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Effects of celiprolol, a cardioselective beta-blocker, on respiratory function in asthmatic patients

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ABSTRACT: **The aim of this study was to compare the pulmonary effects of a single dose of celiprolol 400 mg, *versus* bisoprolol 20 mg and the combination of celiprolol 400 mg plus propranolol 40 mg *versus* placebo plus propranolol 40 mg.**

We conducted a double-blind randomized cross-over study in 10 stable asthmatic patients (mean age±SD 31±7 yrs) with forced expiratory volume in one second (FEV_1): 2.5±0.7 *l*. A three-day washout period preceded each treatment period. Measurements of respiratory function were done before treatment and after 90, 120 and 180 min.

There was a significant increase of FEV_1 (+12%) and forced vital capacity (FVC) (+8%) after celiprolol ($p<0.05$) and a decrease of FEV_1 (-9%) after propranolol. Concerning the combination, celiprolol inhibits the bronchostrictor effects of propranolol. We conclude that celiprolol has bronchosparing properties in asthmatic patients, and even improves some of the ventilatory parameters.
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Beta-blockers are currently used as first-line therapy in the treatment of hypertension and angina pectoris. They are regarded as contraindicated in asthma, since bronchial β_2 receptor blockade can provoke severe bronchospasm in some patients [1, 2]. This risk is particularly high with propranolol [3], but less with the use of more selective β_1 receptor blockers such as atenolol, metoprolol and more recently bisoprolol. However, patients receiving these drugs are still at risk of developing bronchospasm (the risk being dose-dependent). These drugs therefore remain contraindicated in some countries or are used with caution in other countries in this patient group [4, 5]. Among currently available cardioselective beta-blockers, celiprolol (celectol, RORER Laboratory) has β_2 agonist activity which could permit its use in asthmatic patients [6].

This study was carried out in order to evaluate the effects of a single dose of celiprolol on respiratory function in patients with "moderate" asthma. These effects were compared to those of propranolol, and those of a cardioselective drug, bisoprolol. Finally, a study was performed in order to determine whether celiprolol has a protective effect against propranolol-induced bronchoconstriction in asthmatic patients, as observed in animals [7], by simultaneous administration of these two beta-blockers.

Materials and methods

Patients

Ten normotensive patients (4 men and 6 women) with stable asthma and a mean age of 31±7.6 yrs were included in this study.

Normal blood pressure was defined as a diastolic blood pressure of less that 95 mmHg.

A diagnosis of asthma was made on the basis of the clinical history and respiratory function tests. The degree of bronchial obstruction had to be moderate and the measured forced expiratory volume in one second (FEV_1)/predicted FEV_1 between 60% and 80% (table 1) after 24 h of cessation of any bronchodilator drugs. The predicted FEV_1 was calculated with the tables of QUANJER [8].

Only patients with reversible bronchial obstruction were selected, since the study required a group of patients susceptible to developing bronchospasm while receiving beta-blockers [9].

Reversibility was defined by an increase in the FEV_1 of at least 15% of its predicted value following inhalation of 200 micrograms of salbutamol [9].

Exclusion criteria were angina, atrioventricular block, bradycardia (heart rate less than 60 beats per minute), heart failure and beta-blocker therapy.

Table 1. – Patients characteristics, lung function measurements

Patient No.	Sex	Age yrs	Baseline FEV_1 (% predicted)	Baseline FVC (% predicted)
1	M	30	77	101
2	F	31	64	100
3	M	26	78	98
4	F	21	71	90
5	M	27	62	80
6	F	39	65	101
7	M	28	77	89
8	M	27	78	104
9	F	27	84	119
10	F	48	78	97
Mean		31	73	98
SD		7.6	7.4	10.4

FEV_1: forced expiratory volume in 1 second; forced vital capacity.

All antiasthmatic drugs (sustained release theophylline, β_2 stimulants, disodium chromoglycate) were discontinued at least 24 h before the beginning of the study. Patients receiving systemic corticosteroids were also excluded from the study. Patients gave their informed consent before entering the trial, in accordance with principles defined in the Helsinki Declaration.

Study protocol

This study was performed with a randomized, double-blind, crossover design preceded by a washout period of three days (a period greater than five half-lives of the drugs) (fig. 1).

