Tolerance to \( \beta_2 \)-Agonists in Patients with Chronic Obstructive Pulmonary Disease*

D. Georgopoulos, M.D.; D. Wong, M.D.; and Nicholas R. Anthonisen, M.D., Ph.D.

Eleven patients with severe COPD were examined to determine whether tolerance to \( \beta_2 \)-agonists developed after long-term inhalation therapy with these agents. Before the study all patients were on regular treatment with inhaled salbutamol for six months. At the beginning of the study, response of FEV\(_1\), to inhaled salbutamol was measured. Dose-response curves were measured after three weeks of treatment with ipratropium bromide and again after a three-week course of inhaled salbutamol. After ipratropium bromide treatment, responses to low doses of salbutamol tended to be larger than after salbutamol treatment, but differences were not significant. Three hours after the last inhalation of salbutamol the FEV\(_1\) was lower on days 1 and 42 than on day 21. We conclude that long-term inhalation therapy with \( \beta_2 \)-agonists in patients with COPD decreases the duration of the bronchodilation produced by the same agents but does not affect the peak response.

(Chest 1990; 97:280-84)

\( c\text{-AMP} = \) cyclic adenosine 5'-monophosphate

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Tolerance to \( \beta_2 \)-Agonists (Georgopoulos, Wong, Anthonisen)
and consecutive waterless were evaluated.

Three weeks of ipratropium bromide therapy (day 21), a second dose-response curve to inhaled salbutamol was performed with the same principles and in the same manner as the first one. A second three-week period of regular therapy with inhaled salbutamol, at least 800 μg per day (200 μg four times a day), followed, and at the end of this period (day 42) a final dose-response curve to salbutamol was performed.

On each visit all the patients were questioned regarding the use of the drugs and their compliance with the study protocol was evaluated. Patients who did not comply with the study regimen were excluded.

Spirometry was accomplished with the patient seated using a waterless spirometer (Vitalograph). The largest FEV₁ of three consecutive blows was recorded. Salbutamol was given using standard metered-dose inhalers, held and activated by an investigator to make sure that the drug was inhaled during inspiration.

The results were statistically analyzed with multifactorial analysis of variance with repeated measures across one variable. A value of <0.05 was regarded as significant.

RESULTS

Of 12 patients selected, one had an exacerbation of COPD during treatment with ipratropium bromide and was excluded. Baseline clinical data from the 11 patients who successfully completed the study are shown in Table 1. The average patient was elderly, had a significant smoking history, severe airway obstruction and hyperinflation.

Mean values of FEV₁, recorded during dose-response curves, are shown in Table 2. The heart rate did not change significantly during the dose-response curves and these data are not further detailed.

The mean baseline FEV₁ did not differ significantly on the three experimental days. Independent of the day of the study, inhalation of 200 μg of salbutamol resulted in a significant improvement in lung function (p<0.05). After 400 μg of salbutamol was administered, there were no statistically significant increases in FEV₁ with further drug inhalations. The maximal responses of FEV₁ were closely similar on all study days, averaging 15 min after the last inhalation of salbutamol, between 36 and 39 percent of baseline (Table 2). The time course of the increase of FEV₁ was slightly longer on days 1 and 42 than that on day 21, in that on day 21 responses were slightly larger to 200 and 400 μg of salbutamol, but the difference was not significant. Dose-response curves performed on days 1 and 42 did not differ significantly. On day 21, after three weeks of ipratropium bromide treatment, the FEV₁ was significantly higher (p<0.05) 3 h after the last inhalation of salbutamol than those measured after salbutamol therapy, on days 1 and 42 (Table 2).

No serious side effects were observed during the dose-response curves. Four patients experienced slight tremor with the higher doses of salbutamol.

DISCUSSION

The results of this study demonstrated that in patients with severe COPD, therapy with inhaled salbutamol in the usual doses appeared to decrease the duration of the bronchodilation produced by the same agent, while the peak response remained relatively stable.

Stopping sustained-release theophylline for 12 h before study in the laboratory may not be long enough to drop the blood drug concentration to subtherapeutic levels. This probably did not affect the response to inhaled salbutamol. It has been previously shown that in COPD patients systemic theophylline and inhaled salbutamol have an additive bronchodilator effect, and that preexisting theophylline levels did not relate to bronchodilator response in patients who had discontinued long-acting preparations for 12 h.

The doses of salbutamol that were used to construct dose-response curves appeared to achieve maximal or

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Table 1—Baseline Clinical Characteristics*

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Age, yr</th>
<th>Smoking history, pack-years</th>
<th>FEV₁, % predicted</th>
<th>FVC, % predicted</th>
<th>TLC, % predicted</th>
<th>RV, % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>63.5±2.5</td>
<td>40.1±3.9</td>
<td>42.2±3.2</td>
<td>60.5±4.4</td>
<td>120.4±5.9</td>
<td>208.8±9.6</td>
</tr>
</tbody>
</table>

*Values are mean ± SE.

