Dose-effect Relationship of the \(\beta\)-Agonists Fenoterol and Salbutamol in Patients With Asthma*

Michael T. Newhouse, M.D., F.C.C.P.; Myrna B. Dolovich, P.Eng.; and Farouk Kazim, M.A.

**Question:** What is the relative per microgram potency and side effect profile of the \(\beta\)-agonists salbutamol and fenoterol?

**Method:** The relative bronchodilator (\(\Delta\)FEV\(_1\), \(V_{25}, V_{50}\) potency and side effect profile (\(\Delta\)tremor, heart rate, breathlessness, BP) of nebulized salbutamol and fenoterol were evaluated by means of a randomized, double-blind, crossover, cumulative (50 to 2,500 \(\mu\)g) dose-response study. Both \(\beta\)-agonists were administered to 12 patients with stable asthma over 18 years with baseline FEV\(_1\) between 35 to 70 percent predicted.

**Results:** (1) Salbutamol and fenoterol both provided significant bronchodilatation compared with baseline. (2) There was no dose-effect difference between the two \(\beta\)-agonists with respect to bronchodilator response. (3) Overall there was no significant difference between the side effect profiles of the two \(\beta\)-agonists, although at the highest dose of fenoterol, there was marginally greater tremor when measured by accelerometry. (4) There was no difference in the vital signs or subjective patient evaluations of tremor, palpitations, or breathlessness as estimated by a visual analogue scale. (5) No significant adverse reactions occurred.

**Summary and conclusion:** Equivalent bronchodilatation and similar side effect profiles were measured in a group of patients with stable asthma after treatment with nebulized salbutamol or fenoterol in the dose range 50 to 1,250 \(\mu\)g (cumulative, 2,500 \(\mu\)g). This indicates that both \(\beta\)-agonists have similar per microgram potency and side effect profiles. Observed clinical differences in response or side effects associated with fenoterol metered-dose inhaler administration may be a result of its higher dose per puff metered-dose inhaler formulation.

(Chest 1994; 105:1738-42)

Key words: adverse effects; asthma; beta agonists; bioequivalence; nebulization

fenoterol vs salbutamol has not been clearly established.\(^{5,6}\) A cumulative dose-response study comparing nebulized solutions of fenoterol and salbutamol over a range of clinically relevant doses was, therefore, undertaken in patients with stable asthma.

**METHODS**

**Study Design**

A randomized double-blind crossover cumulative response study was performed to establish the therapeutic ratio and side effect profiles between placebo and six dose levels of fenoterol and salbutamol respirator solution (50 to 2,500 \(\mu\)g cumulative at intervals of about 1 h over approximately 6 h) administered by nebulizer to 12 adults with stable asthma.

**Demographics**

Subjects ranged in age from 25 to 67 years. There were three men and nine women. Asthma was defined according to standard American Thoracic Society criteria and had been stable for at least 4 weeks. This older population of asthmatics consisted mainly of patients with nonatopic disease. Baseline FEV\(_1\) varied between 35 to 70 percent predicted normal values and was within \(\pm\) 15 percent of this initial value between the two study days. Prior to entry into the study, all subjects had to show a 15 percent or greater improvement in FEV\(_1\) within 30 min after inhaling two puffs (400 \(\mu\)g) of fenoterol from a MDI. With regard to asthma severity, three were classified as having mild (as occasion requires bronchodilators only, up to twice a day), eight were classified as having moderate (daily inhaled steroids), and one was classified as...
**Table 1—Subject Data, FEV₁, and Current Therapy**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>12^* (3M, 9F)</td>
</tr>
<tr>
<td>Age, yr, mean (SE)</td>
<td>52.2 (3.5)</td>
</tr>
<tr>
<td>Severity of asthma</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
</tr>
<tr>
<td>Duration of disease, yr,</td>
<td>23.1 (4.0)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>Baseline FEV₁, L, Mean (SE)</td>
<td>1.55 (0.11)</td>
</tr>
<tr>
<td>Baseline % predicted FEV₁, L</td>
<td>58 (3)</td>
</tr>
<tr>
<td>Range</td>
<td>36-69</td>
</tr>
<tr>
<td>% increase in FEV₁ after 400 µg of fenoterol MDI,</td>
<td>43 (5)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td></td>
</tr>
</tbody>
</table>

Prior Medication

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>β₂-MDI</th>
<th>Inhaled corticosteroids</th>
<th>Ipratropium bromide</th>
<th>Oral corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

^*Retroactive statistical power of 80 percent to detect differences of 0.18 L or greater between the two regimens in this double-blind, randomized, crossover, cumulative dose-response comparison.

having severe (long-term systemic steroids) asthma on the basis of their history and medication requirements. Asthma had been present for a mean of 23 years (range, 6 to 44 years; median, 18.0 years).