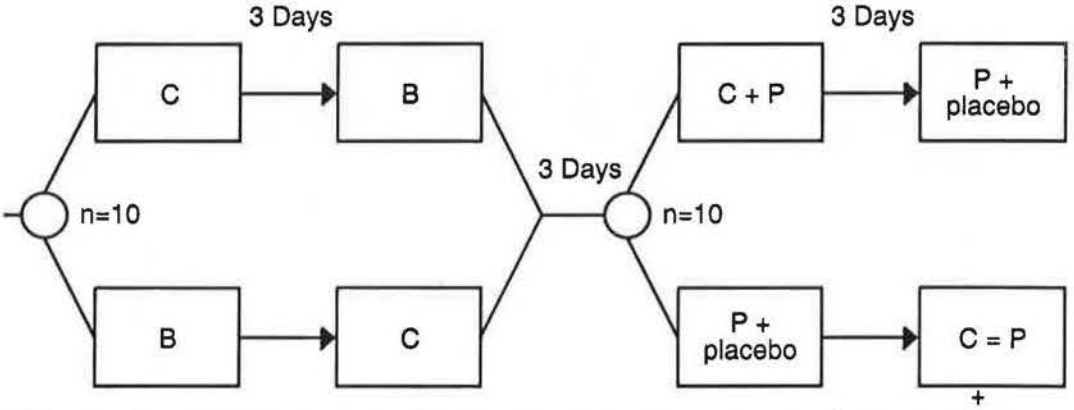

Fig. 1. – Study design. B: Bisoprolol 20 mg; C: Celiprolol 400 mg; P: Propranolol 40 mg; ◯: Randomization

The study was divided into two phases which were conducted in an identical manner except for the order of treatment.

During the first phase, the patients received in accordance with a previously established randomization grid as a single dose: either two 200 mg tablets of celiprolol or two 10 mg tablets of bisoprolol. During the second phase of the study, the patients received (in accordance with a previously established randomization grid as a single dose): either two 200 mg tablets of celiprolol and a 40 mg tablet of propranolol or a 40 mg tablet of propranolol and 2 placebo tablets.

Systolic and diastolic blood pressure together with heart rate were manually measured in order to evaluate the cardiovascular effects of the different treatments.

Measurements were made of the functional residual capacity (FRC), the airway resistance (Raw), the maximal expiratory flow rate, the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), by means of Gould Godart body plethysmograph. The specific airway resistance (sRaw) in relation to the FRC, (and the FEV_1/FVC ratio) was calculated. These parameters enabled evaluation of the effect of the different treatments on respiratory function. The variations observed were expressed in terms of their absolute value and as a percentage of the predicted value [9].

Baseline value of heart rate, blood pressure and spirometric parameters were recorded after 10 min of rest (30 min before administration of each treatment). Repeated measures were made at the time of administration (T_0), after 90 min (T_{0+90}), 120 min (T_{0+120}) and 180 min (T_{0+180}). This last measurement, three hours after administration of the treatment, was made in order to evaluate the maximum beta-blocking effect of the drugs used in the study [6].

The response to inhalation of a β_2 agonist (salbutamol) was evaluated at the end of each study. Patients inhaled 200 micrograms of salbutamol at T_{0+180} and again at T_{0+195} and the maximum expiratory flow rates were measured 15 min after each inhalation (T_{0+195} and T_{0+210}).

Variations in FEV_1, following inhalation of the β_2 agonist were expressed in terms of their absolute value and as a percentage of their value at T_{0+180} and T_{0+195}.

Statistical analysis of the results included crossover analysis of variance with repeated measures over time.

Results

Patients remained clinically stable throughout the study, and did not notice any side effect except one

patient who experienced a moderate dyspnoea under propranolol. There was no significant difference between the cardiovascular and respiratory parameters measured at the beginning of each of the four tests and those measured at T_0 (tables 2 and 3).

Cardiovascular effects (table 2)

The heart rate decreased significantly with all four treatment regimens from T_{0+90} and remained stable up to T_{0+180}. Systolic blood pressure decreased in a similar proportion of patients during the four treatments. Administration of bisoprolol was furthermore associated with a significant decrease of the diastolic blood pressure.

Table 2. – Cardiovascular effects after beta-blockade

	T_0 min	T_{0+90} min	T_{0+180} min
Heart rate bpm			
C	87±10.4	77±8*	76±8.9*
B	85±9.1	65±3.5*	61±3.8*
P	83±8.7	68±6.6*	66±7.5*
C+P	87±11.5	73±6.4*	72±7.4*
Systolic blood pressure mmHg			
C	122±11	113±14*	109±15*
B	123±8	103±3*	103±14*
P	122±12	107±14*	105±15*
C+P	123±10	106±9*	110±15*
Diastolic blood pressure mmHg			
C	78±7.5	75±7.8	75.2±8.6
B	78±5.4	71±7.7*	70±8.5*
P	75±8	74±9	74±8
C+P	78±9	73±7	77±9

*: $p<0.05$ *vs* baseline (T_0); C: Celiprolol; B: Bisoprolol; P: Propranolol.

