Short-term Cardiovascular Effects of Salmeterol*

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The occurrence of cardiovascular side effects is sometimes associated with the utilization of β-adrenoceptor agonists. The most important causes of these undesirable pharmacologic actions are as follows: (1) direct stimulation of cardiac β-adrenoceptors; (2) reflex activation of adrenergic mechanisms due to peripheral vasodilation; (3) hypokalemia; and (4) hypoxemia. The aim of this study was to evaluate the potential short-term, cardiovascular side effects of salmeterol, a long-acting and highly selective β2-adrenoceptor agonist. Eight volunteer healthy subjects and eight patients with reversible airway obstruction and without cardiovascular alterations were treated with 50 µg of salmeterol twice a day for 3 days and then with 100 µg of salmeterol twice a day for a further 3-day period. The 24-h ECG (Holter) monitoring and measurement of arterial BP, performed on the admission day and on the third and the sixth day of pharmacologic treatment, showed that salmeterol did not produce any significant change in mean heart rate, number of supraventricular and ventricular premature complexes, and BP. Furthermore, no ECG abnormality related to myocardial ischemia was recorded during 24-h Holter monitoring. These data suggest that salmeterol, administered in regular and high doses for a short period, does not cause significant cardiovascular effects in both normal subjects and patients with reversible airway obstruction. *(CHEST 1998; 113:1272-76)*

Key words: cardiovascular effects; Holter monitoring; salmeterol

Abbreviation: β-AR=β-adrenergic receptor

Inhaled β-adrenoceptor agonists are the most effective bronchodilators currently available. However, stimulation of β-adrenergic receptors (β-AR) sometimes may also induce cardiovascular side effects,1-3 such as tachycardia, arrhythmias, prolongation of QT interval, and T-wave changes.

These effects, which are quite rare with the use of inhaled β2-selective drugs, depend mainly on reflex release of catecholamines, secondary to peripheral vasodilation, and on direct activation of cardiac β-AR. The latter belong mostly to the β1-subtype, but some β2-receptors coexist with the more numerous β1-subtypes in atria and left ventricle.4 Furthermore, hypoxemia and hypokalemia may also contribute to trigger the cardiac side effects of β-adrenoceptor agonists.

Some studies have reported an increased incidence of arrhythmias in patients who were treated with a combination of β-adrenoceptor agonists and theophylline.5,6 Other authors7,8 have shown that salbutamol, given alone or by inhaled route, increases the risk of myocardial ischemia, contraindicated in patients with left ventricular systolic dysfunction.9 However, it cannot be ruled out that a prolonged, either direct or reflex, stimulation of cardiac β-AR by longer-acting β-adrenoceptor agonists may trigger undesirable cardiovascular effects.

Therefore, we decided to study, by means of 24-h ECG recording in both healthy subjects and patients with reversible bronchial obstruction, the possible onsets of ventricular tachycardia, arrhythmias, and other side effects, after inhalation of regular and high doses of the long-acting salmeterol xinafoate, a partial agonist at β2-AR with the highest β2-selectivity of any of the currently available β-sympathomimetics.10

Materials and Methods

Eight volunteer healthy subjects (five male and three female, 29 to 43 years of age, mean±SD: 33.5±4.1) and eight patients...

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with reversible airway obstruction (4 male and 4 female, 18 to 61 years of age, mean±SD: 40.5±12.8) documented by an increase in FEV₁, within 20 min after inhalation of 200 μg of salbutamol, both >12% and 200 mL, were enrolled in this study. Treatment with inhaled and oral β₂-adrenergic agonists was withheld for 24 h, anticholinergic agents for 12 h, and slow-release theophylline for 36 h. Patients taking inhaled/oral corticosteroids or cromoglycate continued this treatment at a constant dose throughout the study. Smoking and use of caffeine-containing drinks were not allowed during the trial.

Each subject was studied throughout a 7-day period, according to the following experimental design.

**First Day**

On the admission day, baseline pulmonary function tests (flow-volume curve), bronchodilator response, blood gas (oxygen, carbon dioxide) analysis, baseline 24-h ECG ambulatory monitoring (Holter ECG; Model 2448; Elea Medical; Montrouge, France), recording of arterial BP by a mercury sphygmomanometer (FC-110; Focal; Tokyo, Japan), and determination of serum levels of some electrolytes (Na⁺, K⁺, Mg²⁺) were performed. Lung volumes and expiratory flows were obtained using a pneumotachometer (MasterLab; Jaeger; Wurzburg, Germany) and the highest value of three consecutive measurements was chosen. Holter ECG was performed with the subject wearing a set of electrodes taped to the chest and carrying a portable recording device; the 24-h monitoring was then analyzed by a computer system (Anatec; Elea Medical).

