STUDIES OF NEW SYMPATHOMIMETIC BETA-RECEPTOR STIMULATING DRUGS IN ASTHMATIC PATIENTS. I. THE BRONCHODILATOR AND CIRCULATORY EFFECTS OF SUBCUTANEOUS TERBUTALINE

By J. L. Da Costa and B. K. Goh

SYNOPSIS

Terbutaline (Bricanyl, AB Astra, Sweden) a new beta₂ adrenoceptor stimulator was given subcutaneously to 14 asthmatic patients. At a dosage of 0.5 mg, it produced a rapid peak effect within half an hour and this persisted for 2 hours giving a 'ceiling effect'. Furthermore, significant bronchodilatation was still present up to 4 hours after drug administration. Palpitations were noted in only 3 of the 14 patients studied though significant tachycardia was recorded up to 1 hour after terbutaline. It was concluded that terbutaline is a valuable broncholytic drug in acute asthma.

Sympathomimetic amines have been widely used in the treatment of bronchial asthma since Barger and Dale (1910) first used adrenaline as a bronchospasmolytic agent. Following this, ephedrine (Chen and Schmidt, 1923), isoprenaline (Konzett, 1940) and methoxypenamine (Curry et al, 1948) were introduced. However, the main disadvantages of these earlier drugs was their short-lived bronchodilatory effect and the tendency to produce undesirable cardiovascular effects: distressing palpitations with tachycardia and an increased pulse amplitude, intensification of pre-existing hypoaemia (often present even in moderate asthma) by increasing the ventilation-perfusion imbalance in the lungs (Knudson and Constantine, 1967; Tai and Read, 1967). In the hypoxic myocardium this may induce ventricular irritability and fatal arrhythmias (Shapiro and Tate, 1965; Speizer et al, 1968).

Lands et al. (1967) established that cardiac stimulation and bronchodilatation were mediated through the beta₁ and beta₂ adrenoceptors, respectively. Attempts have therefore been made to isolate more selective beta₂ adrenoceptor-stimulating agents with little cardiovascular effects and a more prolonged duration of bronchodilator action. Early ones were isoetharine (Siegmund et al., 1947; Lands et al., 1966; Thiringer et al., 1971) and orciprenaline (Engelhardt et al., 1961). Isoetharine, however, had only a brief effect perorally while orciprenaline still produced considerable cardiac side effects (Kennedy and Simpson, 1969).

Recently more specific beta₂ adrenoceptor stimulators have become available. Salbutamol (Hartley et al., 1968), an isoprenaline derivative, has been shown to be an effective bronchodilator with minimal cardiovascular effects (Choo-Kang et al., 1969; Riding et al., 1970; Da Costa and Goh, 1972). Terbutaline (Bricanyl, AB Astra) is another selective beta₂ adrenoceptor stimulator (Arner, 1970; Persson et al., 1970 and Formgren, 1970). The aim of this study was to demonstrate its broncholytic action and observe if it produced any cardiovascular side effects in asthmatic patients.

MATERIALS AND METHODS

Fourteen patients (10 males and 4 females) with bronchial asthma were investigated. Their mean age was 32 years (range 18-68 years). The reversibility of their airways obstruction was tested the day before the start of the trial. After two inhalations of orciprenaline aerosol (1.5 mg. orciprenaline) they had to show an increase in peak expiratory flow rate (PEFR) of at least 15 per cent. No other bronchodilator drugs were given later than 10 hours before the start of the trial. Six patients who were on oral steroid therapy continued to receive the same dose during the trial.