Effects on respiratory function (table 3 and fig. 2)

Effects of celiprolol. A bronchodilatory effect was observed at T_{0+180}. The sRaw decreased by 30% ($p<0.05$); and at the same time the FEV_1 increased by 12% of its baseline value.

Administration of 200 micrograms of salbutamol resulted in a significant further increase in the FEV_1 (mean increase of 0.49 *l*). Administration of a further 200 mg of salbutamol was associated with an increase in the FEV_1 (mean of 0.6 *l*), *i.e.* 18% of the value measured at T_{0+180}.

Effects of bisoprolol. There was no significant change in the sRaw (table 3) or forced expiratory flow rate following administration of bisoprolol. However, the effects of the β_2 agonist effect was maintained. Inhalation of 200 micrograms of salbutamol was associated with a mean increase in the FEV_1 of 0.53 *l* and administration of a further 200 micrograms of salbutamol increased the FEV_1 by 0.78 *l*, *i.e.* 24% of the value measured at T_{0+180}.

Effects of propranolol. The sRaw was not significantly modified between T_0 and T_{0+180} (table 3). However, the FEV_1 decreased by 0.22 *l*, *i.e.* 9% between T_0 and T_{0+180} ($p<0.05$). Administration of 200 micrograms of salbutamol increased the FEV_1 by a mean of 0.43 *l*($p<0.05$) and inhalation of a further 200 micrograms of salbutamol brought this increase to 0.55 *l*, *i.e.* 19% of the value measured at T_{0+180}.

Table 3. – Respiratory effects after beta-blockade: the measurements of FEV_1 and FVC are done 180 min after a single administration of beta-blocking agents. At T_{0+180} min and T_{0+210} min, 200 µg of salbutamol are given. FEV_1 and FVC are measured 15 min later in order to assess the bronchodilatory effects of salbutamol

	T_0 min	T_{0+180} min	T_{0+195} min	T_{0+210} min
FEV_1 *l*				
C	2.59±0.7	2.90±0.61°	3.39±0.61°	3.50±0.66
B	2.56±0.59	2.60±0.60	3.13±0.62*	3.38±0.69*
P+Placebo	2.57±0.63	2.35±0.64°	2.78±0.70	2.90±0.68
C+P	2.54±0.64	2.58±0.76	2.94±0.70*	3.02±0.65
FVC *l*				
C	4.24±1.04	4.57±0.98°	4.79±0.95*	4.80±0.87
B	4.21±0.92	4.16±0.94	4.58±0.87*	4.67±0.95*
P+Placebo	4.25±0.82	4.12±1.03	4.34±0.91*	4.48±0.98*
C+P	4.35±0.95	4.35±1.02	4.66±1.04	4.62±0.97
sRaw $cmH_2O \cdot s^{-1}$				
C	10.97±3.48	7.62±2.49°	4.34±1.52*	3.58±0.76
B	10.75±3.58	10.68±4.98	5.40±1.87*	3.89±1.45
P+Placebo	10.99±5.63	12.91±4.54	7.24±2.71*	5.75±2.38
C+P	10.36±3.19	11.10±5.43	6.13±1.99*	4.93±1.14

°: $p<0.05$ *vs* baseline (T_0); *: $p<0.05$ *vs* T_{0+180} min; +: $p<0.05$ *vs* T_{0+195} min; C: Celiprolol; B: Bisoprolol; P: Propranolol; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; sRaw: specific airways resistance.

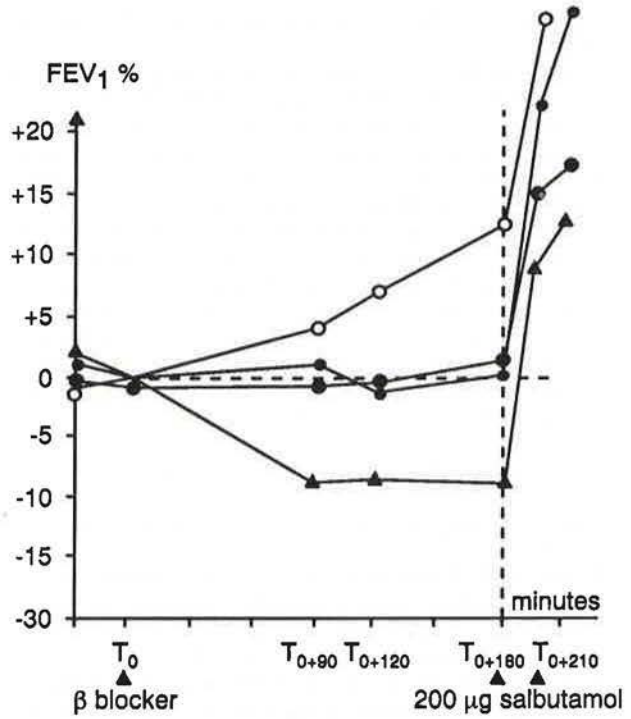

Fig. 2. – Percentage change of forced expiratory volume in one second (FEV_1) after beta-blockade. ○: Celiprolol 400 mg; ●: Celiprolol 400 mg + Propranolol 40 mg; •: Bisopropol 20 mg; ▲: Propranolol 40 mg

