Double-Blind Comparison of Metaproterenol and Isoetharine-Phenylephrine Solutions in Intermittent Positive Pressure Breathing in Bronchospastic Conditions*  
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A 5 percent solution of metaproterenol sulfate (Alupent) and a fixed-combination solution of isoproterenol and phenylephrine were compared in a single-dose double-blind study in a total of 27 patients with reversible bronchospastic disease. The patients were assigned to parallel groups for treatment and received the usual dose of 0.3 ml of metaproterenol and 0.5 ml of the isoproterenol-phenylephrine solution via equipment for intermittent positive-pressure breathing. Tests of pulmonary function, blood pressure, and pulse rate were performed before the treatment and at intervals of 30 minutes to six hours after administration. The duration of effect (defined as an increase over baseline in the forced expiratory volume in one second [FEV₁] of at least 15 percent) of metaproterenol averaged four hours, as compared with one hour for the reference solution. The overall response of FEV₁ to metaproterenol was significantly (P = 0.01) superior to the response to the isoproterenol-phenylephrine solution. Metaproterenol also surpassed the reference drug in terms of increases in the mean forced expiratory flow during the middle half of the forced vital capacity (FEF25-75%) to a degree approaching statistical significance. Changes in blood pressure and pulse rate were clinically insignificant with both drugs, and the total number of adverse experiences was substantially the same with both solutions.

In the planning of clinical trials, it is customary to evaluate a new therapeutic agent first in comparison with a placebo and then with the so-called “standard agent” in its therapeutic class; however, for the clinician the critical comparison is between the new agent and the one he or a majority of his colleagues would normally rely on in an actual therapeutic situation.

At Memorial Hospital Medical Center, Long Beach, Calif, a combination solution of isoproterenol and phenylephrine (Bronkosol) has supplanted isoproterenol as the preferred bronchodilator agent for use with intermittent positive pressure breathing (IPPB) in patients with reversible bronchospasm. Reports of several well-controlled studies have suggested that metaproterenol (Alupent) might offer important advantages over the isoproterenol-phenylephrine solution, particularly in duration of action. Emirgil et al have reported that the inhaler providing a metered dose of metaproterenol has a significantly longer duration of action than the metered-dose aerosol of the isoproterenol-phenylephrine combination (Bronkometer). Therefore, when metaproterenol became available for study in a 5 percent solution suitable for use in IPPB equipment or hand-bulb nebulizers, we decided to undertake a controlled evaluation of this new form in our hospital.

Metaproterenol is representative of the “second generation” of sympathomimetic bronchodilator drugs, which differ pharmacologically from isoproterenol in β-adrenergic receptor selectivity or resistance to enzymatic degradation by catechol-O-methyltransferase and sulfatase. This degradation shortens the activity span of isoproterenol. Metaproterenol has repeatedly been shown to surpass isoproterenol in duration of effect.

For patients sufficiently ill to require regular treatment with IPPB, the importance of sustaining the relief afforded by each individual session of treatment can hardly be overstated. Our study was designed to determine objectively whether the bronchodilator effect of the metaproterenol solution persists measurably longer than that of the isoproterenol-phenylephrine solution and, if so, whether the effects of these two solutions are comparable in degree and are similarly unencumbered by serious adverse reactions.

Materials and Methods

Twenty-seven hospitalized patients (ten men and 17 women) with reversible bronchospastic conditions requiring

*From Memorial Hospital Medical Center, Long Beach, Calif. The combination product of isoproterenol-phenylephrine solution is no longer being manufactured. Isoetharine is now available as a single-entity 1 percent solution.

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treatment with IPPB with bronchodilator drugs were entered into the study. Patients with significant cardiovascular, metabolic, or hepatic disease and those with known sensitivity or intolerance to sympathomimetic agents or with pulmonary conditions in which IPPB was contraindicated were excluded.

The patients ranged in age from 20 to 79 years. Twenty-four had asthma, and in 15 of these patients, the asthma was moderate to severe. The duration of the illness was ten years or longer in slightly more than half of the group.

Using a double-blind parallel design for the study, we assigned patients at random to one of two groups for treatment. Each group received a single treatment with IPPB lasting 10 to 15 minutes, during which one of the two tested agents was administered under parallel conditions, with the aid of a machine (Bennett PR-1). To ensure double-blindness, a third party not involved in any phase of the testing or evaluation placed the appropriate medication (0.3 ml of a 5 percent metaproterenol solution or 0.5 ml of the fixed-combination isoetharine-phenylephrine solution) in the machine and diluted it with saline solution to a constant volume of 2.5 ml.

