Acute Respiratory and Cardiovascular Effects of Inhaled Ketanserin in Chronic Obstructive Pulmonary Disease*
A Comparative Study with Intravenously Administered Ketanserin

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In a double-blind, crossover study, nebulized ketanserin, a 5-HT2 receptor antagonist, and a placebo were given to eight patients with moderate to severe nonasthmatic COPD. Intravenous ketanserin had rapid onset of action and induced a longer lasting bronchial response than inhaled ketanserin. These results confirm that ketanserin acts as a mild bronchodilator in patients with COPD and demonstrate that the inhaled route has no advantage over the intravenous route in terms of effectiveness. Thus, 5-HT may play a role in bronchomotor tone, at least in patients with chronic airway obstruction. (Chest 1990; 97:901-05)

5-HT = 5-hydroxytryptamine

The role of 5-HT (serotonin) as a mediator of hyperreactivity in man is controversial. Experiments with human tracheal muscle strips and bronchial spirals have shown that 5-HT causes weak contractions (10 percent of maximum), 1 although it relaxes bronchioles and bronchi.2 In vivo 5-HT does not elicit a response in healthy subjects3 but causes a prompt decrease in expiratory flow and vital capacity in a fair number of asthmatic patients.4,5 Contraction induced by 5-HT is partly reflex, but may be mainly due to direct stimulation of bronchial smooth muscle.6 Some data suggest that tracheal contraction due to 5-HT is mediated by its interaction with the 5-HT2 receptor,9,10 but there have been no studies on 5-HT receptor subtypes in human airway smooth muscle.

Ketanserin, a new antihypertensive drug which has been shown to be a specific competitive inhibitor of the 5-HT2 receptor, can elicit mild bronchodilation in patients with COPD when given at a 10-mg intravenous dose.11 However, this effect has just been demonstrated in adult atopic asthmatic patients when given a single 40-mg oral dose.12

We have performed the present study to investigate whether ketanserin acts as a bronchodilator when administered by inhalation. In addition, we have compared changes produced by ketanserin given by inhalation with those elicited by the same agent administered intravenously.

Methods

Subjects

Eight patients (six men and two women), all normotensive and with moderate to severe COPD, participated in the study after giving their informed consent. The diagnosis of obstructive chronic bronchitis was consistent with the diagnostic standards of the American Thoracic Society.13 All patients were clinically stable at the time of testing and demonstrated at least a 15 percent increase in FEV1 after inhalation of a beta2-adrenergic agent. The anthropometric data and baseline changes in pulmonary function of the population studied are presented in Table 1. All patients were taking oral theophylline or inhaled beta2-adrenergic agents, or both, but bronchodilator therapy was discontinued at least 12 h before the investigation started.

Experimental Procedure

An initial protocol was performed using a randomized double-blind, crossover method. Ketanserin tartrate and placebo were prepared in identical containers and coded. The treatment code and pulmonary function results were not revealed until the studies of all eight patients were completed. Medications (ketanserin, 10 mg in 5 ml of sterile water; placebo, 5 ml of sterile water) were delivered to the airways from a Klava ultrasonic nebulizer (model 6000; GmbH and Co., Detmold, Germany for 5 min. The volume...
Table 1—Anthropometric Data and Pulmonary Function of Studied Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV₁ (L)</th>
<th>Theoretical FEV₁ (L)</th>
<th>FEF50% (L/s)</th>
<th>Theoretical FEF50% (L/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>53</td>
<td>145</td>
<td>51</td>
<td>1.54</td>
<td>2.61</td>
<td>1.8</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>161</td>
<td>73</td>
<td>1.76</td>
<td>2.52</td>
<td>1.5</td>
<td>4.3</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>66</td>
<td>159</td>
<td>63</td>
<td>0.99</td>
<td>2.29</td>
<td>0.9</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>71</td>
<td>163</td>
<td>65</td>
<td>0.99</td>
<td>2.69</td>
<td>0.6</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>35</td>
<td>170</td>
<td>69</td>
<td>2.10</td>
<td>3.78</td>
<td>1.3</td>
<td>5.7</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>60</td>
<td>166</td>
<td>74</td>
<td>1.29</td>
<td>3.05</td>
<td>0.8</td>
<td>4.8</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>47</td>
<td>161</td>
<td>69</td>
<td>0.77</td>
<td>3.17</td>
<td>0.4</td>
<td>5.1</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>65</td>
<td>174</td>
<td>90</td>
<td>1.79</td>
<td>3.07</td>
<td>1.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

output of the nebulizer was adjusted to the maximal amplitude of oscillation (30 W); the flow meter was calibrated at 20 L/min. The nebulizer produced a mass median aerodynamic diameter of 2.8 μm (range, 1 to 6 μm).

In a second protocol, six patients (patients 2, 3, 4, 5, 7 and 8) received 10 mg of intravenous ketanserin. All experiments began at 9 AM to avoid well-known interference with the circadian rhythm on bronchomotor tone.