**Exclusions**

Patients with known cardiac arrhythmias or sinus tachycardia and those with known hypersensitivity to sympathomimetic compounds were excluded, as were smokers, lactating or pregnant women, and those of child-bearing potential not using an approved birth control method. Subjects with other significant systemic medical illnesses or concomitant drug use that might limit their participation were also excluded. Written informed consent was obtained from each participant. The study was approved by the St. Joseph's Hospital Ethics Committee.

**Study Protocol**

On two consecutive days and using computer-generated randomization, subjects received placebo followed by six cumulative doses (50, 125, 250, 625, 1,250, and 2,500 µg) of either nebulized fenoterol or salbutamol nebulizer solutions. The β-agonists were administered via an updraft nebulizer (Hudson) and facemask, driven by compressed air at a rate of 8 L/min. The time interval between successive doses was 52 to 56 min. All doses were prepared in a total volume of 3 ml using 1 mg of either 5 mg/ml of fenoterol or 5 mg/ml of salbutamol stock solutions and phosphate-buffered isotonic saline solution to volume. Aerosol was administered to seated patients at rest breathing at their preferred tidal volume. Before each test day, subjects refrained from taking inhaled bronchodilators or short-acting theophyllines for at least 8 h, oral β-agonist bronchodilators for 24 h, or long-acting theophylline preparations for 48 h.

Subjects had pulmonary function testing (FEV₁, FVC, maximum flow rate at 50 percent of vital capacity [V50], and maximum flow rate at 25 percent of vital capacity [V25]) at baseline and 30 to 45 min after completion of nebulization of each successive dose. Respiratory rate, systolic blood pressure, diastolic blood pressure, and pulse rate were also measured. Muscle tremor was evaluated using an accelerometer (Bruel and Kjaer, model 4366) attached to the index finger of the right hand. Five tremor measurements were made over an 8-min interval. Patients also made a subjective evaluation of their symptoms (breathlessness, hand tremor, and palpitations), quantified using a visual analogue scale (VAS) scored from 0 (no symptoms) to 5 (maximum symptoms). Side effects and adverse reactions were monitored and their severity recorded. No dropouts occurred. Patient demographics and prior medication are shown in Table 1. The sample size of 12 was found to be adequate to enable the detection of differences of more than 0.18 L of increase in FEV₁ between the two regimens with a power of 0.8.

**Statistical Evaluation**

Statistical analysis was accomplished using analysis of variance appropriate to a two-factor repeated measures model with repeated measures on both factors, drug and dose, given at a specific time point. The raw data values as well as the absolute changes from baseline of the ventilatory function parameters were used as measures of drug efficacy. The cardiovascular response parameters, as well as the log-transformed means and standard deviations of hand tremor, measured using the accelerometer, and the side effect profiles as estimated on the VAS being approximately of normal distribution, were compared using the same robust methods.

The presence of an order effect was evaluated and none was found; thus, we combined the two orders of administration.

**RESULTS**

Twelve subjects with stable asthma entered the study and successfully completed the 2 days of testing. The mean baseline FEV₁ was 1.53 L (SEM, 0.11 L) or 57.5 percent predicted (SEM, 2.9 percent predicted). All baseline FEV₁s were between 35 to 70 percent predicted normal and all subjects showed a greater than 15 percent improvement in FEV₁. The mean increase in FEV₁ on the reversibility test day following two puffs (400 µg) of fenoterol administered by MDI was 42.9 percent (SEM, 4.8 percent). The mean FEV₁ values and absolute FEV₁ change from baseline after increasing doses of fenoterol or salbutamol are shown in Figure 1. There was no statistically significant difference in baseline FEV₁ before the two treatment regimens. Each successive active dose of either fenoterol or salbutamol resulted in progressively greater bronchodilatation compared with baseline (p<0.00005) with the response to fenoterol being slightly, but not significantly, greater than that to salbutamol at each dose level (p=0.38).

After the highest dose (1,250 µg; cumulative, 2,500 µg), there was a statistically significant (101 ml) greater absolute response in FEV₁ after fenoterol than after salbutamol (2.263 L vs 2.125 L; p<0.05). When related to the baseline FEV₁ on each test day, this difference amounted to only a 70-ml difference in the increase in FEV₁ above baseline between the response to the two β-agonists in favor of fenoterol, and this difference did not reach significance (p=0.26).

In essence, both fenoterol and salbutamol provided...
similar bronchodilatation over the dose range tested. Similar responses were also seen with respect to FVC, V50, and V25.