Before the study, all concomitant medication was reduced to a minimum consistent with the patient’s well-being, and no bronchodilator was given orally, by inhalation, or parenterally for at least six hours before administration of the tested agents.

Response was evaluated in terms of pulmonary function measured immediately before and 0.5, 1, 2, 3, 4, and 6 hours after treatment. Pulse rate and blood pressure were recorded at the same intervals. The tests of pulmonary function consisted of the forced vital capacity (FVC), the forced expiratory volume in one second (FEV₁), the airway resistance (Raw), and the mean forced expiratory flow over the middle half of the FVC (FEF25-75%).

RESULTS

Except for the FVC at 30 minutes, the observed mean changes from baseline values produced by administration of metaproterenol were greater at all times in all measures of pulmonary function than those produced by the isoetharine-phenylephrine preparation. These changes represented increases in FEV₁, FEF25-75%, and FVC and reductions in Raw.

![Figure 1](image1.png)

**Figure 1.** Mean changes in percentage in FEV₁ from baseline after treatment.

![Figure 2](image2.png)

**Figure 2.** Mean changes in FEF25-75% from baseline after treatment.

Administration of metaproterenol produced a clinically significant mean increase of 15 percent or more in FEV₁ for at least four hours (Fig 1) and a mean increase of 20 percent or more in FEF25-75% for six hours (Fig 2). Comparable increases in response to administration of the isoetharine-phenylephrine solution lasted only one hour. Moreover, at

![Figure 3](image3.png)

**Figure 3.** Mean changes in Raw from baseline after treatment. Mean baseline value in group receiving metaproterenol was 7.34 cm H₂O/L/sec and in group receiving isoetharine-phenylephrine solution was 5.45 cm H₂O/L/sec.
four hours the mean increase in FEF25-75% and the mean decrease in Raw (Fig 3) in the group receiving metaproterenol exceeded the maximum mean changes in the patients treated with the isoetharine-phenylephrine solution.

A comparison of the mean percentage of change over time from the baseline values for FEV₁ in the two groups showed that from two hours on, the magnitude of the increase in those receiving metaproterenol was more than double that in the group receiving the isoetharine-phenylephrine solution (Fig 1).

Analysis by the Hotelling $t^2$ test showed a significant overall difference ($P = 0.01$) in the response of FEV₁, in favor of metaproterenol. The same test, when applied to the overall effect on FEF25-75%, also revealed a superior effect of metaproterenol, but the difference between the two drugs only approached statistical significance ($P = 0.07$), owing to considerable variation of the individual data.

**Adverse Effects**

Since the chief advantage of the isoetharine-phenylephrine combination over isoproterenol is its relative paucity of side effects, this factor ranks high in importance in comparisons with other bronchodilator agents as well. In this study, diastolic and systolic blood pressure and pulse rate were measured concurrently with pulmonary function in all patients. Throughout the study, changes in diastolic and systolic pressure were small after administration of both solutions and were not clinically significant. Both solutions caused detectable increases in pulse rate, most notably so at half an hour after administration. While analysis of the pulse rate disclosed a greater mean increase in the group receiving metaproterenol, the differences fell short of statistical significance.

The numbers of patients experiencing side effects were comparable in the two groups (Table 1). The reactions were of the types commonly encountered with $\beta$-adrenergic drugs.

**DISCUSSION**

The results of this double-blind comparative study of treatments with IPPB demonstrate the superiority of this new dosage form of metaproterenol over the isoetharine-phenylephrine solution in terms of the magnitude and, most particularly, the duration of the bronchodilator effect. Metaproterenol provided

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**Table 1—Adverse Experiences after Administration of Metaproterenol Solution and Isoetharine-Phenylephrine Solution**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Metaproterenol Solution</th>
<th>Isoetharine-Phenylephrine Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Adverse experience*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaking; tremor</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Effects on central nervous system (dizziness; sleepiness; tiredness)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*No statistically significant difference between groups for any of adverse experiences.

Clinically significant bronchodilation for at least four hours, while the effect of the isoetharine-phenylephrine combination lasted only one hour. By each of the objective criteria of pulmonary function that we applied, the response favored metaproterenol; and in the case of the overall response of FEV₁, the difference between the two solutions was statistically significant.

The prolonged duration of action of the inhaled metaproterenol solution offers important economic as well as therapeutic advantages in therapy with IPPB, which is costly and time-consuming for both the hospital and the patient. Our experience with this new form of metaproterenol suggests that it could become the standard bronchodilator for use in therapy with IPPB.

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