**Second Day**

After baseline registration of FEV₁, 50 μg (two puffs) of salmeterol was administered by metered-dose aerosol. FEV₁ measurements were repeated 2 h thereafter. Inhalation of 50 μg (two puffs) of salmeterol was repeated 12 h after the first drug administration.

**Third Day**

Administration of salmeterol was continued following the same schedule of the second day (inhalaion of 50 μg of salmeterol twice a day).

**Fourth Day**

Administration of salmeterol was continued following the same schedule of the second and third day. Furthermore, Holter ECG was performed, serum electrolyte levels were measured, and arterial BP was determined 2 h after the first drug inhalation.

**Fifth Day**

After baseline registration of FEV₁, 100 μg (four puffs) of salmeterol was administered by metered-dose aerosol. FEV₁ measurements were repeated 2 h thereafter. Inhalation of 100 μg (four puffs) of salmeterol was repeated 12 h after the first drug administration.

**Sixth Day**

Administration of salmeterol was continued following the same schedule of the fifth day.

**Seventh Day**

Administration of salmeterol was continued following the same schedule of the fifth and sixth day. Furthermore, Holter ECG was performed, serum electrolyte levels were measured, and arterial BP was determined 2 h after the first drug inhalation.

This protocol was approved by the institutional review board for human studies and an informed written consent was obtained from each of the 16 subjects.

**Statistical Analysis**

The Student’s t test for paired data was used for statistical comparison of the results; a p value <0.05 was considered as significant.

**Results**

**Normal Subjects**

The individual characteristics of the eight healthy subjects and their bronchodilator response to salmeterol (measured 2 h after drug administration), expressed as percent changes in FEV₁, are shown in Table 1. Salmeterol induced a slight, but not significant, increase in FEV₁.

Comparative evaluation of the individual data recorded in each subject before and after salmeterol administration, at both daily doses of 100 and 200 μg, did not show any significant change either in 24-h average heart rate, expressed as beats per minute (baseline vs salmeterol 100 and 200 μg: mean±SD = 75.25±11.67; 80.12±8.49; and

<p>| Table 1—Subject Characteristics and Percent Changes in FEV₁ 2 h After Inhalation of 50 and 100 μg of Salmeterol Xinafoate* |</p>
<table>
<thead>
<tr>
<th>Subject No./Sex/Age, yr</th>
<th>FEV₁, % Predicted</th>
<th>50 μg</th>
<th>100 μg</th>
<th>% FEV₁ Changes 2 h After S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/33</td>
<td>116</td>
<td>0</td>
<td>0</td>
<td>2.13</td>
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<td>2/F/34</td>
<td>120</td>
<td>+3</td>
<td>+5</td>
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<td>104</td>
<td>+2</td>
<td>+5</td>
<td>2.27</td>
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<td>4/M/29</td>
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<td>0</td>
<td>4</td>
<td>1.86</td>
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<tr>
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<td>4</td>
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</tr>
<tr>
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<td>+1</td>
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</tr>
<tr>
<td>7/F/33</td>
<td>125</td>
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<td>0</td>
<td>1.86</td>
</tr>
<tr>
<td>8/M/32</td>
<td>105</td>
<td>0</td>
<td>5</td>
<td>1.86</td>
</tr>
<tr>
<td>Mean 110.25</td>
<td>1.25</td>
<td>3.37</td>
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</tr>
<tr>
<td>SD 4.11</td>
<td>7.59</td>
<td>1.58</td>
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<tr>
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<td>+49.0</td>
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<tr>
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<td>+36.5</td>
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</tr>
<tr>
<td>Mean 71.37</td>
<td>31.09</td>
<td>34.66</td>
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<tr>
<td>SD 12.84</td>
<td>6.13</td>
<td>7.47</td>
<td>8.08</td>
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</tbody>
</table>

*S=salmeterol. No. 1 to 8=normal subjects; No. 9 to 16=patients with reversible airway obstruction.
79.50±10.06, respectively) (Fig 1), or in the 24-h number of supraventricular and ventricular premature complexes (baseline vs salmeterol 100 and 200 μg; mean±SD=41.37±31.91; 47.00±56.41; and 55.87±48.75, respectively) (Fig 2). Furthermore, no significant change in systolic and diastolic arterial BP (Table 2) was detected. Finally, no ECG abnormality related to myocardial ischemia was recorded during 24-h Holter monitoring performed before and after salmeterol administration.

