Long-Term Efficacy and Safety of Nebulized Metaproterenol Solution in Bronchial Asthma*

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A 5-percent solution of the sympathomimetic bronchodilator, metaproterenol sulfate (Alupent) was evaluated by comparison with an 0.5-percent solution of isoproterenol in a double-blind crossover study before and after 60 days of inhalation of metaproterenol administered at least four times daily via a hand-bulb nebulizer. Data from tests of pulmonary function obtained in 27 asthmatic patients indicated that metaproterenol sulfate in this dose form surpassed isoproterenol in the duration of effect after seven weeks of continuous administration. Side effects did not necessitate the interruption of metaproterenol therapy. No evidence of the development of tolerance to the drug was shown by any of the patients at the end of the study.

The pharmacologic therapy of reversible obstructive pulmonary disease has been enhanced by the development of derivatives of the basic sympathomimetic catecholamine, β-phenylethylamine.1-3 The drug used in the United States as a reference standard for the effectiveness of bronchodilator drugs is isoproterenol, probably because it has been available for approximately 25 years. Potential problems with the use of aerosol bronchodilator drugs include pharmacologic side effects, toxicity of the products of metabolic breakdown, and toxic effects of the diluting fluids, propellants such as Freons, and preservatives. Also, one can encounter infections from contaminated aerosol apparatus, psychic dependence upon aerosol treatment, and allergic reactions to bronchodilator drugs. The possible development of tolerance and the inadequate medication due to improper techniques of inhalation should be considered.1,2,4,5

This study was performed to determine the effectiveness and safety in human subjects of a form of metaproterenol not yet available in the United States. It has been available as a metered-dose inhaler, as 20-mg tablets and, more recently, as a syrup providing a dosage of 10 mg/5 ml. We studied

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maintained at essentially constant dose levels during the study. Thirteen patients received oral therapy with corticosteroids, 23 patients received oral therapy with bronchodilator drugs, and 15 used oral or parenteral preparations of antihistamines. On the days of the double-blind crossover studies and on the qualifying day prior to admission to the study, no bronchodilator drug was taken for at least eight hours before testing of pulmonary function testing and during the six-hour period of testing.

The drug was administered during a 60-day open-label trial that was preceded and terminated by a two-day double-blind crossover test to compare metaproterenol with isoproterenol and to show if the effects of metaproterenol persisted in long-term therapy. At the beginning of the study (days 0 and 1) and at the end of the study (days 59 and 60), each patient received, in a random sequence unknown to the investigators and approximately at the same time of day, a single test dose of the 5-percent solution of metaproterenol sulfate on one day and a single test dose of the 0.5-percent solution of isoproterenol sulfate on the other day, each test dose consisting of ten inhalations of the test drug via a hand-bulb nebulizer (DeVilbiss 40). This is approximately equivalent to 1.5 mg of metaproterenol sulfate and 0.15 mg of isoproterenol sulfate. After the completion of the initial crossover test, patients were placed on the continuous, open-label treatment schedule consisting of ten inhalations of metaproterenol at least four times daily, but the drug could be taken as often as every four hours if needed.

The following values for pulmonary function were measured on the four crossover testing days: forced expiratory volume (FEV1), FEV1, and maximum expiratory flow rate (MEFR). These measurements were made using a waterless spirometer (Jones Pulmonary), before administration of the test dose (baseline), and 30 minutes, as well as one, two, three, four, and six hours after each test dose.

At two-week intervals during the course of the study and also at the end of the study, global evaluations were made. The following scales were used in consideration of the severity, altitude, and frequency of concurrent medications, the adverse reactions to the inhaled metaproterenol, the patients’ general condition, and the changes in specific symptoms, such as breathlessness, cough, wheezing, and chest tightness, as well as in sputum volume, tolerance of exercise and activity, ability to sleep at night, frequency and severity of asthmatic attacks, sense of well-being, and overall asthmatic pattern. The patients themselves were asked to make a final overall assessment of the degree to which they benefited from the 60 days of treatment.

The five-point scale of ratings used to express the results of these evaluations was as follows: 5, excellent results; 4, good results; and 3, fair results; 2, no change; and 1, worse. The patients’ responses on the two double-blind crossover testing days were similarly rated.

Statistical Analysis

In the statistical analysis of the results, changes from baseline at each time of measurement in the crossover tests were analyzed by a split-plot crossover method (unpublished method, J. L. Cinemara). Differences between mean baseline values on different testing days were analyzed using a modification (to allow for unequal group sizes) of the method presented by Cochran and Cox. For differences between mean changes after administration of metaproterenol and after administration of isoproterenol, the standard error for the t-test, the degrees of freedom, and the 95-percent confidence limits were determined for each drug at each time of measurement. The mean percent changes in FEV1 were analyzed by means of McNemar’s test.
with isoproterenol therapy.

In the final crossover test (only data from the first day could be analyzed), the mean increases at one-half, one, two, three, and six hours after metaproterenol administration exceeded those after isoproterenol administration to a statistically significant degree (P < 0.05), ranging from 23 to 41 percent, as compared with zero to 14 percent after isoproterenol administration. The proportion of patients achieving at least a 15-percent increase in FEV₁ after inhalation of the 5 percent solution of metaproterenol sulfate in the initial test did not differ to a statistically significant degree from the corresponding proportion of patients with such an increase after inhalation of isoproterenol; however, in the crossover test at the end of the two-month open-label treatment period, the proportion of patients showing an increase in FEV₁ of at least 15 percent was significantly greater (P < 0.05 to P < 0.01) after inhalation of metaproterenol than after inhalation of isoproterenol at one-half, two, and six hours. On the other hand, comparison between the initial and final crossover tests for metaproterenol showed that there was no statistically significant difference between the two tests in the proportion of patients achieving an increase in FEV₁ of this magnitude.

