Effects of Single Oral Doses of Bisoprolol and Atenolol on Airway Function in Nonasthmatic Chronic Obstructive Lung Disease and Angina Pectoris

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Summary. A randomized, placebo-controlled, double-blind crossover investigation in 12 patients with non-asthmatic chronic obstructive lung disease and co-existing stable angina pectoris was done to compare two β_1-selective adrenoceptor blocking agents, atenolol 100 mg and bisoprolol 20 mg. Systolic and diastolic blood pressures (SBP, DBP), heart rate (HR) as well as airway resistance (AWR, and less frequently forced expiratory volume in 1 s (FEV_1) and intrathoracic gas volume (ITGV) were measured in the sitting position before and at various times up to 24 h after drug intake.

During the first 4 h both beta-blockers produced a significant reduction in HR in comparison to placebo ($p < 0.01$). Atenolol 100 mg significantly increased AWR relative to placebo and bisoprolol ($p < 0.05$). After 24 h, a significant reduction in HR ($p < 0.01$) could only be demonstrated after bisoprolol, whereas atenolol alone led to a significant elevation in AWR relative to placebo and bisoprolol ($p < 0.05$) at that time.

It is concluded that bisoprolol appears to have a high degree of beta$_1$-selectivity, thus providing a wide split between beta$_1$- and beta$_2$-adrenoceptor blockade. Bisoprolol in its therapeutic dose range is expected to be relatively safe as regards bronchoconstriction in patients suffering both from hypertension and/or angina pectoris and chronic obstructive lung disease.

Key words: bisoprolol, atenolol, angina pectoris; β_1-/β_2-blockade selectivity, lung function parameters, non-asthmatic chronic obstructive lung disease

Bronchomotor tone in part is modulated by the sympathetic nervous system resulting in bronchodilatation on β-adrenergic stimulation. Beta-adrenoceptor antagonists block bronchial β_2-receptors and may produce bronchoconstriction in asthmatic patients through inhibition of the sympathetic drive to the bronchial smooth muscles. Non-selective β-blockers are contraindicated in asthmatic patients. For therapeutic use of β-adrenoceptor antagonists, therefore, a high degree of selectivity for the β_1-receptor subclass is desirable, so as to avoid bronchospasm. However, even β_1-selective (cardioselective) β-adrenoceptor antagonists may induce bronchoconstriction in certain susceptible patients with chronic obstructive lung disease (COLD). That side-effect can be explained by their low degree of β_1-selectivity. Cardioselectivity is a dose-dependent phenomenon [2, 5, 10, 13, 18], so the dose employed is of crucial importance in any investigation of receptor selectivity. In addition, it has been shown that β_1-receptors are also present in the bronchi in addition to the preponderance of β_2-receptors [1]. Under these circumstances therapeutic progress can only be achieved by finding β-adrenoceptor antagonists with a very high affinity for β_1-receptors which would provide a dose range for therapeutic use that was significantly different from that in which β_2-receptors were also affected.

According to pharmacological studies [18, 20], bisoprolol displays the highest degree of β_1-selectivity amongst current cardioselective β-blockers, such as atenolol, metoprolol, betaxolol and celiprolol.

In clinico-pharmacological investigations in healthy volunteers [20], asthmatic patients [4, 14] and/or patients with COLD [8], bisoprolol in the dose range proposed for therapeutic use (5–10 mg once a day), and up to 20 mg as a single dose, proved to be highly β_1-selective. However, probably due to the presence of functional β_1-receptors in the airways [1], bisoprolol 10 mg and 20 mg and 100 mg metoprolol caused a decrease in peak expiratory

