STUDIES OF NEW SYMPATHOMIMETIC BETA-RECEPTOR STIMULATING DRUGS IN ASTHMATIC PATIENTS: III. A COMPARATIVE TRIAL OF SUBCUTANEOUS TERBUTALINE AND TRIMETOQUINOL

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SYNOPSIS

A comparative study of the effect of subcutaneous terbutaline (0·5 mg.) and trimetoquinol (0·1 mg.) on the relief of airway obstruction and the heart rate was carried out in 14 asthmatic patients. Terbutaline produced significantly greater increases ($p < 0.001$) in PEFR than trimetoquinol up to three hours after parenteral drug administration. Both drugs produced significant increases in heart rate up to thirty minutes after drug administration but there were no differences between the two drugs in this respect and side effects were negligible. It was concluded that in the dosages used terbutaline produced a superior bronchodilator effect with a greater peak level and a longer duration of action than trimetoquinol.

Lands *et al* (1967) established that sympthomimetic amines stimulated the heart and produced bronchodilatation through activation of the $beta_1$ and $beta_2$ adrenoreceptors. This prompted the development of more selective bronchodilator ($beta_2$ adrenoreceptor stimulators) agents with little cardiovascular effects. Salbutamol (Hartley *et al*, 1968) has been shown to be a selective $beta_2$ adrenoreceptor stimulator and is now widely used in asthmatic patients. Recently, two other drugs terbutaline (Formgren, 1970; Arner *et al*, 1970; Da Costa and Goh, 1973) and trimetoquinol (Iwasawa and Kiyomoto, 1967; Yamamura and Kishimoto, 1968) have been shown to have powerful selective bronchodilator activity. This paper reports the effect of subcutaneous terbutaline and of trimetoquinol on the relief of airway obstruction and the heart rate.

MATERIALS AND METHODS

Fourteen patients (10 males and 4 females) with bronchial asthma were investigated. Their mean age was 32 years (range 18—58 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 trial was performed as a cross-over study, the tests being performed between 9 a.m. and 3 p.m. on two consecutive days as far as possible. A subcutaneous dose of 0·1 mg. trimetoquinol or 0·5 mg. terbutaline was given on different days, consecutively. The drugs were 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.

RESULTS

(a) PEFR

Mean values of the PEFR in the 14 asthmatic patients studied before and after parenteral ad-

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ministration of terbutaline and trimetoquinol, respectively, are given in Table I. It was not possible to make a statistical evaluation beyond 3 hours as in some patients the test was discontinued after this period because the PEFR had fallen below the baseline.

Both drugs had a rapid onset of action reaching a peak within ½ hour (Fig. 1). The PEFR after terbutaline remained at this peak level for 2 hours and then fell slightly and at 3 hours it was still significantly raised ($p<0.001$). After trimetoquinol however there was a rapid fall of the PEFR from the peak level at 15 minutes and it reached the basal level by 2 hours. Comparison of the differences between the changes produced by both drugs showed that terbutaline produced significantly greater ($p<0.001$) increases in PEFR at all specified time intervals (Table I).

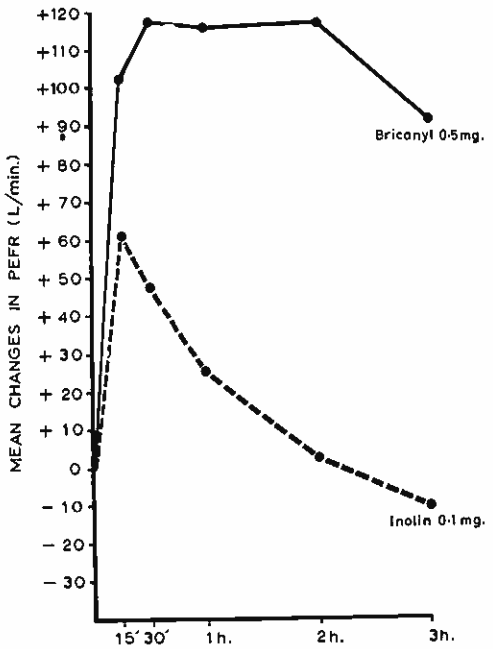

Fig. 1. Peak Expiratory Flow Rate (PEFR) (L/min): Mean values in 14 asthmatic patients before and at specified intervals after subcutaneous injection of terbutaline and trimetoquinol.