**FEV₁.** Inhalation of metaproterenol produced greater increases in FEV than inhalation of isoproterenol at all measurement times in both crossover tests. The differences between the mean changes obtained with the two drugs were not statistically significant in the initial test. As a matter of fact, only the data from the first day of the final crossover test (ie, day 59) could be evaluated, since a statistically significant difference was found between the mean changes over baseline on the two testing days. In the final test, the increases in FEV₁ after inhalation of metaproterenol were significantly greater than those after inhalation of isoproterenol at 30 minutes (P < 0.01) and at one, two, and six hours (P < 0.05).

**MEFR.** The geometric mean changes recorded after inhalation of metaproterenol were at all times greater than those after inhalation of isoproterenol in both crossover tests. A significant period-time interaction during the initial tests permitted analysis of the data from day 0 only. On this day the geometric mean increase obtained after inhalation of metaproterenol was significantly greater (P < 0.05) than that obtained after inhalation of isoproterenol at the five-hour and six-hour intervals. In the final crossover test the geometric mean changes recorded after inhalation of metaproterenol and of isoproterenol, respectively, showed no significant differences.

### Global Evaluations

Evaluation of the overall responses to test doses at the beginning of the period of study yielded mean ratings for metaproterenol (3.7) and isoproterenol (3.6) that did not differ significantly. In the final crossover test the mean score for metaproterenol (3.8) exceeded that for isoproterenol (2.9) to a highly significant degree (P < 0.01).

Interim evaluations of the patients’ responses to continued treatment with the 5-percent solution of metaproterenol sulfate ranged from 3.3 during the last two weeks (weeks 7 and 8) to 4.3 during the third two-week period (weeks 5 and 6). The mean ratings for the first and third biweekly periods were significantly higher (P < 0.01) than the mean for the last two-week period.

The patients' own final appraisal of their response to 60 days of metaproterenol therapy yielded a mean score of 4.4. This came very close to our medical evaluation (4.2).

### Safety

No patient complained of any adverse reaction other than an unusual taste after the test doses of metaproterenol. One patient complained of chest tightness after a test dose of isoproterenol.

During the 60-day open trial, 13 of 27 patients occasionally complained of mild symptoms that might possibly be due to the metaproterenol used in the study. Cough was experienced by four patients, headache by three, and mild tachycardia by three; no reaction was severe enough to require the individual to stop using the drug at any time during the study. When the patients with headache and tachycardia were instructed to pause for several breaths between inhalation and to breathe slowly during each dose of ten inhalations, these symptoms disappeared. No significant changes in pulse rate or in systolic or diastolic blood pressure occurred during the study with inhalation of either metaproterenol or isoproterenol. No remarkable changes in the findings from physical examination occurred during the 60-day period of treatment. No abnormal results were obtained on laboratory tests, with the exception of an elevated serum concentration of calcium in one patient at the end of the study; when checked several weeks later, the level was normal again, and the elevation was probably not due to administration of the drug.

### Discussion

During this 60-day trial of a 5-percent solution of metaproterenol sulfate administered by hand-bulb nebulizer, no significant toxicity or side effects oc-
curved. All patients with bronchial obstruction benefited from the trial, with several patients being able to decrease or stop therapy with other medications. Although tachyphylaxis or tolerance to β-sympathomimetic aerosols has been reported, none of our patients showed any evidence of it. On the basis of the studies of pulmonary function and the evaluation by both patient and physician, metaproterenol was found to be continuously effective and markedly superior to isoproterenol.

While few controlled long-term studies comparing the effectiveness of metaproterenol and isoproterenol have been reported, Chervinsky and Belinkoff found that metaproterenol aerosol produced a more prolonged and consistent bronchodilating effect than isoproterenol in a double-blind crossover study of 14 patients with bronchoconstrictive disease before, during, and after a two-month course of therapy with each drug. Metaproterenol maintained its effect over this prolonged period not only in terms of total improvement in pulmonary function but also in terms of duration of action. Although Chervinsky and Belinkoff used metered-dose inhalers, their results agree with ours. A recent review by Leifer and Wittig of the experience with β-sympathomimetic aerosols in the treatment of asthma reaffirms that the resorcinol structure of metaproterenol with the terminal isopropyl group increases β2-adrenergic selectivity and duration of action by comparison with isoproterenol or isopraedrine.

The results of our study show that long-acting metaproterenol is at present the β-adrenergic drug of choice in the inhalation treatment of acute or chronic bronchospastic disease, at least until other, even more effective bronchodilator drugs become available in the United States.

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Medical Officers of Ancient Rome

The Roman military system was made up of some twenty-five legions. Each legion contained ten cohorts, and perhaps 7,000 men served in a cohort. To each cohort was assigned a physician. The troop assigned to serve as police and firemen each had their own unit physician. Julius Caesar, noting the importance of physicians, granted citizenship to any doctor who would practice in Rome, in order to attract physicians to the city. These military physicians were given freedom from combat duty and were ranked as officers, although most of them were equal to noncommissioned officers in other respects.


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