Table 1. Details of individual patients

Patient number	Sex	Age (years)	Height (cm)	Weight (kg)	Duration of COLD (months; years)	CHD	Pretreatment baseline values[a] BP (mmHg)	FEV$_1$ (l)	AWR (cmH$_2$O/l/s)
1	M	46	175	84	6 mo	3 y	150/100	1.6	6.4
2	M	48	186	100	8 mo	5 mo	150/95	1.5	7.5
3	M	44	171	72	6 mo	2 mo	133/95	1.5	7.5
4	F	50	162	66	5 y	1 y	125/90	1.5	8.2
5	M	48	182	75	8 y	2 y	180/92	1.6	8.4
6	M	46	172	86	10 y	3 y	172/100	1.3	8.8
7	M	59	171	78	18 y	4 y	130/80	1.5	7.1
8	M	38	167	65	4 y	3 mo	127/88	1.8	8.5
9	M	34	175	77	6 y	6 mo	147/100	2.0	7.5
10	M	46	175	78	10 y	4 y	130/80	1.4	8.7
11	M	40	188	90	8 y	1 mo	132/73	1.8	7.4
12	M	50	176	80	10 y	1 y	123/80	1.6	8.6

Definitions of abbreviations:
COLD = chronic obstructive lung disease; CHD = coronary heart disease; angina pectoris; FEV$_1$ = forced expired volume in 1 second; AWR = airway resistance; [a]Mean of 3 baseline measurements on the study days before drug intake
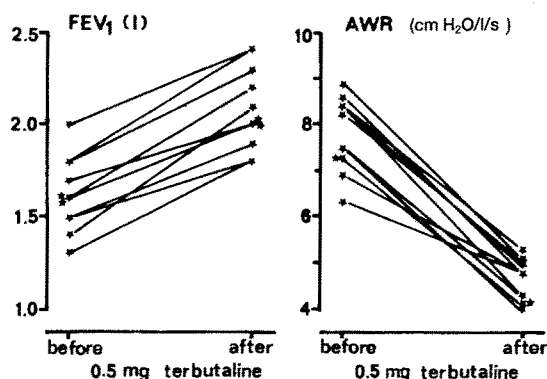

Fig. 1. Terbutaline test: FEV$_1$ and airway resistance (AWR) before and 15 min after inhalation of 0.5 mg terbutaline

flow rate 2 h after treatment of asthmatic patients [14].

It was the aim of the present study to compare the influence of 20 mg bisoprolol and 100 mg atenolol on respiratory function parameters in patients with non-asthmatic chronic obstructive lung disease and co-existing stable angina pectoris.

Patients and Methods

Twelve out-patients, aged 34 to 59 years, with reversible non-asthmatic chronic obstructive lung disease (COLD) in a stable phase and co-existing stable angina pectoris were recruited for the study (Table 1). COLD was diagnosed in accordance with the standards of the American Thoracic Society. The reversibility of the airway obstruction was demonstrated by a terbutaline test (Fig. 1). Stable angina pectoris

was proven by an exercise ECG and an appropriate medical history.

Criteria for exclusion included allergic obstructive lung disease, spontaneous angina (angina at rest), cardiac arrhythmias, AV-block of more than the first degree, cardiac failure and serious abnormalities of cerebral, hepatic, renal, metabolic or haemopoetic function.

Informed consent was given by each subject after the purpose, risks, and course of the study had been explained to them.

Patients were asked to discontinue all cardiovascular drug therapy apart from nitrates for at least 2 weeks prior to the study period. Nitrates apart from sublingual nitroglycerin, were discontinued at least 24 h prior to the trial. To alleviate bronchospastic symptoms β_2-adrenoceptor stimulant aerosols were allowed between the tests and on the study days if presented by a physician. No patient took advantage of this option.

Each patient attended on 4 mornings, at the same time of day. On the first day a terbutaline test was performed: respiratory function was assessed by measuring forced expiratory volume in one second (FEV$_1$), airway resistance (AWR) and intrathoracic gas volume (ITGV) before and 15 min after 0.5 mg terbutaline aerosol.

The patients then entered a double blind crossover study in which they received in random order single oral doses of placebo, 20 mg bisoprolol and 100 mg atenolol. They came to the hospital on three different occasions. Each visit was separated by at least 3 days.

