Safety and Effectiveness of Terbutaline in Children with Chronic Asthma*

Librada M. Manaligod, M.D.;** Uma D. Gavani, M.D.;**  
John S. Hyde, M.D., F.C.C.P.;† and Saroj Khurana, M.D.**

The bronchodilator and cardiovascular effects of orally administered tablets containing 2.5 mg of terbutaline and 25 mg of ephedrine were compared in a double-blind parallel manner in children (ages 7 to 14 years) weighing 25 to 50 kg (44 to 110 lb). Both drugs produced bronchodilation within one-half hour, and this effect was maintained up to six hours, with a peak between two and three hours. Small increases in the pulse rate were measured within an hour following administration of both drugs. No significant variation was noted in blood pressure. No adverse effects (including tachyphylaxis and tremor) were observed for either drug during a three-month period. Both bronchodilator agents were shown to be equally effective in the dosages used. Terbutaline is a safe bronchodilator drug when administered orally in 2.5-mg doses for children with chronic asthma in this range of ages and weights, with minimal cardiovascular side effects and effective bronchodilation.

During the past ten years, several attempts have been made to find new orally active drugs with sustained and maximal bronchodilator responses and minimal side effects. Some sympathomimetic agents relieving bronchospasm are known to produce cardiovascular side effects by stimulating both $\alpha$-adrenergic and $\beta$-adrenergic receptors.1 Lands et al2 further subdivided $\beta$-adrenergic receptors into a $\beta_1$-adrenergic group on cardiac muscle and a $\beta_2$-adrenergic group on bronchial and vascular smooth muscle. Of importance is the fact that some side-chain modifications of catecholamines yielded $\beta_2$-adrenergic selective stimulants.3 Recent studies on the metabolism of isoproterenol, which has a relatively short duration of action, indicate that inhaled isoproterenol diffuses into the bloodstream and is actively transported to cells, where it is activated by catechol-o-methyl transferase.3 Both the mechanism of transport and the metabolism are specific for catechol. Replacing the catechol function of catecholamine with resorcinol produces compounds which retain activity at $\beta$-adrenergic receptors but resist rapid degradation in the body. Subsequently, a number of orally effective noncatechol $\beta_2$-adrenergic stimulating agents were developed, including terbutaline.4,5

Terbutaline, the structure of which is shown in Figure 1, is a sympathomimetic amine which is relatively selective for $\beta$-adrenergic stimulation of the $\beta_2$-adrenergic receptors, including those located in bronchial smooth muscle. Replacement of the catechol group by resorcinol and the introduction of the N-alkyl substituent has resulted in terbutaline's longer duration of action and greater selectivity for $\beta_2$-adrenergic receptors. Terbutaline has a longer duration of action than other $\beta_2$-adrenergic agonists (for example, metaproterenol) following subcutane-
ous injection, oral administration, or inhalation. This effect was ascribed to the diminished susceptibility to the action of monoamine oxidase because of the larger N-alkyl substituent. Significant and long-acting bronchodilator effects of orally administered terbutaline have been demonstrated in adults and children by clinical trials in Europe and the United States.

The purposes of the present study are (1) to compare in children the efficacy of single orally administered doses of terbutaline and ephedrine, (2) to determine whether such efficacy could be sustained upon continued daily treatment, (3) to determine if this treatment is accompanied by an increase in the incidence or severity of adverse effects.

**Materials and Methods**

**Design of the Study**

The study was conducted in a double-blind parallel manner with 32 children divided randomly into two groups. One group of 17 children (15 boys and two girls) received 2.5 mg of terbutaline sulfate (Bricanyl) three or four times daily, and the other group of 15 children (13 boys and two girls) received 25 mg of ephedrine sulfate three to four times daily. Treatment was given at intervals of six to eight hours, with meals and at bedtime. Both groups received this treatment during a 12-week period. Cardiopulmonary and other possible effects of treatment were monitored carefully during this course.

**Subjects**

The children in the study were selected according to the following criteria: subjects between the ages of 7 and 14 years with chronic bronchial asthma were given doses of commonly used bronchodilator drugs every six hours. Their weights ranged from 20 to 50 kg (44 to 110 lb), and they did not have diabetes or cardiac disease. The forced expiratory volume in one second (FEV₁) and the peak expiratory flow were 70 percent or less of the predicted value for the subject's age, height, and sex. Also, an increase of at least 15 percent in the FEV₁ and PEF was demonstrated for each subject following the inhalation of isoproterenol. Written informed consent was obtained on all subjects from parents or guardians after the nature of the procedures had been fully explained.

**Procedure**

Prior to the beginning of treatment, there was a two-week period of observation. During that period the subjects were seen twice in the clinic at Presbyterian-St. Luke's Hospital (at two weeks and at one week before beginning clinical trials). During those two control visits, the subjects participated in the same evaluations as they were going to during the visits to the clinic while receiving their tested drug. After the period of observation, therapy with their routine bronchodilator medication was discontinued. On the third visit, designated as visit 1, the tested drug was started in a coded randomized manner. Both the subject and the investigator were unaware of which drug was given.

There were five visits to the clinic during the period of treatment. These were designated as visits 1, 2, 3, 4, and 5, representing the first day of treatment and subsequent visits at 3, 4, 8, and 12 weeks of treatment, respectively. On the days of the visits to the clinic, the subjects did not receive medication for at least eight hours prior to the period of testing in the morning, and the morning doses of drug were given by the investigator.