The mean values of the sRaw, FEV_1 and FVC observed at T_{0+180} were greater in patients receiving celiprolol than those observed in patients receiving propranolol and bisoprolol but these differences were not statistically significant.

Effects of combined administration of celiprolol and propranolol. This was not associated with any significant change in sRaw or FEV_1 (table 3) between T_0 and T_{0+180}. Administration of 200 micrograms of salbutamol significantly increased the FEV_1 by a mean of 0.36 *l* and administration of a further 200 micrograms of salbutamol increased the FEV_1 by 0.44 *l*, 15% of the value measured at T_{0+180} $p<0.05$).

One patient complained of moderate dyspnoea following administration of propranolol, which rapidly subsided after administration of 200 micrograms of salbutamol.

Discussion

We studied the effects of three beta-blockers on respiratory function in asthmatic patients. The chosen dose of each drug was based on data from the literature in order to induce comparable cardiovascular effects without exposing the patients to the risk of severe bronchospasm [5, 10]. The results confirmed the appropriateness of this choice. The effects on heart rate and systolic blood pressure were similar with the different treatments and there was no report of clinically severe bronchospasm.

The risk of developing bronchospasm following administration of beta-blockers is particularly high in asthmatic patients. This phenomenon can probably be explained by simultaneous blockade of β_1 and β_2 receptors [11]. The persistence of a bronchodilatory effect with salbutamol confirms that with the doses that were used, all β_2 receptors were not blocked by propranolol.

In these patients, celiprolol had a paradoxical bronchodilating effect while bisoprolol appeared to have no effect on the respiratory tract. The effects of bisoprolol and celiprolol observed in this study are in concordance with the results of previous *in vitro* [12] and *in vivo* [10] comparative studies.

While bisoprolol is highly cardioselective, it still has a dose-dependent bronchoconstrictory effect [13]. At a dose of 20 mg it usually has no effect on respiratory function while remaining active at a cardiovascular level [13]. Furthermore, at this dose it does not inhibit the bronchodilatory effect of β_2 agonists. In our study, there was no change in the FEV_1 following administration of 20 mg of bisoprolol nor did this inhibit the effect of salbutamol.

Celiprolol is a novel drug. This study is in concordance with the findings of previous studies carried out in asthmatic patients [16, 10, 11]. Unlike propranolol, celiprolol did not provoke bronchoconstriction but on the contrary, it induced bronchodilatation. The FEV_1 was significantly increased 90 min after administration of 400 mg of celiprolol and was still increased after 180 min. This period corresponded to the time of the peak plasma concentration of the drug.

Despite this bronchodilatation, the bronchodilatory effect of β_2 agonists was maintained in these patients (26% increase in the FEV_1 after inhalation of 400 micrograms of salbutamol). The fact that additional bronchodilatation could be obtained with salbutamol suggests that the β_2 agonistic effect of celiprolol is moderate compared to that of salbutamol.

Celiprolol maintained a bronchodilatory effect in animals despite total β-receptor blockade by propranolol [7, 14]. An identical result was obtained in asthmatic patients. This activity was not associated with an increase in the cardiovascular potency of the two drugs (no difference in terms of heart rate or blood pressure between the two treatments). Nor was it associated with a decrease in the bronchodilatory potential of β_2 mimetic agents, since the FEV_1 increased by 15% after inhalation of 400 micrograms of salbutamol. This effect of celiprolol cannot be explained either by its cardioselectivity or by its β_2 stimulating potential. Other intrinsic properties such as direct relaxation of smooth muscle fibres [15] should be considered.

Irrespective of its mode of action, our findings suggest that celiprolol may be prescribed with greater security than other cardioselective beta-blockers in the treatment of asthmatic patients. However, the limitation of a single dose in this study, in a small number of patients, with moderate asthma should be

considered. All beta-blockers should always be considered potentially dangerous in asthmatic patients. When other treatments have failed only cardioselective beta-blockers may be used and should always be combined with a β_2 stimulant drug. Among the various cardioselective beta-blockers tested in our study celiprolol appears to be the best tolerated.

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