Respiratory function measurements (body plethysmograph; FEV$_1$, AWR and ITGV) were made

with the patient sitting, using the Siregnost FD 88 (Siemens). In addition, systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were recorded.

The schedule of each visit was: at 8.00 a.m. baseline measurements were made. A single oral dose of one of the drugs was then given and measurements (SBP, DBP, HR, AWR) were repeated after 1, 2, 3, 4, 6, 8, 12 and 24 h (FEV_1 and ITGV only before and after 2, 4, 6, and 8 h).

On the test days the patients were kept under supervision until the evening. They were seen on the next morning for the measurements 24 h after drug intake. Three of the 12 patients did not participate in the 12 and 24 h AWR investigations for personal reasons.

Statistical Analysis

Both beta-blockers are known to have their maximal plasma concentrations (t_{max}) and their maximal effects on heart rate during the first 4 hours after oral administration [3, 9, 16]. The measurements of SBP, DBP, HR, AWR, FEV_1 and ITGV were parametrized by calculating the areas between the baseline values and the values after 1, 2, 3 and 4 h (for FEV_1 and ITGV only after 2 and 4 h).

Comparison of medications for these areas were made by analysis of variance for a 2 factor experiment (factors: medication, patient). In case of a significant medication effect ($p < 0.05$), the Tukey test was used for pairwise comparison of medications. To investigate the duration of action of the 3 medications, the values after 24 h were taken and analysis of variance was again used.

Results

There was no variation in the degree of airway obstruction or cardiovascular parameters between study days. All patients showed an elevated AWR and a decreased FEV_1, indicating clinically significant airway obstruction (Table 1; Fig. 1), which was reduced by terbutaline as proof of reversibility (Fig. 1). Of the 12 patients 5 were hypertensive (Table 1) and had an elevated blood pressure on each of the three test days.

Acute Effects

Both beta-blockers caused decrease in SBP and HR (Fig. 2). The calculated areas up to 4 h p.a. are depicted in Fig. 3. The decrease in HR (area) was significantly greater after the two beta-blockers than after
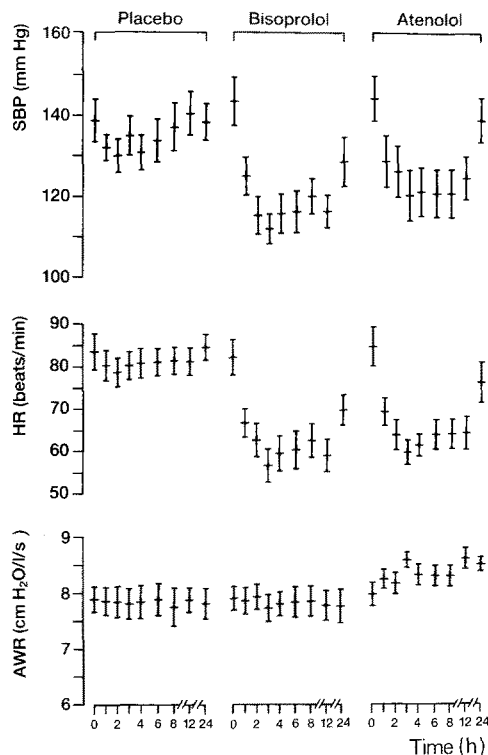

Fig. 2. Time course (0–24 h) of the effects of single oral doses of placebo, 20 mg bisoprolol and 100 mg atenolol on systolic blood pressure (SBP), heart rate (HR) and airway resistance (AWR). Mean ± SEM

placebo ($p < 0.01$). There was no significant difference between the effects after bisoprolol and atenolol. Compared to placebo, the effects of bisoprolol and atenolol on SBP were significant ($p < 0.01$; $p < 0.05$ respectively), but there was no a significant difference between the two active treatments. There was no particular decrease in DBP after the two beta-blockers as compared to placebo.