**Hand Tremor**

Both fenoterol and salbutamol resulted in similar, marginally increased tremor at cumulative doses greater than 625 μg, with somewhat higher values for fenoterol. Even after the 1,250-μg dose (cumulative dose, 2,500 μg), however, this difference corrected for baseline did not reach statistical significance (p=0.29).

**Vital Signs**

Heart rate, systolic blood pressure, and diastolic blood pressure were evaluated at the same time points. Compared with baseline, the heart rate fell 6 (SEM, 5) bpm on average up to the 75-μg dose (cumulative, 125 μg) for both β-agonists, then rose to 1 to 2 (SEM, 6) bpm above baseline in response to the 125-μg dose (cumulative, 250 μg) with no further change to 1,250 μg (2,500 μg cumulative). Changes were small and not significant. The maximum rise in systolic blood pressure was 8 mm Hg after 50 μg of salbutamol. Fenoterol caused no increase and a maximum fall of −5 mm Hg in systolic blood pressure after the 625-μg dose. The diastolic pressure fell minimally. The maximum fall from baseline was −3.5 mm Hg for fenoterol and −2.5 mm Hg for salbutamol after the 625-μg dose.

**Symptoms**

Patients’ subjective evaluations of tremor, breathlessness, and palpitations estimated using the VAS showed no statistically significant effects due to either treatment regimen.

**Adverse Reactions**

One subject reported headache and dizziness, both described as moderate while receiving the penultimate dose of salbutamol. No other adverse reactions were recorded.

**DISCUSSION**

This study has shown that in adults with stable asthma, nebulized fenoterol and salbutamol provide similar bronchodilatation per microgram in the cumulative dose range 50 to 2,500 μg. Approximately 66 percent of the maximum bronchodilatation, as measured by the FEV1, ultimately achieved with a cumulative dose of 2,500 μg, had been accomplished by a cumulative dose of 250 μg. A gradual further increase in FEV1 occurred with increasing doses until the cumulative dose of 2,500 μg was administered. However, even then no clear plateau was reached, although the slope of the response curve had decreased markedly. A similar response pattern was observed with either fenoterol or salbutamol when airway caliber was evaluated using V50 and V25 or FVC.

There has been the clinical impression that fenot-
erol causes more tremor than salbutamol. By means of accelerometry, however, despite a trend to greater tremor at a dose of 625 μg or greater of fenoterol, no statistically significant difference between the two medications was noted. The VAS scores for tremor and palpitations also showed no difference between the two medications indicating that the subjects were also unable to subjectively distinguish the small differences measured.

Thus, it appears that there is microgram equivalence for nebulized fenoterol and salbutamol, both with respect to the bronchodilator effect and common side effects in the clinically relevant dose range tested. While in this study, subjects received the β-agonist medication by nebulizer to allow dose-response curves to be obtained starting with low doses of the β-agonists, MDI-generated β-agonist aerosols should provide similar benefits and side effects. Because the MDI is generally more efficient, threefold to sixfold smaller doses are usually capable of providing equivalent therapeutic benefit even in life-threatening asthma.7-12 Indeed, the mean increase in FEV₁ measured after 400 μg (two puffs) of fenoterol MDI on the “reversibility day” was 42.9 percent, similar to the change measured after the final, 1,250-μg dose of fenoterol solution administered representing a cumulative nominal dose of 2,500 μg. Thus, given the time elapsed (approximately 6 h) since administration of the first β-agonist dose and assuming that the effective cumulative dose was likely closer to 2,250 μg resulting from the previous three doses administered, the approximate dose ratio compared with MDI is 5.5, within the range of previous studies.8-11

The previous disagreement regarding per microgram vs per puff equivalence of fenoterol and salbutamol in patients with stable asthma is largely explained by this study since a cumulative nebulized dose of only 250 μg (Fic 1) was sufficient to provide about 66 percent of bronchodilatation achievable by a tenfold greater dose. Considering the greater efficiency of aerosol delivery with the MDI even in patients with severe asthma,12 it is unlikely that a difference could be shown between one 200-μg puff of fenoterol and one 100-μg puff of salbutamol in studies that evaluated dose equivalence in patients with stable asthma using standard MDIs.