Respiratory Function Measurement

Spirometry was made with a dry spirometer (Mijnhardt D 101 computer system). Three acceptable forced expiratory maneuvers were performed in order to obtain two reproducible results for the FVC and the FEV₁. The best FEV₁ and FEF50% obtained from one or the other of the reproducible curves was kept for analysis. In each patient the effect that resulted in the highest FEV₁, and FEF50% was used for analysis at the following times: immediately before (as baseline value) and at 5, 15, 30, 60, 120 and 180 min after individual coded treatment.

Recording of Cardiovascular Effects

In order to evaluate possible systemic effects induced by ketanserin, we monitored blood pressure and pulse rate before treatment and at 5, 15, 30, 60, 120 and 180 min after administration of inhaled or intravenously administered ketanserin as well as inhaled placebo. In addition, the electrocardiogram (Hellige, EK 26 cardiograph) was recorded before treatment and after 60 and 180 min.

Statistical Analysis

Statistical analysis was by repeated measures of analysis of variance using the Microstat statistical package. A p<0.05 value was considered statistically significant. All pulmonary function responses to ketanserin or placebo are presented as percentage of change (100 × [value after treatment − value before treatment]/[value before treatment]). The baseline was always indicated as 100 percent.

RESULTS

Pulmonary Function Data for Inhaled Ketanserin vs Placebo

Although day-to-day variation in the baseline values was noted in some of the patients, there was no statistically significant difference (p>0.05) between the highest and the lowest average values in FEV₁ and FEF50%.

The mean individual percentage of change in FEV₁ and FEF50% after administration of ketanserin or placebo at the observed times are shown in Figures 1 and 2. The mean increase in FEV₁ after ketanserin administration was significantly different from the baseline value only at 30 min. The FEF50% also changed significantly from baseline values at 30 and 60 min after administration of ketanserin. However, FEF50% was not significantly improved at 120 min. The mean changes in FEV₁ and FEF50% were higher after ketanserin than after placebo administration at all test times.

Table 2—Changes in Heart Rate and Blood Pressure in Eight Normotensive Patients with COPD Treated with Inhaled Placebo and Inhaled Ketanserin*

<table>
<thead>
<tr>
<th>Times</th>
<th>Inhaled Placebo</th>
<th>Inhaled Ketanserin</th>
<th>Inhaled Placebo</th>
<th>Inhaled Ketanserin</th>
<th>Inhaled Placebo</th>
<th>Inhaled Ketanserin</th>
<th>Inhaled Placebo</th>
<th>Inhaled Ketanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>79.0 ± 4.1</td>
<td>79.7 ± 4.2</td>
<td>121.2 ± 6.9</td>
<td>121.9 ± 7.9</td>
<td>78.1 ± 3.9</td>
<td>76.2 ± 2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>78.3 ± 3.9</td>
<td>79.2 ± 4.3</td>
<td>119.9 ± 4.8</td>
<td>118.7 ± 7.9</td>
<td>77.4 ± 3.8</td>
<td>75.0 ± 2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>79.5 ± 4.2</td>
<td>80.5 ± 3.3</td>
<td>120.1 ± 5.5</td>
<td>115.6 ± 7.21</td>
<td>78.2 ± 3.1</td>
<td>73.1 ± 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>81.4 ± 4.2</td>
<td>79.5 ± 3.7</td>
<td>122.2 ± 6.6</td>
<td>113.7 ± 7.1</td>
<td>77.5 ± 2.9</td>
<td>74.4 ± 3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>79.5 ± 3.8</td>
<td>78.5 ± 2.7</td>
<td>120.4 ± 6.2</td>
<td>110.0 ± 5.7</td>
<td>76.9 ± 3.4</td>
<td>72.5 ± 3.1†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>80.1 ± 3.4</td>
<td>77.0 ± 3.4</td>
<td>121.4 ± 4.8</td>
<td>109.4 ± 5.7†</td>
<td>78.0 ± 2.9</td>
<td>72.5 ± 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>79.7 ± 3.7</td>
<td>79.5 ± 4.2</td>
<td>122.7 ± 4.6</td>
<td>111.9 ± 6.3†</td>
<td>77.6 ± 2.6</td>
<td>71.9 ± 2.3†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SE.
†p<0.05.

Respiratory and Cardiovascular Effects of Ketanserin in COPD (Cazzola)
Pulmonary Function Data for Inhaled vs Intravenously Administered Ketanserin

The mean individual percentage of change in FEV₁ and FEF50% after administration of inhaled or intravenously administered ketanserin at the observed times in the six patients who received ketanserin by both routes are presented in Figure 3 and 4. The onset of action of intravenous ketanserin, determined by a 15 percent increase in the mean FEV₁ over the baseline values, occurred between 5 and 30 min. Using the same criteria, the action onset of inhaled ketanserin occurred between 15 and 60 min. A significant increase from baseline values in FEV₁ and FEF50% continued to be observed for 60 min after intravenous administration of ketanserin, but only at 30 min after ketanserin inhalation.