There was an increase in AWR after atenolol, whereas the mean value remained unchanged after bisoprolol compared to placebo. The areas up to 4 h p.a. are shown in Fig. 3. There was a significant increase in AWR after atenolol compared to placebo ($p < 0.05$) and bisoprolol ($p < 0.05$). No significant difference was observed upon comparison of the effects of placebo and bisoprolol on AWR ($p > 0.05$). For FEV_1 (areas: placebo −0,008, atenolol −0,167, bisoprolol +0,025 1 × h) and ITGV (areas: placebo 0, atenolol +0,083, bisoprolol −0,067 1 × h) the analysis of variance did not reveal a significant effect of medication ($p > 0.05$).

Values After 24 Hours

After bisoprolol HR was significantly lower than after placebo (70 vs 85 beats/min; $p < 0.01$). There was
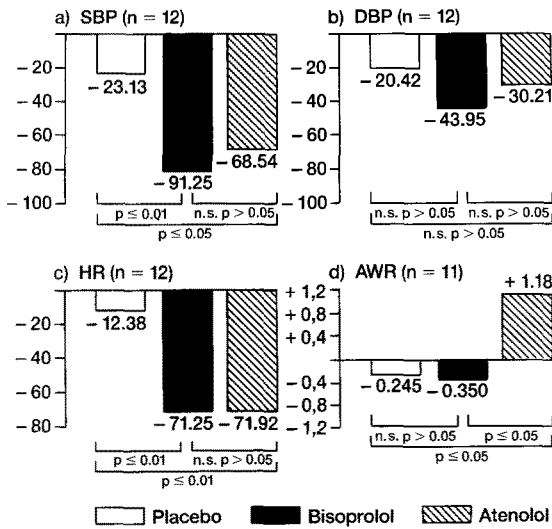
Fig. 3. Calculated areas between the baseline values and values 1, 2, 3 and 4 h after drug intake (Placebo; 20 mg bisoprolol; 100 mg atenolol) for systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and airway resistance (AWR). Units: SBP and DBP Δ mmHg × h; HR Δ beats/min × h; AWR Δ cm $H_2O/l/$ s × h

Fig. 4. Individual course of heart rate (HR; beats/min) and airway resistance (AWR; cm $H_2O/l/s$) patients in 1, 7 and 12 before and after single oral doses of placebo (■), 20 mg bisoprolol (○) and 100 mg atenolol (△)

no significant difference between either active treatment or placebo in SBP and DBP. AWR was significantly higher after atenolol (8,5 cm $H_2O/l/s$) than after bisoprolol (7,7 cm $H_2O/l/s$; $p < 0.05$) and placebo (7,8 cm $H_2O/l/s$; $p < 0.05$). The values after bisoprolol and placebo did not differ ($p > 0.05$).

Individual Responses

Throughout the entire 24-h period of the investigation, two patients (Nos. 1 and 7) showed a distinct and one other (No. 12) showed a small increase in AWR after atenolol, whereas there were no differences in the course of AWR values in any of the 3 patients after bisoprolol and placebo (Fig. 4). In Patients 7 and 12 there was a greater decrease in HR after bisoprolol than after atenolol. None of the patients reported any feelings of increased wheeziness or shortness of breath.

Discussion

Beta-adrenoceptor antagonists may induce bronchospasm in susceptible patients, presumably by unmasking parasympathetic and other bronchoconstrictor factors subsequent to the blockade of bronchial β_2-receptors. β-Blockers preferentially acting on β_1-type receptors (β_1-selective or cardioselective β-blockers) are less likely to precipitate bronchospasm, which in any case can be counteracted by a β_2-receptor stimulant.

Much research has been devoted to the influence of various β-adrenoceptor antagonists on ventilatory function parameters as in man [7, 11, 12]. The methodologies used in the various studies has differed considerably. The patient population and the design of the present study met the criteria proposed for such investigations [7, 12]. After dosing measurements were made at several times throughout the next 24 h, since basal variation in lung function may make it difficult to in interpret the results if only a few measurements are made at long intervals.

