
S: 5 min	91.4 ± 4	68 ± 3	66 ± 2	67 ± 2	140 ± 5	131 ± 4	131 ± 5	130 ± 5	88 ± 2	82 ± 1	83 ± 2	84 ± 3
S: 2 h	92.4 ± 4	68 ± 3	68 ± 2	66 ± 2	145 ± 5	138 ± 5	137 ± 4	135 ± 4	90 ± 2	86 ± 1	86 ± 2	85 ± 2

Means ± SEM.

All treatments produced a significant reduction in SBP from baseline, and a significantly greater reduction in comparison with placebo ($p < 0.01$), but no difference between active medications could be demonstrated. All active treatments decreased DBP significantly compared with baseline. Apart from a significantly greater reduction of DBP with 10 mg bisoprolol, compared with placebo ($p < 0.05$), no other significant differences in reduction between groups could be demonstrated.

Respiratory function. All active treatments produced small reductions in PEFR, FEV_1, and VC, compared with baseline (Table 2), whereas there were slight increases in PEFR and FEV_1 after placebo. None of the treatment and placebo effects were statistically significant, and there were no significant differences between the four groups. Bisoprolol at both dose levels had only minor influence on AWR, whereas there were greater changes in AWR with placebo (decrease) and atenolol (increase), compared with baseline (Fig. 1). None of these changes were statistically significant, but a significant between-group increase in resistance was shown between atenolol and placebo ($p < 0.05$).

Results following salbutamol challenge

HR, SBP, and DBP. Five and 120 min after salbutamol challenge, no influence on HR, SBP, and DBP could be demonstrated after all four treatments (Table 3). Thus, the reductions in cardiovascular parameters produced by the three active treatments remained unchanged throughout the entire observation period, until 4 h after dosing.

Respiratory function. Five and 120 min after salbutamol challenge, AWR was significantly reduced, and FEV_1, PEFR, and VC parameters increased in all four treatment groups ($p < 0.001$) over prechallenge values, but there were no significant differences between groups (Table 4).

DISCUSSION

All patients suffered from marked but reversible obstructive pulmonary disease. Respiratory function baseline values were comparable on the 4 study days as an indication for a stable ventilatory state during the 3-week trial period.

The present study confirmed the cardiac β-blockade effect of bisoprolol at two dose levels (10 and 20 mg), as demonstrated by the depression of HR, SBP, and DBP. The results were comparable to those obtained with 100 mg atenolol. Since 20 mg bisoprolol had no stronger effects than 10 mg bisoprolol, and since 10 mg bisoprolol was equipotent with 100 mg atenolol, it may

TABLE 4. *Effects of salbutamol (S) expressed as changes (Δ) from prechallenge values on airway resistance (AWR), forced expiratory volume in 1 s (FEV_1), peak expiratory flow rate (PEFR), and vital capacity (VC) 5 min and 2 h postsalbutamol challenge*

	Pl	B10	B20	A100
	AWR (cm H_2O/l/s)			
S:5 min	− 1.4 ± 0.2	− 2.7 ± 0.5	− 1.5 ± 0.4	− 2.1 ± 0.5
S: 2 h	− 1.7 ± 0.5	− 2.8 ± 0.5	− 2.0 ± 0.6	− 2.7 ± 0.6
	FEV_1 (l)			
S:5 min	+ 0.27 ± 0.05	+ 0.29 ± 0.10	+ 0.19 ± 0.04	+ 0.24 ± 0.08
S: 2 h	+ 0.24 ± 0.43	+ 0.27 ± 0.05	+ 0.21 ± 0.05	+ 0.23 ± 0.07
	PEFR (l/min)			
S:5 min	+ 30.8 ± 9.2	+ 28.8 ± 10.6	+ 35.0 ± 13.9	+ 23.4 ± 11.4
S: 2 h	+ 40.3 ± 9.7	+ 32.8 ± 10.9	+ 40.0 ± 9.2	+ 30.3 ± 12.9
	VC (l)			
S:5 min	+ 0.45 ± 0.13	+ 0.09 ± 0.15	+ 0.15 ± 0.07	+ 0.26 ± 0.17
S: 2 h	+ 0.21 ± 0.11	+ 0.19 ± 0.12	+ 0.06 ± 0.10	+ 0.01 ± 0.13

Mean ± SEM: n = 12.

Pl, placebo; B10, bisoprolol 10 mg; B20, bisoprolol 20 mg; A100, atenolol 100 mg.

be concluded that 10 mg bisoprolol would be sufficient for therapeutic use.

In accordance with previous findings, the specific β_2-agonist salbutamol had no influence on HR and BP with and without preceding β-blocker treatment.