Cardiovascular Responses for Inhaled Ketanserin vs Placebo

In both treatments nondetectable changes occurred in mean heart rate (Table 2). Ketanserin evoked a progressive decrease in blood pressure that was sometimes significant and this effect was observed throughout the 3-h period. The ECG did not change after ketanserin administration.
Table 3—Changes in Heart Rate and Blood Pressure in Normotensive Patients with COPD Treated with Intravenously Administered and Inhaled Ketanserin*

<table>
<thead>
<tr>
<th>Times</th>
<th>Intravenous Ketanserin</th>
<th>Inhaled Ketanserin</th>
<th>Intravenous Ketanserin</th>
<th>Inhaled Ketanserin</th>
<th>Intravenous Ketanserin</th>
<th>Inhaled Ketanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart Rate (Beats per Minute)</td>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>78.3±5.7</td>
<td>134.2±8.5</td>
<td>80.8±4.2</td>
<td>75.0±3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>83.3±5.3</td>
<td>120.7±7.7</td>
<td>75.0±2.6</td>
<td>74.2±3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>84.0±5.5</td>
<td>112.5±6.8</td>
<td>70.8±2.4</td>
<td>71.7±4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>83.3±5.0</td>
<td>106.7±6.1†</td>
<td>68.3±2.1†</td>
<td>73.3±4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>83.7±7.9</td>
<td>108.3±7.0†</td>
<td>70.8±3.7†</td>
<td>70.8±2.7†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>80.0±5.1</td>
<td>115.0±8.5†</td>
<td>68.3±4.0†</td>
<td>70.0±3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>78.0±5.3</td>
<td>119.2±6.6†</td>
<td>71.7±3.1†</td>
<td>70.0±2.3†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SE.
† = p < 0.05.

Cardiovascular Responses for Inhaled vs Intravenously Administered Ketanserin

No significant change from the baseline values occurred in heart rate measurement following administration of inhaled or parenterally administered ketanserin, even though intravenously administered ketanserin induced a transient increase in pulse rate (Table 3). Both treatments caused a decrease in blood pressure, which was significant for the whole period following the intravenous administration; conversely, the decrease in blood pressure was significant only at 60 and 180 min after inhalation of ketanserin. The ECG did not show any change in the tracing after inhaled or intravenously administered ketanserin.

Discussion

We have demonstrated that inhaled ketanserin induces a mild bronchodilation in patients with COPD. These data may be in agreement with the presence of 5-HT₂ receptors in airway smooth muscle. However, it is possible that 5-HT₂ receptors do not play a major role in the control of resting bronchomotor tone, since experiments with isolated human tracheal or bronchial tissue have shown that 5-HT either does not affect basal tone or at high concentrations causes relaxation. This effect suggests a 5-HT, agonistic effect, since it has been demonstrated that ketanserin does not antagonize the 5-HT relaxant effects in human isolated bronchial tissues. In order to explain the bronchodilation elicited by ketanserin, one could postulate the presence of 5-HT receptors in the parasympathetic ganglia or in the postganglionic nerve terminal, where their activity may play a modulatory role on nervous system transmission. These 5-HT receptors must be 5-HT₂ sites since ketanserin lacks interaction with 5-HT₁ binding sites.

In autonomic ganglia 5-HT has a presynaptic effect on the release of acetylcholine. In the lung, 5-HT potentiates the bronchomotor effect of electrical stimulation of vagal efferents. Consequently, 5-HT may be important as a modulator of synaptic transmission in the bronchomotor pathway, even in humans in whom contractile airway response is inconsequential. Furthermore, we suggest that ketanserin may interfere with efferent cholinergic pathway by means of 5-HT receptor blockade at the cholinergic neuroeffector junction.

The relative intensity of the respiratory functional effect of ketanserin varies transiently with the route of administration, since the extent of drug absorption and the amount that ultimately reaches the systemic circulation are different. The inhaled route presents some disadvantages in that drug effectiveness might be altered, since aerosol penetration and distribution become less efficient with increasing airway obstruction. In addition, only approximately 10 percent of a nebulized drug given by inhalation reaches the mouth and 1 percent of the original dose may be deposited on airways. These mechanisms may partially explain the differences observed between the route of administration and the functional response produced by ketanserin.

In conclusion, the results of this study have confirmed that ketanserin acts as a mild bronchodilator in patients with COPD. Moreover, there is apparently no advantage to administering ketanserin by aerosol.

Acknowledgments: We thank Janssen Farmaceutici (Rome, Italy) for supplying ketanserin and Mrs. Anna Zuccaro and Mr. Ciro Sepe for their excellent technical assistance. We also thank our friend Charles Brink for his suggestions.

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Hypoxia

This Third Annual Sam Stein Memorial Lecture will be presented May 18 at the Teaching Center Auditorium, Long Island Jewish Medical Center, New Hyde Park, New York. Sponsors are the Division of Pulmonary Medicine, Department of Medicine, Long Island Jewish Medical Center, New Hyde Park. For information, contact Ms. Ann J. Boehme, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, New York 11042 (718:470-8650).