Prior to the start of the evaluation of the bronchodilator drug and again after the 12-week period of treatment with terbutaline or ephedrine, ophthalmologic examinations and chest x-ray films were obtained. For each child, complete blood cell counts and levels of electrolytes, glucose, alkaline phosphatase, blood urea nitrogen, and cholesterol were determined on the first day and after 4 and 12 weeks of treatment. Urinalyses were also performed during these same visits to the clinic. Full 12-lead electrocardiograms were obtained at the beginning and end of each day of evaluation.

On each day at the clinic, the following measurements were observed and recorded: heart rate; blood pressure; the pattern of the tracing from lead 2 on the ECC; FEV₁; PEF; and physical findings. These determinations plus any side effects were monitored 30 and 15 minutes before administration of the drug and at 0.5, 1, 2, 3, 4, 5, and 6 hours after administration. The patient's progress at home was recorded in logs recording symptoms and treatments, which were kept by the parents.

**Concomitant Medication**

Patients receiving corticosteroids were allowed to continue therapy with this medication through the study. In case of an acute asthmatic attack or an acute episode of shortness of breath, an aerosol bronchodilator drug or injectable theophylline was administered.

**Statistical Analysis**

Five male subjects had incomplete sets of data and were not included in the analysis of results. The data were analyzed using the Hotelling $t^2$-test described by Lindquist.

**Results**

**Pulmonary Function**

For all of the visits to the clinic for treatment, statistical analysis of the mean changes in the percentage of predicted PEF and FEV₁ obtained before and after treatment revealed a significant improvement in pulmonary function, as reflected by an increase in both forced expiratory volumes ($P < 0.05$); however, the analysis did not show any difference in the responses to the two drugs. No evidence of tachyphylaxis was noted with continuation of the treatment. In observations of PEF and FEV₁ (Table 1), there was a peak increase in the mean percentage of predicted PEF from 50 to 59 percent for terbutaline at two hours and from 68 to 73 percent for ephedrine at four hours; however, the effect of the drugs was sustained for the next five to six hours. The peak increase in the percentage of predicted FEV₁ occurred for terbutaline (72 percent) at two hours and for ephedrine (86 percent) at four hours and was sustained up to six hours.

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Table 1—Mean Changes in Percent of Predicted PEF and FEV1

<table>
<thead>
<tr>
<th>Hours after Dose</th>
<th>Predicted PEF (%)</th>
<th>Predicted FEV1 (%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Ephedrine</td>
<td>Terbutaline</td>
</tr>
<tr>
<td>0</td>
<td>68</td>
<td>50</td>
</tr>
<tr>
<td>0.5</td>
<td>69</td>
<td>54</td>
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<td>56</td>
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<td>6</td>
<td>67</td>
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Cardiovascular and Other Functions

Treatment was not associated with any changes in either systolic or diastolic blood pressures. Variations in both measurements were not statistically significant (Table 2). The heart rate showed significant peak increases of 8 to 10 beats per minute at one to two hours after administration for both drugs, and these changes were sustained through the six-hour period. The chest X-ray films and ophthalmologic examinations failed to reveal any consistent or obvious treatment-related changes. Analysis of electrocardiographic strips did not reveal any alterations in rhythm or morphologic findings. Results of examinations of blood and urine remained within normal limits.

Discussion

Certain patients who have theophylline-dependent chronic asthma tend to need added doses of sympathomimetic drugs (orally or aerosol) over a period of time. Based on studies in animals, as well as humans, resistance of the bronchial receptors was suspected to develop against the long-acting bronchoselective sympathomimetic agents,12 however, our results showed a consistent increase in forced expiratory volumes and did not support this hypothesis.

Tremor was the main side effect of oral therapy with terbutaline in adult patients.5,12 In addition to the bronchial smooth muscle, skeletal muscle also has β2-adrenergic receptors. In susceptible patients the clinical response to increased levels of cyclic 3'5' adenosine monophosphate in skeletal muscle is physiologic tremor, usually noted in the hands. This tremor is an extension of the β2-adrenergic action of terbutaline and is not a central action of the drug. This has been shown by experiments in which a β-adrenergic antagonist, propranolol, blocks the effect of terbutaline in skeletal muscle.13 The presence of tremor in patients is an indication of marked production of cyclic 3'5' adenosine monophosphate, which should assure easier breathing.

An important characteristic of therapy with terbutaline is that tremor tends to diminish and even disappear, sometimes within a few days and often within two to three weeks; but while the tremor diminishes, the bronchodilator effect of terbutaline continues at significantly high levels, as reported by Formgren.12 None of our children developed tremor during the period of treatment with terbutaline or ephedrine. The hyperglycemic responses reported following administration of β-adrenergic agonists were not found among our patients.

The small but significant increase in heart rate among our patients agrees with some previous reports of tachycardia following administration of terbutaline.14,15 None of our children demonstrated the decrease in diastolic blood pressure following administration of terbutaline that has been reported by others.16,17 Tachycardia and a drop in diastolic blood pressure following administration of terbutaline may be a baroreceptor-mediated reflex response to decreased systemic vascular resistance. This could be due to direct cardiac stimulation.17

Previous studies reported that a bronchodilator response to administration of terbutaline was earlier in onset, greater in magnitude, and more prolonged in duration than that of ephedrine,5,18 but our study showed that both drugs produced similar bronchodilator responses with equal magnitude and duration of action. This dissimilarity could be due to higher orally administered dose (namely, 5 mg of terbutaline used by previous investigators in adults, compared to 2.5 mg of terbutaline sulfate used by...
our children). The higher incidence of the undesirable side effects (mainly palpitations and tremors) also was associated with the higher dosage of terbutaline (5 mg).18

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