Table 2—FEV₁ (L) during the Dose-Response Curves to Salbutamol on the Three Study Days*

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time (min)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60†</th>
<th>75</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0.92±0.13</td>
<td>1.16±0.17</td>
<td>1.19±0.15</td>
<td>1.24±0.17</td>
<td>1.27±0.17</td>
<td>1.28±0.17</td>
<td>1.27±0.17</td>
<td>1.32±0.17</td>
<td>1.27±0.17</td>
<td>1.21‡</td>
</tr>
<tr>
<td>21</td>
<td>0.94±0.13</td>
<td>1.04±0.18</td>
<td>1.23±0.18</td>
<td>1.29±0.17</td>
<td>1.29±0.17</td>
<td>1.29±0.17</td>
<td>1.30±0.18</td>
<td>1.31±0.17</td>
<td>1.31±0.17</td>
<td>1.34±0.17</td>
<td>1.36</td>
</tr>
<tr>
<td>42</td>
<td>0.96±0.11</td>
<td>1.21±0.18</td>
<td>1.22±0.16</td>
<td>1.27±0.17</td>
<td>1.28±0.17</td>
<td>1.28±0.17</td>
<td>1.31±0.18</td>
<td>1.29±0.17</td>
<td>1.30±0.17</td>
<td>1.36±0.17</td>
<td>1.18*</td>
</tr>
</tbody>
</table>

*Values are mean ± SE. Day 1: Baseline. Day 21: After three weeks of treatment with ipratropium bromide. Day 42: After three weeks of treatment with inhaled salbutamol.
†Last dose of salbutamol.
‡Significantly different from the corresponding values of day 21.
near maximal bronchodilation. Most evidence presented in the literature suggests that in the majority of patients with obstructive disease, maximum bronchodilation occurs with doses of salbutamol of 600 to 800 μg. In our study substantial increases in FEV₁ were observed after 200 μg and no further significant increase was observed with doses greater than 400 μg (Table 2), although a few patients exhibited responses to doses as high as 800 μg. Thus, our data indicate that in our group of patients, 1,000 μg of salbutamol produced the maximal bronchodilation observable with this agent.

We had no objective way of ascertaining whether or not our patients complied with the prescribed treatment protocols. However, the patients were selected on the basis of compliance and reliability and on each visit, they were carefully questioned regarding the use of the drugs, and all indicated that they had carefully followed instructions. We believe that they did so.

We selected three-week periods of salbutamol abstinence and use because there is good evidence that if tolerance develops it will do so in three weeks, and three weeks of abstinence is sufficient to reverse tolerance. Several studies have shown that β₂-receptor down-regulation, as expressed by the reduction of β-adrenergic binding sites on lymphocytes or in the production of c-AMP with adrenergic stimulation, develops fully after two weeks of treatment with β-agonists. These parameters return to normal levels ten to 14 days after cessation of therapy. In addition, in normal people a decrease in the lung function response to β-agonists after two to three weeks of adrenergic therapy has been demonstrated. This decrease persists for seven to ten days after the drugs are discontinued. Finally, when the first dose-response curve was obtained in our patients, they had been receiving therapy with adrenergic agents for at least six months prior to the study. This dose-response curve did not differ from that done after the three-week salbutamol treatment, which followed the wash-out period, so that in this group of COPD patients, alterations in β₂-receptors in airways was unlikely to have developed after more than three weeks of treatment.

Our study did not show any evidence that long-term therapy with adrenergic agents significantly altered the peak bronchodilating effect of these drugs. However, with submaximal stimulation of β₂-receptors, the effect of salbutamol showed a trend to be greater after the wash-out period, suggesting the development of some degree of tolerance to β-agonists. Indeed, after 200 and 400 μg of salbutamol, the FEV₁ was 1.23 and 1.29 L, respectively, after the wash-out period, whereas the corresponding values after the two salbutamol periods were 1.16 and 1.19 L (day 1), respectively, and 1.21 and 1.22 L (day 42), respectively. Given the variability of the patients studied, we would have required approximately 25 patients to prove that this small difference was significant. Whatever its statistical significance, the difference was of trivial clinical significance. On the other hand, the maximal response did not differ between the various study days and 15 min after the last inhalation of salbutamol the FEV₁ was closely similar, averaging 1.28, 1.30 and 1.31 L on days 1, 21 and 42, respectively, with a range of response between 36 and 39 percent of baseline (Table 2).

Our results agree with studies in asthmatic subjects that did not find any significant reduction in the acute response to β-agonists after long-term therapy with adrenergic drugs. Harvey and Tattersfield constructed dose-response curves to inhaled salbutamol in normal and asthmatic subjects and demonstrated that four weeks of treatment with inhaled salbutamol reduced the response in normal but not in asthmatic subjects. This difference between normal and asthmatic subjects has been confirmed by other studies, with the reason for this discrepancy being totally obscure. In this respect, our study indicates that COPD patients behave like asthmatic subjects; there was no evidence of significant change in acute response to salbutamol associated with adrenergic therapy.