(b) **Heart Rate** (Table II and Fig. 2)

After administration of both drugs maximal increase in heart rate occurred within 30 minutes

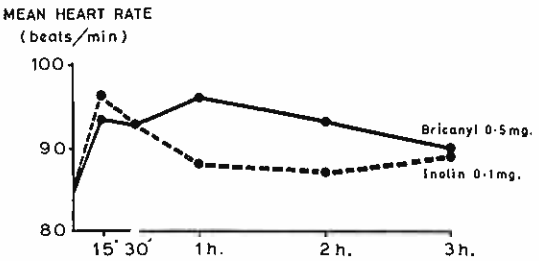

Fig. 2. Heart Rate (beats/min): Mean values of the heart rate in 14 asthmatic patients before and at specified intervals after subcutaneous injection of terbutaline and trimetoquinol.

TABLE I

PEAK EXPIRATORY FLOW RATE (PEFR): MEAN VALUES IN 14 ASTHMATIC PATIENTS BEFORE AND MEAN VALUES OF INDIVIDUAL CHANGES AT SPECIFIED INTERVALS AFTER SUBCUTANEOUS INJECTION OF TERBUTALINE AND TRIMETOQUINOL

Drug	Dose (mg.)	Initial Value	PEFR (L/min) CHANGES AFTER SPECIFIED INTERVALS				
			15 mins	30 mins	1 hour	2 hours	3 hours
		M SEM	M SEM	M SEM	M SEM	M SEM	M SEM
Terbutaline	0·5	233 25·7	+101‡ 8·4	+117‡ 9·9	+116‡ 10·9	+117‡ 10·8	+92‡ 11·5
Trimetoquinol	0·1	252 26·2	+61‡ 8·7	+48‡ 7·9	+25* 11·2	+3 8·1	—10 8·0
Difference between changes			4·77‡	6·32‡	5·97‡	8·96‡	6·23‡

* Almost significant ($p<0.05$)
† Significant ($p<0.01$)
‡ Highly significant ($p<0.001$)

M = mean
SEM = standard error of mean.

TABLE II

HEART RATE: MEAN VALUES IN 14 ASTHMATIC PATIENTS BEFORE AND MEAN VALUES OF INDIVIDUAL CHANGES AT SPECIFIED INTERVALS AFTER SUBCUTANEOUS INJECTION OF TERBUTALINE AND TRIMETOQUINOL

Drug	Dose (mg.)	Initial Value	HEART RATE BEATS/MIN				
			CHANGES AFTER SPECIFIED INTERVALS				
			15 mins	30 mins	1 hour	2 hours	3 hours
			M SEM	M SEM	M SEM	M SEM	M SEM
Terbutaline	0·5	85·3 4·3	+ 8·4† 2·5	+7·7† 2·2	+11·0 3·7	+8·0 4·1	+4·6 3·5
Trimetoquinol	0·1	85·1 3·9	+11·1‡ 2·3	+8·4‡ 1·9	+ 3·3 1·9	+1·7 2·0	+3·9* 1·5
Difference between changes			1·1	0·3	2·1	1·36	0·2

* Almost significant ($p<0·05$)
† Significant ($p<0·01$)
‡ Highly significant ($p<0·001$)

M = mean
SEM = standard error of mean

and thereafter showed no significant increase over the basal level. There was no significant difference between the changes produced by each drug.

(c) Side effects

Two patients complained of palpitations after terbutaline within 15 minutes of drug administration while 1 had palpitations after trimetoquinol at 5 minutes.

DISCUSSION

Trimetoquinol a recently synthesized bronchodilator has been shown in recommended doses to have more selective bronchodilator activity with a negligible affect on the cardiovascular system (Kiyomoto *et al*, 1969). When inhaled as an aerosol it has been shown to have similar bronchodilator activity and effect on the pulse rate as salbutamol (Scherrer and Bachofer, 1972). Terbutaline (0·5 mg.) when used subcutaneously has been shown to be a powerful bronchodilator with a significantly longer duration of action than adrenaline (Da Costa and Goh, 1972) and little cardiovascular side effects (Da Costa and Goh, 1973). When compared with salbutamol, inhaled as an aerosol, it has been shown to be an equally effective bronchodilator agent (Choo-Kang *et al*, 1973). It was thus of interest to compare the effects of trimetoquinol and terbutaline given subcutaneously as this has not been done before.

In the recommended therapeutic dosages used, terbutaline (0·5 mg.) demonstrated a superior bronchodilator effect to trimetoquinol (0·1 mg.) with a greater peak effect and a significantly longer duration of action. There was no significant difference in the effects on the cardiovascular system. 0·1 mg. trimetoquinol did not produce as great a peak effect as 0·5 mg. terbutaline in this study showing that they were not equipotential dosages. It would thus be of interest to study the effect of a higher or equipotential dosage of trimetoquinol. Preliminary studies, however, have demonstrated a greater incidence of cardiovascular side effects with a dosage of 0·2 mg. trimetoquinol and patient tolerance has been poor (Da Costa and Goh, unpublished observations).

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