It is, therefore, reasonable to assume that on a weight basis, a single 200-μg puff of fenoterol (Berotec) could be considered essentially equivalent both in its bronchodilator effect and in its side effects to two puffs of salbutamol (Ventolin, 100 μg per puff). Since most patients are advised to take two puffs of their MDI-generated bronchodilator medication at a time, they would usually, for maintenance therapy or for asthma attacks, self-administer twice the dose of fenoterol (400 μg in two puffs) compared with salbutamol (200 μg in two puffs). This dose difference is the most plausible explanation for why, in general, greater and/or more prolonged bronchodilatation has been demonstrated with fenoterol, while at the same time more side effects such as tremor and tachycardia have been reported. In the study of König et al13 that compared MDI therapy using fenoterol, two puffs (400 μg), with salbutamol, two puffs (200 μg), in 24 patients with mild asthma, the peak bronchodilator response was similar for both β₂-agonists but the duration of effect (bronchodilator response greater than 15 percent above baseline) for fenoterol was 6 h compared with 3 h for salbutamol. Eleven of the 24 patients receiving fenoterol, but none of the patients receiving salbutamol, experienced mild tremor and headache, and none of the patients in either group experienced cardiac arrhythmias or electrocardiographic changes. These authors attributed both the increased benefits and side effects to the greater total dose of fenoterol administered. Similar conclusions about the greater dose of fenoterol per puff causing increased side effects were drawn by Wong et al14 who, in ten patients with mild and stable asthma given 2, 6, and 18 puffs, compared fenoterol (200 μg/puff), salbutamol (250 μg/puff), and terbutaline (100 μg/puff) with respect to FEV₁, heart rate, QTc interval, serum potassium, tremor, and the histamine provocation test. They showed that, whereas all three bronchodilators produced a similar change in FEV₁, fenoterol caused a significantly greater heart rate with maximum increase over baseline of 29 beats/min after 18 puffs compared with an increase of 8 beats/min for both salbutamol and terbutaline. Fenoterol also caused the greatest fall in serum potassium level. There was no difference among the three β-agonists with respect to protection from bronchoconstriction in the histamine bronchoprovocation test. These authors suggested that for fenoterol, the maximum number of puffs recommended in the British Thoracic Society asthma treatment guidelines should be reduced.

To explain the apparent association between fenoterol use and asthma mortality, Crane et al12,5 postulated that fenoterol, like isoproterenol, might have less β₂-selectivity or alternatively that fenoterol abuse might lead to β-receptor subsensitivity. Indeed, despite the fact that in vitro salbutamol is almost twice as selective for β-receptors as fenoterol (salbutamol 107 X and fenoterol 57 X compared with isoproterenol),15 it seems unlikely, given the large therapeutic “window,” that such relatively small differences would be sufficient to account for the increased asthma mortality in New Zealand, even if twice as much fenoterol was routinely used. Furthermore, in man, fenoterol and salbutamol β-selectivity are sim-
ilar as evidenced by (clinically irrelevant) minor differences in chronotropic, inotropic, and ECG effects at inhaled doses of 1,000 and 4,000 µg in normal subjects. Thus, the β₂-selectivity of fenoterol, like salbutamol, is retained even at much higher than usual doses. Lipworth treated 14 asthmatics with doubling cumulative doses between 100 µg and 4,000 µg of salbutamol. Only 1 of 14 achieved maximum bronchodilatation at 200 µg while 4 patients required 2,000 µg and 6 of 14 required as much as 4,000 µg. There was no correlation between the percent reduction in baseline FEV₁ from predicted and the dose needed to achieve maximum bronchodilatation. This is in contrast to the findings of several emergency department studies of rescue from life-threatening asthma in adults and children. Dose-dependent systemic adverse effects included tremor, hypokalemia, an increase in the QTc interval on the ECG, as well as chronotropic and inotropic responses. With salbutamol, systemic effects did not occur under 500 µg but were linear above that and dose dependent.

The question of β-agonist-related tachyphylaxis or β-receptor subsensitivity in patients with asthma has been addressed in recent studies. These have shown no evidence of tachyphylaxis for the bronchodilator effect but clinically relevant subsensitivity of systemic β-receptors even at a cumulative dose of 4,000 µg of salbutamol. This outcome is opposite to that expected if adrenoceptor agonists were contributing to increased asthma mortality via the mechanism proposed by Crane et al.

In conclusion, a per microgram equivalence in bronchodilatation and side effect profiles has been shown for fenoterol and salbutamol nebulizer solutions. Thus, they can be interchanged clinically. While not directly compared in this study, it is possible that observed clinical differences between fenoterol and salbutamol MDI formulations may be attributable to the greater per puff dose of bronchodilator available from the 200 µg per puff fenoterol MDI. This suggests that patients should be advised to take one puff of fenoterol, 200 µg per puff or one-two puffs of a 100-µg per puff formulation to achieve similar safety and efficacy to the more commonly prescribed one-two puffs of the salbutamol, 100 µg per puff formulation.

REFERENCES
6. Lipworth BJ. Risks versus benefits of inhaled β₂-agonists in the management of asthma. Drug Safety 1992; 7:54-70
9. Hodder RV, Calcutt LE, Leach JA. Metered dose inhaler with spacer is superior to wet nebulisation for emergency room treatment of acute, severe asthma. Chest 1988; 94:725-28