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 $beta_2$ adrenoreceptor 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 methoxyphenamine (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 hypoxaemia (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 $beta_1$ and $beta_2$ adrenoreceptors, respectively. Attempts have therefore been made to isolate more selective $beta_2$ adrenoreceptor-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 $beta_2$ 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 $beta_2$ 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

Department of Medicine, University of Singapore, Medical Unit I, General Hospital, Singapore.

J. L. DA COSTA, A.M., M.D.(S'pore), M.R.C.P.(G), F.R.C.P.(Ed.), F.C.C.P.(USA), Associate Professor.

B. K. GOH, Laboratory Technician.

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.

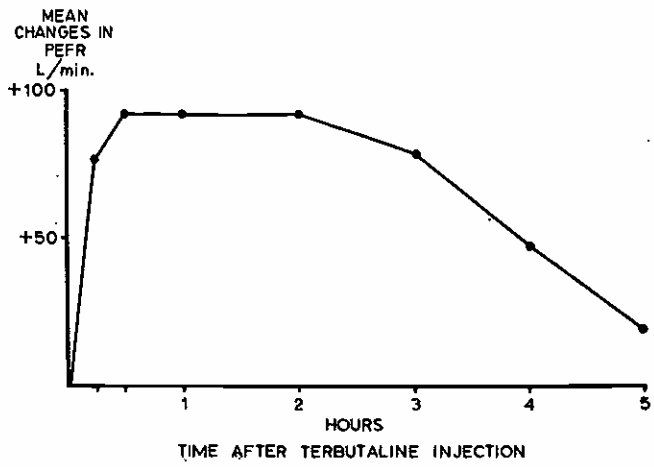

Fig. 1. Peak expiratory flow rate (PEFR) (1/min.). Mean changes in PEFR at specified time intervals after subcutaneous injection terbutaline 0·5 mg. (n = 14).

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

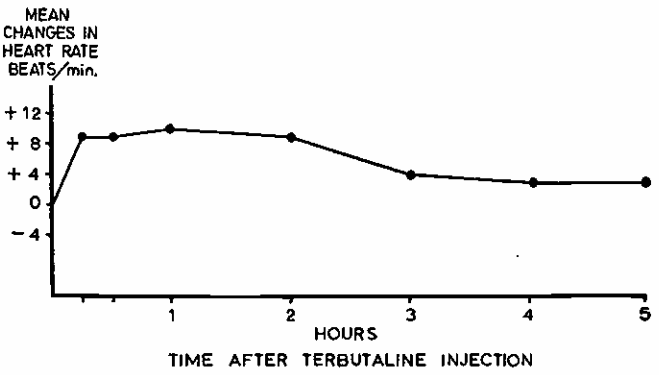

Fig. 2. Heart rate (beats/min.). Mean changes in heart rate at specified time intervals after subcutaneous injection terbutaline 0·5 mg. (n = 14).

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

We are grateful to Professor P. K. Wong for permission to study the patients, to AB Astra for supplies of terbutaline (Bricanyl) and to Dr. E. Pihlsgård for the statistical analysis.

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.

Drug	Dose (mg.)	PEFR (l/min.)							
		Changes After							
		Initial Value	15 mins.	30 mins.	1 hour	2 hours	3 hours	4 hours	5 hours
		M	M	M	M	M	M	M	M
Terbutaline	0·5	288·9 (27·1)	+77·1*** (7·7)	+98·8*** (8·7)	+91·8*** (9·1)	+92·1*** (11·1)	+79·3*** (14·4)	+46·8* (17·7)	+19·3 (17·5)

M = Mean
Standard error of mean given in parenthesis.
* = $p<0·05$
** = $p<0·01$
*** = $p<0·001$

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.

Drug	Dose (mg.)	HEART RATE (beats/min.)							
		Changes After							
		Initial Value	15 mins.	30 mins.	1 hour	2 hours	3 hours	4 hours	5 hours
		M	M	M	M	M	M	M	M
Terbutaline	0·5	88·9 (4·0)	+9·3* (3·3)	+9·0* (2·6)	+10·1* (3·0)	+9·3* (4·0)	+4·3 (3·6)	+3·0 (3·3)	+2·6 (3·0)

M = Mean
Standard error of mean given in parenthesis.
* = $p<0·05$
** = $p<0·01$
*** = $p<0·001$

