training and standardization of exercise response. Bronchodilators were excluded for eight to 12 hours, cromolyn sodium for two weeks, and anyone on corticosteroids was consistently tested on either medication days or on "off" days. Any subject who was obviously wheezing was asked to return on another day for testing.

The results were compared by an analysis of variance technique.

RESULTS

The results of part 1 are summarized in Figure 1. Following exercise during standardization runs, all pulmonary functions decreased, but changes in FVC were smaller (8 percent) than either FEV₁ (25 percent) or FEF₂₅₋₇₅ (46 percent). Fenoterol premedication inhibited the response while neither ephedrine nor placebo had a significant effect (FVC: F = 5.29, P = .01; FEV₁: F = 5.64, P = .01; FEF₂₅₋₇₅: F = 16.1, P < .01).

As shown by the FEV₁ changes in Figure 2, fenoterol suppression of exercise-induced asthma persisted for five hours. The changes in part 2 seen at 1, 3 and 5 hours after the three drugs was very similar to those seen in part 1 (P < .01). Of the 12 subjects participating in both parts, eight had the same suppression, or lack of it, on both trials with the medications.

The suppression of exercise-induced asthma by fenoterol is similar to that seen with other oral adrenergic agonists; ephedrine has also been shown to be ineffective by others. However, this protocol was not designed to evaluate bronchodilation, since pulmonary functions were not measured before medications were given, and ephedrine has been shown by others to be an effective bronchodilator although somewhat less effective than the newer selective β₂ agonists. When pre-exercise pulmonary functions were compared, the small differences between placebo and active agents were not statistically different (FVC: F = 1.26, P = .3; FEV₁: F = 1.15, P = .3; FEF₂₅₋₇₅: F = 0.361, P = .4).

Despite the similar degree of mild bronchodilation produced by the two agonists, there was a clear difference in their ability to inhibit exercise-induced asthma. This suggests that exercise-induced asthma may be modulated by adrenergic agonists through their effects on tissues other than bronchial smooth muscle, such as mast cells or skeletal muscle. Future studies are needed to better define these mechanisms in order to allow more rational use of adrenergic agents and perhaps to direct development of agents with more selective activity.

ACKNOWLEDGMENTS: We would like to gratefully acknowledge the technical assistance of Patsy Beasley, R.N., and the statistical analysis of Nancy Walrath of Boehringer Ingelheim Ltd.

REFERENCES

4 Bierman CW, Pierson WE, Shapiro GC: The pharmacological assessment of single drugs and drug combinations in exercise-induced asthma. Pediatrics 56 (suppl):919, 1975

Controlled Assessment of Beta₂ Adrenergic Therapy for Childhood Asthma

Constantine J. Falliers, M.D., F.C.C.P.

Single-entity sympathomimetic bronchodilators are often the primary therapeutic modality for asthma in children, especially when avoidance of the systemic adverse effects of the methyldxanthines and the corticosteroids is of major concern. Metaproterenol, a recognized beta₂ adrenergic agonist resistant to deactivation by catechol-o-methyl-transferase, was the object of two double-blind studies in Denver, among children 6 to 16 years of age, with a confirmed diagnosis of variable obstructive airways disease.

In the first study, 29 patients were given 10 mg metaproterenol orally in the form of Alupent syrup containing 10 mg/5 ml. Their responses were compared to the effect of equivalent doses (5 ml) of two common, commercially available preparations, Quadrinal and Brondecon, given in random sequence, consistently in the early morning. Quadrinal is known to contain ephedrine HC1 12 mg, theophylline calcium salicylate 65 mg (equivalent to 32.5 mg anhydrous theophylline), KI 180 mg and phenobarbital 12 mg per 5 ml. An equal volume of Brondecon contains 100 mg oxtiphrphine (equivalent to 64 mg anhydrous theophylline) and guaifenesin 50 mg. Spirometric measurements showed a statistically significant superiority of metaproterenol, over the control preparations at 90 minutes after drug administration. Noticeable differences in terms of FEV₁ and FEF₂₅₋₇₅ were already evident at 30 min after ingestion of the medication, even though these responses were not as consistent as to attain significance statistically. No side effects were noted.