The tests were performed between 9 a.m. and 3 p.m. A subcutaneous dose of 0.5 mg. terbutaline was injected slowly over 3 minutes. PEFR was recorded using a Wright's peak flow meter (Wright et al., 1959) before, and at 15 and 30 minutes and 1, 2, 3, 4, 5 and 6 hours after the injection. All
measurements were made with the same apparatus while the subjects were seated. The best value of five measurements at each time period was used for the calculations. The heart rate was also measured at the same periods before and after each injection and any side effects experienced by the patients were also recorded. The test was discontinued if the PEFR fell below the baseline during the observation period. This was done because it has been our experience and that of other workers (Mattila and Muittari, 1966) that patients may be distressed with increasing bronchospasm after repeated PEFR measurements when the bronchodilator effect has worn off.

Student's t-test was used for statistical analysis of the results.

RESULTS

Tables I and II give the PEFR and heart rate in 14 asthmatic patients up to 5 hours after administration of 0·5 mg. terbutaline subcutaneously. As patients did not carry on the study after this period due to sub-baseline PEFR values, statistical analysis was not carried out beyond the 5-hour period.

Terbutaline was found to have a rapid onset of action reaching a peak effect within 30 minutes. This was maintained for 2 hours producing a 'ceiling effect' (Fig. 1). The increase in PEFR was highly significant up to 3 hours after terbutaline. The increase was significant at 4 hours but was seen to fall steadily and though the mean change at 5 hours was +19·3 L/min. this increase was not statistically significant.

Three of the 14 patients tested complained of palpitations after terbutaline and the heart rate (Table II) showed a significant (P < 0·01) increase up to 1 hour after drug administration but fell steadily thereafter to baseline levels (Fig. 2).

DISCUSSION

Terbutaline 0·5 mg. given subcutaneously, has been found in this study to produce rapid and sustained bronchodilatation for up to 4 hours after drug administration. An added advantage was that this dosage could be given rapidly (3 minutes) without significant cardiovascular side effects. Although the heart rate was significantly raised up to 1 hour after administration of the drug it produced palpitations in only 3 out of the 14 patients studied.

Similar results were reported in earlier studies by Arner et al (1970) and Arner (1970). Arner, however, recommended the suboptimal dose of 0·25 mg. terbutaline as it produced effective bronchodilatation with negligible side effects. Subcutaneous dosages of 0·25 mg. were furthermore shown by Hedstrand (1970) to reduce the expiratory flow resistance and resistive work of breathing for up to one hour after administration while Da Costa and Hedstrand (1970) demonstrated that at this dosage there was no significant intensification of hypoxaemia. However, this dose of terbutaline has been shown to have a shorter duration of action than 0·5 mg. adrenaline (Nõu, 1971). 0·5 mg. terbutaline on the other hand has a significantly longer duration of action than 0·5 mg. adrenaline (Da Costa and Goh, 1973).

It would thus appear that terbutaline is an effective bronchodilator with a rapid and prolonged duration of action and little cardiovascular side effects even at the optimal bronchodilator dosage of 0·5 mg.

ACKNOWLEDGEMENTS

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### TABLE I

**PEAK EXPIRATORY FLOW RATE (PEFR)**

Mean values in 14 asthmatic patients before, and the mean values of the individual changes 15 and 30 minutes, and 1, 2, 3, 4 and 5 hours after subcutaneous injection of terbutaline.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg.)</th>
<th>PEFR (l/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Value</td>
<td>15 mins.</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>0.5</td>
<td>288.9 (27.1)</td>
</tr>
</tbody>
</table>

\* = p<0.05  
\** = p<0.01  
\*** = p<0.001

Mean = Mean
Standard error of mean given in parenthesis.

### TABLE II

**HEART RATE**

Mean values in 14 asthmatic patients before, and the mean values of the individual changes 15 and 30 minutes, and 1, 2, 3, 4 and 5 hours after subcutaneous injection of terbutaline.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg.)</th>
<th>HEART RATE (beats/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Value</td>
<td>15 mins.</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>0.5</td>
<td>88.9 (4.0)</td>
</tr>
</tbody>
</table>

\* = p<0.05  
\** = p<0.01  
\*** = p<0.001

Mean = Mean
Standard error of mean given in parenthesis.
REFERENCES


