The Development of Drug Tolerance During Long-term Beta₂-Agonist Bronchodilator Therapy

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In a series of double-blind studies we have conducted involving many of the newer beta, adrenergic drugs, a fairly consistent pattern has emerged which indicates that repetitive doses of these drugs will result in only a relatively minor decrease in their initial effect, but a relatively marked decrease in the duration of effect.

In a study comparing metaproterenol and isoproterenol over a two-month period, the percentage of improvement in FEV₁ noted on day 1 of the trial was almost matched on day 60, but the four-hour duration noted on day 1 decreased to less than three hours on day 60. The patient on isoproterenol fared even worse; the initial effect on day 60 was markedly diminished from that on day 1 and the duration was less than an hour.

In another study in 28 asthmatic patients utilizing 5 percent metaproterenol solution in a hand-bulb nebulizer and using a relatively large dose of ten sprays four times a day for a 60-day period, it was noted at the conclusion of the study that there was still a good response to metaproterenol, but the duration of response was less than at the start of the study.

In a similar study using metaproterenol solution administered by IPPB three to four times a day over a 90-day period persistence of the initial response was noted on day 90, but the duration again was markedly decreased (Fig 1).

In a study of 33 asthmatic patients comparing ephedrine tablets and metaproterenol tablets over a 60-day period, there was a marked trend toward a decrease in both initial response and duration of response to metaproterenol after 60 days. This study was done as a double-blind cross-over test, but when we analyzed the data, we found that the baselines had changed so that it was impossible to evaluate the crossover data with any statistical significance. An interesting point was noted, however. Although response to ephedrine was poor in the initial group studied, the group on metaproterenol for 60 days and then placed on ephedrine showed an excellent response to ephedrine. This response was lost, however, when tested at 30 and 60 days. This would seem to indicate that effects other than refractoriness of beta-adrenergic receptors was involved as these patients had been on metaproterenol with only a three-day washout period before they were placed on ephedrine.

To confuse us further, a study of metaproterenol syrup in a pediatric population showed an excellent duration
greater increase in FEV1, within 30 minutes after inhaling 0.15 mg (two breaths) of isoproterenol from a metered dose inhaler (MDI), were selected. Using a randomized double-blind approach, 14 subjects were treated with 0.15 mg isoproterenol MDI (two inhalations) and 11 with 0.40 mg fenoterol MDI (two inhalations) for 90 days after a one-month period of observation. The criteria for selection of the subjects, control of concomitant medications, frequency and methods of testing, observations made and methods of analysis are identical to those described in the opening statement of the workshop.

During the month preceding use of the MDI, all subjects requiring continuous medication for control of attacks received oxtriphylline, which was subsequently continued at the same dose throughout the study. Two persons in each group received ephedrine 24 mg three or four times daily. One person in each group received 0.15 mg isoproterenol MDI tid. No other adrenergic drugs were used during the month preceding the study. All testing was done at the same time of day. The age, race, sex, and physician's impression of the severity of the asthma was not significantly different in the two groups. Duration of asthma for those receiving fenoterol MDI was 18 years and was 15 years for the isoproterenol group. During the 90-day treatment period, one subject receiving fenoterol used one aminophylline suppository and five received daily prednisone. Among those receiving isoproterenol, one subject required one dose of intramuscular epinephrine and three received prednisone. Cromolyn was used throughout the pre-treatment and treatment period by one person receiving fenoterol.

**Efficacy and Side Effects of Fenoterol Compared with Isoproterenol Administered by Metered Dose Inhalers in Asthma**

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Twenty-five patients with asthma, with reversible airways obstruction demonstrated by a 20 percent or

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![](image.png)

**Figure 1.** Mean change from baseline FEV1 after treatment with fenoterol or isoproterenol.

![](image.png)

**Figure 2.** Mean percent changes in FEV1 on days 1 and 42 after administration of 5 mg fenoterol or terbutaline in 15 patients each.

Of effect at the end of 60 days. The response to metaproterenol at the end of 60 days was just as good as the response at the onset of the study. Whether this is due to the fact that this was a pediatric population and the drug is metabolized differently or whether other factors are involved is not clear.

Of great interest is our most recent study comparing the effectiveness of terbutaline and fenoterol tablets. In this instance, over a 42-day period, there was no apparent decrease in either initial effect or duration of effectiveness with either drug (Fig 2). This would indicate that the mode of administration may be of considerable significance and the larger side chains which characterize the configuration of these drugs significantly decrease the rate of metabolism by body enzymes and/or their ability to be bound by albumin.

The whole question of drug refractoriness may be academic as far as clinical utilization of these drugs is concerned. In a multifaceted disease such as asthma it is naive to expect complete control through stimulation of beta-adrenergic receptors. Most likely there are multiple mechanisms which result in the decreased benefit frequently seen with these drugs after prolonged use. In most cases, this is due more to a change in the patient’s disease than to diminished effectiveness of the drug.

**Figure 1.** Mean change from baseline FEV1 after treatment with fenoterol or isoproterenol.