The second study aimed at ascertaining the responses of 40 pediatric patients to five different doses of metaproterenol sulfate 5 percent solution, administered via an IPPB aerosol. Incremental doses of 5, 10, 12.5, 15 and 20 mg (expressed in volume units these were 0.1, 0.2, 0.25, 0.3 and 0.4 ml) of metaproterenol solution were compared, in random order, to isoproterenol HC1 1:200 solution, 0.25 ml (1.25 mg), all diluted with water to a total nebulized volume of 2.0 ml. Treatments were administered at least 48 hours apart and always in the early
morning. A placebo aerosol of 2.0 ml was also administered, in random order, between treatments. Spirometric and plethysmographic measurements, as well as physical examinations over a six-hour span following medication, revealed a distinct dose-response relationship for metaproterenol aerosol inhalations and a statistically significant superiority to placebo (Fig 1, 2). There was, as was to be expected (Falliers and Cato: Excerpta Med 300: 103, 1973) a measurable improvement after placebo administration, probably attributable to circadian rhythmic changes and to the restful clean laboratory environment. In no case, however, did these changes approximate the airways responses to the medication given. Already 5 min after aerosol treatment with the active solutions, FEV₁ increased by 5-12 percent of baseline and showed a peak between 30 and 60 min after treatment. Except for metaproterenol 5 and 10 mg, the improvement in FEV₁ was maintained at or above the 15 percent level for four hours or more after treatment. The dose of metaproterenol most closely approximating the effect of the control drug, isoproterenol was between 0.25 and 0.40 ml, i.e., 12.5 to 20 mg. The 0.3 mg dose was selected for a more detailed comparison with isoproterenol and placebo, in terms of all the spirometric and plethysmographic data obtained. FEV₁ and FVC measurements showed significant (greater than 15 percent) improvement before or at 30 min after aerosol administration and, like FEV₁, a sustained effect for four hours, or longer, in most cases. Plethysmographic measurements, expressed as specific airways resistance (Raw × V₅₀ or SRaw) showed a better than 10 percent reduction when placebo aerosols were inhaled (again, most likely a physiologic circadian, or environmentally-induced change) and a 20-28 percent improvement following isoproterenol and metaproterenol 15 mg aerosol treatment (Fig 2).

No distressing subjective side effects were noted, with occasional complaints being limited to irritability, diz-
The Effect of Metaproterenol in Chronic Asthmatic Children Receiving Therapeutic Doses of Theophylline

Stanley P. Galant, M.D.

The purpose of this study was to determine whether metaproterenol could improve pulmonary function in asthmatic children who were receiving therapeutic doses of theophylline. The study was done in conjunction with Drs. Charles E. Groncy, Sarvalakshmi Duriseti and Lawrence Strick. All patients were taking an around-the-clock dose of theophylline adequate to give a peak serum theophylline level of at least 10 micrograms per ml.

The 12 boys and 5 girls, ranging from 7 to 14 years, had a mean age of 9.7 years. The measurements evaluated included the pulmonary function tests FEV₁, MMEFR (FEF₂₅₋₇₅%), and FVC. Pulse and respiratory rate, blood pressure and plasma theophylline done by high pressure liquid chromatography were also performed. In order to fulfill the major criteria of having each child's baseline pulmonary function FEV₁ ≤ 75 percent of predicted on each study day, we withheld all medication for 12 hours prior to baseline measurements. After these baseline measurements were made the patient was given his usual theophylline dose, plus metaproterenol or placebo. Children under 60 pounds received one teaspoon (10 milligrams), whereas children above 60 pounds received two teaspoonsful.

After the medication was given, the above measurements were repeated at 1.5 hours, and then hourly for six hours. A plasma theophylline level was determined at 1.5 and six hours. After that day of study, the patient continued to take theophylline plus either metaproterenol or placebo every six hours, for the next two days. On day 4 the measurements were repeated as on day 1. This was followed by a two-day washout period, at which time the patient took only theophylline. After the washout period the study was repeated using the alternate drug in the same manner as the first drug. Test drugs were administered in a double-blind crossover design.

We found that at 1.5 hours there was a statistically significant difference (P < .05) in percentage of increase of FEV₁ above baseline between the metaproterenol and placebo of 17. The difference of 15 percent at two hours showed a P value .05 < 0.1. The metaproterenol effect on MMEFR was even more striking with increases over placebo of more than 80 percent at 1.5 hours and two hours (P < .0025) and 30 percent at three and four hours (P < .05).

The mean peak theophylline level for both metaproterenol and placebo treatment days was 10 μg/ml, while the trough was 6 μg/ml. No increase in adverse effects using the metaproterenol-theophylline combination compared to the placebo-theophylline was observed.

In conclusion, we have found that metaproterenol added to moderate doses of theophylline produces significant improvement in large and small airway function above that seen with theophylline alone in asthmatic children without causing increased side effects.

Management of Obstructive Airways Disease in Pediatric Patients with New Beta₂ Sympathomimetic Bronchodilators

Meyer B. Marks, M.D.

Metaproterenol Administration in Children Under Six Years Old with Asthma

To determine the safety and efficacy of treatment with metaproterenol in children under six years, 23 asthmatic pediatric patients between the ages of 1% and six years were selected. Nine showed mild symptoms; nine had moderate symptoms; and five had severe asthma. Patients with significant cardiovascular, renal, hepatic or metabolic disease, as well as those with known intolerance to sympathomimetic agents were excluded.

Patients were randomly assigned by order of admission to either metaproterenol sulfate (Alupent) or placebo in a two-month, double-blind crossover study. Concurrent medication during the study was recorded. Ephedrine and ephedrine-containing preparations and cromolyn sodium, as well as other investigational drugs, were excluded from the study. Xanthisines, expectorants, steroids, antibiotics, antihistamines, sedatives, and tranquilizers were allowed when necessary.

For patients aged four to six years, Alupent syrup was administered in 5 mg (2.5 ml) doses qid. The same liquid volumes were used for placebo. The patients were treated for one month with either Alupent syrup or placebo and crossed over for another month.

The physician's and mothers' global evaluations of patient response were obtained every two weeks. Physician's evaluations were recorded on the following: wheeze, cough, dyspnea, sleep pattern, and patient's color. Hospital visits were recorded.

Reprint requests: Dr. Marks, 333 Arthur Godfrey Road, Miami Beach 33140.