REFERENCES

1. Arner, B.: "A comparative clinical trial of different subcutaneous doses of terbutaline and orciprenaline in bronchial asthma." Acta Med. Scand. Suppl., 512, 45, 1970.
2. Arner, B., Bertler, A., Karlefors, T. and Westling, H.: "Bronchodilator effect of a new sympathomimetic ß-receptor-stimulating agent, Terbutaline given subcutaneously to asthmatic patients." Acta Med. Scand. Suppl., 512, 41, 1970.
3. Barger, G. and Dale, H. H.: "Chemical structure and sympathomimetic action of amines." J. Physiol. (Lond.), 41, 19, 1910.
4. Chen, K. K. and Schmidt, C. F.: "The action of ephedrine, an alkaloid from Ma Huang." Proc. Soc. Exper. Biol. and Med., N.Y., 21, 351, 1923.
5. Choo Kang, Y. F. J., Simpson, W. T. and Grant, I. W.B.: "Controlled comparison of the bronchodilator effects of three beta adrenergic stimulant drugs administered by inhalation to patients with asthma." Brit. Med. J., 2, 287, 1969.
6. Curry, J. J., Fuchs, J. E. and Leard, S. E.: "Clinical implications of effect of various anticholinergic agents in modifying pulmonary response of asthmatic subjects to injection methacholine." Bull. New. Eng. Med. Center, 10, 164, 1948.
7. Da Costa, J. L. and Goh B. K.: "A comparative trial of three metered bronchialaor aerosols in asthma." Sing. Med. J., 13, 313, 1972.
8. Da Costa, J. L. and Hedstrand, U.: "The effect of a new sympathomimetic beta-receptor stimulating drug (Terbutaline) on arterial blood gases in bronchial asthma." Scand. J. Resp. Dis., 51, 212, 1970.
9. Da Costa, J. L. and Goh, B. K.: "A comparative trial of Subcutaneous terbutaline, Th1165a and Adrenaline in Bronchial Asthma," Med. J. Aust., 1973. In press.
10. Engelhardt, A., Hoefke, W. and Wick, H.: "Zur Pharmakologie des Sympathomimeticums 1-(3, 5-dihydroxyphenyl)-1-Hydroxy-2-isopropylaminoathan." Arzneimittel-Forsch., 11, 521, 1961.
11. Formgren, H.: "A clinical comparison of the effect of oral terbutaline and orciprenaline." Scand. J. Resp. Dis., 51, 195, 1970.
12. Hartley, D., Jack, D., Lunts, L. H. C. and Ritchie, A. C.: "A new class of selective stimulants of beta-adrenergic receptors." Nature (Lond.), 219, 861, 1968.
13. Kennedy, M. C. S. and Simpson, W. T.: "Human pharmacological and clinical studies on salbutamol: A specific beta adrenergic bronchodilator." Brit. J. Dis. Chest, 63, 165, 1969.
14. Knudson, R. J. and Constantine H. P.: "An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subjects." J. Appl. Physiol., 22, 402, 1967.
15. Konzett, H.: "Neues zur Asthmatherapie." Klin. Wschr., 19, 1803, 1940.
16. Lands, A. M., Arnold, A., McAuliff, J. P., Luduena, F. P. and Brown, T. G. Jr.: "Differentiation of receptor systems activated by sympathomimetic amines." Nature (Lond.), 214, 597, 1967.
17. Lands, A. M., Groblewski, G. E. and Brown, T. G. Jr.: "Comparison of the action of isoproterenol and several related compounds on blood pressure, heart and bronchioles." Arch. Int. Pharmacodyn., 16 (1) 68, 1966.
18. Mattila, M. J. and Muittari, A.: "The effect of bronchodilator aerosols on the peak expiratory flow rate in asthmatic patients." Acta Med. Scand., 180, 421, 1966.
19. Nou, E.: "Clinical Comparison of subcutaneous doses of Terbutaline and Adrenaline in Bronchial asthma." Scand. J. Resp. Dis., 52, 192, 1971.
20. Persson, H. and Olsson, T.: "Some pharmacological properties of Terbutaline (INN), 1-(3:5-dihydroxyphenyl)-2(t-butylamino)-ethanol. A new sympathomimetic beta-receptor stimulating agent." Acta Med. Scand. Suppl., 512, 11, 1970.
21. Riding, W. D., Dinda, P. and Chatterjee, S. S.: "The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma." Brit. J. Dis. Chest, 64, 37, 1970.
22. Shapiro, J. B. and Tate, C. F.: "Death in status asthmaticus: A clinical analysis of eighteen cases." Dis. Chest, 48, 484, 1965.
23. Siegmund, O. H., Granger, H. R. and Lands, A. M.: "Bronchodilator action of compounds structurally related to epinephrine." J. Pharmacol-exp. Ther., 90, 254, 1947.
24. Speizer, F. E., Doll, R. and Heaf, P.: "Observations on recent increase in mortality from asthma." Brit. Med. J., 1, 335, 1968.
25. Tai, E. and Read, J.: "Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma." Thorax, 22, 543, 1967.
26. Thiringer, G., Bergh, N. P. and Svedmyr, N.: "A comparative study of the effects of isoetharine and some other adrenergic beta stimulators in chronic obstructive lung disease." Scand. J. Resp. Dis., 52, 183, 1971.
27. Wright, B. and McKerrow, C. B.: "Maximum forced expiratory flow as a measure of ventilatory capacity." Brit. Med. J., 2, 1041, 1959.