The assessments were carried out at different times after dosing up to 2 h. It is at that point in time when, according to pharmacokinetic data (12,13), almost maximum plasma concentrations are reached with both drugs. Marked beneficial pharmacodynamic effects were present at this time (HR depression was most pronounced 2 h after dosing). Also, at this time, undesirable pharmacodynamic effects of β-blockers, which in susceptible patients may induce an impairment of bronchomotor function, may become apparent. Bisoprolol at both dose levels produced strong β_1-receptor blocking effects, indicated by a pronounced decrease in HR, but had no influence on lung function parameters (Fig. 1), thus indicating a low affinity for β_2-adrenoceptors located in bronchial smooth muscles. 100 mg atenolol, while eliciting β_1-receptor blocking effects comparable to both dose levels of bisoprolol, produced a significant increase in AWR over placebo, indicating a binding of atenolol to bronchial β_2-receptors, and thus less cardioselectivity than bisoprolol at equipotent therapeutic dose levels.

This observation is in keeping with results of other investigators who, in healthy volunteers (5–7) and patients (9,11), have demonstrated a superior β_1-selectivity of bisoprolol, compared with atenolol.

After both β-blockers, salbutamol challenge produced pronounced bronchodilator effects comparable in degree with changes after placebo, indicating a good β_1-selectivity of both drugs in the therapeutic setting when the large doses of β_2-agonists normally applied may obscure differences in the degree of β_1-selectivity of β-blockers.

In hypertensive patients with concurrent chronic obstructive pulmonary disease, β-blocker treatment may well be required. The choice of the β-blocker and the level of medication is governed by the degree of β_1-selectivity of the agent and its low affinity for bronchial smooth muscle β_2-receptors. Under such circumstances, a highly cardioselective agent with a low dose-relation effect, which will preserve the β_2-stimulant effect of the bronchodilator, is clearly indicated. In this study, bisoprolol has been shown to be an effective hypotensive agent with greater β_1-selectivity than atenolol.

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REFERENCES

1. Manalan AS, Besch HR Jr, Watanabe AM. Characterization of 3H (±) carazolol binding to β-adrenergic receptors. Application to study of β-adrenergic receptor subtypes in canine ventricular myocardium and lung. *Circ Res* 1981;49:326–36.
2. Harting J, Becker KH, Bergmann R et al. Pharmacodynamic profile of the selective β_1-adrenoreceptor antagonist bisoprolol. *Arzneimittelforsch* 1986;36(I):200–8.
3. Schliep HJ, Schulze E, Harting J, Haeusler G. Antagonistic effects of bisoprolol on several β-adrenoceptor mediated actions in anaesthetized cats. *Eur J Pharmacol* 1986; 123:253–61.
4. Tattersfield AE, Cragg DJ, Bacon RJ. Assessment of β-adrenoceptor selectivity of a new β-adrenoceptor antagonist, bisoprolol, in man. *Br J Clin Pharmacol* 1984;18:343–7.
5. Chang PC, van Veen S, Vermeij P, van Brummelen P. Double-blind comparison of the β_1-selectivity of single doses of bisoprolol and atenolol. *J Cardiovasc Pharmacol* 1986;8(Suppl 11): S58–60.
6. Wellstein A, Palm D, Belz GG, Leopold G, Bühring KU, Pabst J. Concentration kinetics of propranolol, bisoprolol and atenolol in humans assessed with chemical detection and a subtype-selective β-adrenoceptor assay. *J Cardiovasc Pharmacol* 1986; 8(Suppl 11):S41–5.
7. Wellstein A, Palm D, Belz GG. Affinity and selectivity of β-adrenoceptor antagonists in vitro. *J. Cardiovasc Pharmacol* 1986;8(Suppl 11):S36–40.
8. Dorow P, Tönnesmann U. Dose–response relationship of the β-adrenoceptor antagonist bisoprolol in patients with coronary heart disease and chronic obstructive bronchitis. *Eur J Clin Pharmacol* 1984;27:135–9.
9. Dorow P, Bethge H, Tönnesmann U. Effects of single oral doses of bisoprolol and atenolol on airway function in nonasthmatic chronic obstructive lung disease and angina pectoris. *Eur J Clin Pharmacol* 1986;31:143–7.
10. Lammers JWJ, Folgering HThM, van Herwaarden CLA. Respiratory tolerance of bisoprolol and metoprolol in asthmatic patients. *J Cardiovasc Pharmacol* 1986;8(Suppl 11):S69–73.
11. Bolli P, Müller FB, Linder L, Ji BH, Bühler FR. Cardiac and vascular β-adrenoceptor mediated responses before and during treatment with bisoprolol or atenolol. *J Cardiovasc Pharmacol* 1986;8(Suppl 11):S61–4.
12. Leopold G, Pabst J, Ungethüm W, Bühring KU. Basic pharmacokinetics of bisoprolol, a new highly beta$_1$-selective adrenoceptor antagonist. *J. Clin Pharmacol* 1986;26:616–27.
13. Fitzgerald JD, Ruffin R, Smedstad KG, Roberts R, McAinsh J. Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. *Eur J Clin Pharmacol* 1978;13:81–9.