It is not clear why our study on patients with COPD and other studies on asthmatic subjects did not find any significant change in the acute response of lung function to β-agonists, when there is good evidence in the literature that during adrenergic therapy significant alterations in β-receptors function occur in various other tissues. Indeed, drug-induced β₂-receptor down-regulation clearly has been demonstrated in studies that examined the effects of β-agonists on metabolic parameters, c-AMP responses of isolated leukocytes to adrenergic stimulation, and β₂-receptor density. However, there is a lack of correlation between findings obtained by the previously noted studies and changes in lung function, suggesting that there might be a difference between the various tissues in the ease with which they develop resistance to β-agonists. This hypothesis is supported by the study of Hasegawa and Townley which demonstrated that the number of β-receptors in splenic tissue of rats decreased after six days of therapy with terbutaline, while it remained stable in lung parenchyma. These results, however, must be interpreted with caution. When whole lung homogenates are used, the receptors studied may well not be located on the cells which mediate the bronchodilating effect. The elegant autoradiographic studies of Barnes et al have shown that less than 5 percent of the total β-receptors in the lung are likely to be derived from airways, so changes in
total lung β-receptor density probably do not reflect changes in airways. Of greater significance are the results of Holmberg et al who observed in guinea pigs a selective development of tolerance to the effects of β-agonists in skeletal muscle as compared with their effects in tracheal smooth muscle.

In our study, inhaled salbutamol therapy involved the usual doses of this drug and it might be argued that larger doses would have resulted in different responses. Carefully designed studies in asthmatic subjects failed to demonstrate any loss of the β-agonist reactivity of airways after doses as high as 2,000 μg of salbutamol daily. Conversely, normal subjects develop tachyphylaxis with the usual inhaled doses of β-agonists.

Particular mention should be made of the study of Weber et al who on a group of asthmatic subjects. They found that 12 weeks of treatment with inhaled terbutaline resulted in a decrease in the peak response of FEV₁ to terbutaline. These results seem to differ from ours though the designs of the two studies were similar. However, baseline FEV₁ after 12 weeks of adrenergic therapy averaged 0.1 L more than before. This difference may have influenced the results, particularly regarding the peak response, a point that already has been discussed by Bruynzeel et al. In our study, baseline FEV₁ was almost the same during the three study days and the peak response was not significantly influenced by pretreatment.

Tashkin et al produced indirect evidence that long-term β₂-agonist treatment in COPD patients may cause tolerance to these agents; the response of FEV₁ to inhaled metaproterenol was slightly lower after 45 and 90 days of adrenergic therapy than before. However, the study was not designed to examine the development of tolerance and the data were not analyzed regarding this matter. In addition, the response of FEV₁ was evaluated after a single, relatively small, dose of inhaled metaproterenol. In this case, the maximum effect of the drug probably was not achieved, making the comparison with our study complex.

Four of our patients were receiving therapy with small doses of inhaled beclomethasone. It has been suggested that corticosteroids may reverse or prevent the development of β₂-receptor down-regulation. However, this effect is controversial and usually has been demonstrated with large systemic doses of steroids. It is unlikely that small doses of beclomethasone in these four patients influenced the conclusions of the study. Our hypothesis is supported by Molema et al who did not find any influence of inhaled beclomethasone, in doses as high as 2,000 μg, on the dose-response curve to salbutamol.

We did show that long-term therapy with β₂-agonists reduced the duration of action of these agents, whereas the acute peak response remained relatively stable. Three hours after the last inhalation of salbutamol, FEV₁ averaged 132 and 123 percent of baseline on days 1 and 42, respectively, while it remained at peak levels (145 percent) after the three weeks of ipratropium bromide treatment (day 21). Our results are in close agreement with those of Repsher et al who demonstrated in asthmatic subjects that long-term treatment with albuterol caused a reduction of the duration of drug effect, while the size of the acute effect remained unchanged. The reduction in the duration of drug action we observed was modest in magnitude and our patients, independent of pretreatment, demonstrated significant bronchodilation 3 hs after the last inhalation of salbutamol. The decrease in the duration of drug activity probably reached a maximum at three weeks of adrenergic treatment because no difference could be detected between the first and third dose-response curve. Unfortunately, we did not examine lung function for longer than a 4-h period and it is possible that had we done so the differences in duration of action would have been more evident.

In conclusion, long-term therapy with adrenergic bronchodilators in patients with COPD results in a decrease in the duration of bronchodilation produced by these agents. The peak drug effect does not change significantly, suggesting clinical stability of β₂-receptors in airways.

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