**Patients With Reversible Airway Obstruction**

The individual characteristics of the eight patients with reversible airway obstruction and their bronchodilator response to salmeterol (measured 2 h after drug administration), expressed as percent changes in FEV₁, are shown in Table 1. Salmeterol induced a significant increase in FEV₁ (p<0.05) at both single doses of 50 and 100 μg.

No significant changes in 24-h average heart rate (baseline vs salmeterol 100 and 200 μg; mean±SD=62.25±10.63; 68.12±9.57; and 69.25±8.34, respectively) (Fig 3), as well as in the 24-h number of supraventricular and ventricular premature complexes (baseline vs salmeterol 100 and 200 μg; mean±SD=30.00±35.32; 27.37±31.73; and 39.50±43.43, respectively) (Fig 4), and in systolic and diastolic arterial BP (Table 2), were observed with both salmeterol daily doses of 100 and 200 μg. Furthermore, no ECG abnormality related to myocardial ischemia was recorded during 24-h Holter monitoring performed before and after salmeterol administration.

In both groups, salmeterol did not produce any significant change in either PaO₂ or PaCO₂ values, or serum levels of sodium, potassium, and magnesium (data not shown). Furthermore, no cardiovascular symptom was reported by any of the subjects enrolled in the study.

**DISCUSSION**

The results of our short-term trial have shown that inhaled salmeterol, at both daily doses of 100 and 200 μg, did not induce cardiovascular side effects in either normal subjects or patients with reversible airway obstruction during the 6 days of pharmacologic treatment. In particular, 24-h Holter ECG monitoring demonstrated that salmeterol did not cause any clinically relevant change either in the average heart rate or in the number of supraventricular and ventricular premature complexes. Furthermore, no ECG alteration related to myocardial ischemia was recorded and no significant modification of systolic and/or diastolic arterial BP was detected.

Our data are consistent with those of other authors. Analyzing the results of a multicenter study involving about 700 asthmatic patients, Britton et al12 did not find any significant change in systolic and diastolic BP or ECG pattern during several months of treatment with either salbutamol (200 μg qid) or salmeterol (50 μg bid). Furthermore, an analogous multicenter trial performed by Pearlman et al,13 including 234 asthmatics randomly assigned to three different groups (placebo, salbutamol, and salmeterol groups), showed no significant difference among the groups in the occurrence of supraventricular and/or ventricular ectopy during 24-h ambulatory ECG.

Several factors may account for the lack of cardio-

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21765/ on 06/13/2017)

**Figure 1.** Effects of salmeterol xinafoate (S) on 24-h average heart rate (HR) in eight normal subjects.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21765/ on 06/13/2017)

**Figure 2.** Effects of salmeterol (S) on the 24-h number of supraventricular and ventricular premature complexes (PCs) in eight normal subjects.
vascular side effects observed in our study. It is possible that the stimulation of cardiac β-AR induced by salmeterol does not reach the threshold of clinical relevance because it is not sufficient to cause significant modifications of heart rate, rhythm, and/or oxygen consumption. In fact, plasma levels of salmeterol after inhalation are very low and, moreover, most cardiac β-ARs belong to the β1-subtype. Another factor might concern the potential development of receptor homologous desensitization subsequent to a prolonged activation of cardiac β-AR. In fact, a reduced responsiveness of β-AR may theoretically occur as a consequence of a continuous or repeated exposure to a β-adrenoceptor agonist.14

In conclusion, according to the results of our trial, essentially based on Holter ECG monitoring and BP measurements, a short-term treatment with both regular and high doses of salmeterol does not appear to induce cardiovascular side effects in either normal subjects or patients with reversible airway obstruction. This suggests that the long-lasting stimulation of β-AR occurring during bronchodilator therapy
with salmeterol should not represent a significant risk for subjects with no preexistent cardiovascular alteration. However, further long-term studies are still needed to confirm our preliminary findings concerning salmeterol safety.

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