As judged by HR, both beta-blockers reached their maximal effect on beta₁-receptors by 2–4 h p. a. This corresponds to the timing (t_{max}) of the peak blood levels of the two substances after oral administration [3, 9, 16]. It would be expected that any beta₂-blocking effect would be detected during that period, since it has been demonstrated many times that beta₁-selectivity is a phenomenon related to dose or blood level [2, 5, 10, 13, 18].

The results of the present study of single oral doses cannot necessarily be extrapolated to prolonged oral treatment. Nevertheless, the conclusions drawn from this type of investigation are generally
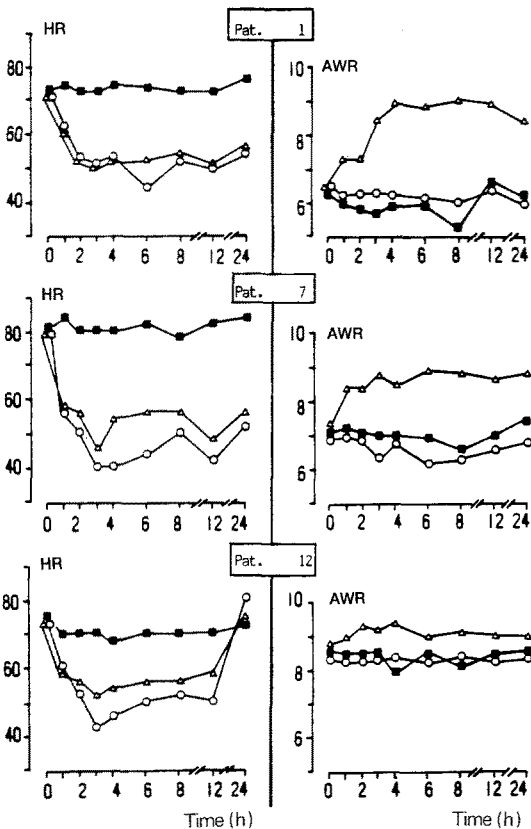
accepted as valid in predicting how β-blockers will act in patients with chronic obstructive lung disease.

The two beta-blockers at the doses studied here, namely 20 mg bisoprolol and 100 mg atenolol, had a comparable and marked acute effect on HR. Over the same period there was a significant increase in airway resistance only with atenolol. Thus, 100 mg atenolol not only affected cardiac $beta_1$-receptors but also bronchial $beta_2$-receptors. Bisoprolol 20 mg appeared to be completely β_1-selective.

In accordance with the difference in elimination half-life between bisoprolol (10.6 ± 1.4 h SEM; [16]) and atenolol (6.36 ± 0.55 SEM h; 3), an effect on HR lasting up to 24 h was found only after bisoprolol. As there was no longer any difference between atenolol and placebo 24 h p.a. with regard to heart rate, the slight, but statistically significant increase in airway resistance after atenolol compared to placebo and bisoprolol was all the more striking.

According to previous studies of respiratory function, asthmatic and non-asthmatic patients with bronchial obstruction fall into two categories, namely "responders" and "non-responders", when challenged with selective or non-selective β-adrenoceptor blocking agents [2, 5, 6, 13, 15]. As with other types of unwanted effects of drugs, statistical analysis of the entire group of patients, including both "responders" and "non-responders", may be misleading in revealing a clinically significant toward effect in an individual subject. For this reason it was important to describe 3 patients in more detail. The more marked effect of bisoprolol on heart rate as compared to atenolol, together with the absence of any effect of bisoprolol on airway resistance in contrast ot the long-lasting effect of atenolol, can be interpreted to mean that in individual patients the superior β_1-selectivity of bisoprolol should be of clinical relevance.

It is concluded that, in accordance with previous results [4, 8, 14, 20], bisoprolol appears to be a highly β_1-selective adrenoceptor blocking agent. In its therapeutic dose range (5–20 mg once a day) bisoprolol may be expected to be relatively safe in patients suffering from hypertension and/or angina pectoris and COLD. However, calcium antagonists are preferable in this situation and in general asthmatics should not treated with beta-blocking agents.

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