subnormal responses found in patients given intermittent corticosteroid therapy by Malone *et al.* (1970). This finding, together with the satisfactory clinical response in these patients with severe disease, suggests that a therapeutic trial of depot tetracosactrin in a dose of 0·5 mg twice weekly should be considered for the control of disease requiring steroid therapy over a prolonged period. The effect of other dosage schedules on hypothalamic-pituitary-adrenal functon remains to be investigated. If these findings are confirmed in a larger series they may explain the clinical impression that it is easier to stop corticotrophin therapy than oral steroids and may therefore justify the use of depot tetracosactrin therapy in the treatment of exacerbations of chronic diseases.

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Trial of New Bronchodilator, Terbutaline, in Asthma

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Summary

Terbutaline, a new bronchodilator acting on β-adrenergic receptors, was given to 10 asthmatic patients, who received on separate days 5 mg orally, 10 mg orally, and 0·25 mg subcutaneously. The ventilatory response was assessed by measurement of the FEV_1 before and at intervals after administration. The cardiovascular response was assessed by measurement of the heart rate and blood pressure and by electrocardiography at the same times as spirometry was performed.

The ventilatory response to all three doses and by both routes was satisfactory. The maximal increase in FEV_1 after 5 mg orally was only slightly less than that after 10 mg. The maximal increase in heart rate after 5 mg orally was about half that which occurred after 10 mg. It is concluded that 5 mg orally and 0·25 mg subcutaneously are suitable doses.

In general a modest fall in blood pressure affected the diastolic more than the systolic. On E.C.G. the T wave was often depressed, and in one patient, it was inverted. A trough-like depression of the QRS baseline occurred several times. The significance of the E.C.G. changes is uncertain.

Introduction

In the search for a bronchodilator drug with optimal adrenergic activity on β-receptors, Bergman *et al.* (1969) studied several compounds for their balance of β_1 and β_2 activity (Lands *et al.*, 1966, 1967). Terbutaline, synthesized by Wetterlin and Svensson in 1966, was selected for further study. Its structural formula (Fig. 1) differs from that of orciprenaline in having a tertiary butyl group at the nitrogen atom instead of an isopropyl group. Relatively large β_2 and small β_1 effects were observed and subsequently confirmed by Persson and Olsson (1970). Arner *et al.* (1970a) found that equal subcutaneous doses of terbutaline and orciprenaline caused similar maximal increases in heart rate which appeared to persist slightly longer after terbutaline. Orally terbutaline 5 mg and orciprenaline 20 mg caused equal increases in heart rate but orciprenaline caused a greater stroke volume. Carlström and Westling (1970) confirmed a preferential action on β_2-receptors. A bronchodilator response in asthmatics was observed after terbutaline was given subcutaneously (Arner *et al.*, 1970b) and orally (Mattila and Muittari, 1969; Arner, 1970; Formgren, 1971).

The following is an account of the ventilatory and cardiovascular response to terbutaline in 10 asthmatic patients.

Materials and Methods

The patients were selected for their known responsiveness to bronchodilator drugs and for the small spontaneous variation in the degree of their bronchospasm over comparatively long periods. At the time of testing they were in remission from acute exacerbation. Their clinical characteristics are shown in Table I.

Terbutaline was administered on separate days, 5 mg orally, 10 mg orally, and 0·25 mg subcutaneously. It was given on three consecutive days or at weekly intervals according to the patient's convenience. The order of these three presentations was randomized. To ensure rapid absorption the oral tablets were fragmented and taken with 7 oz (200 ml) of water three hours after a light breakfast.

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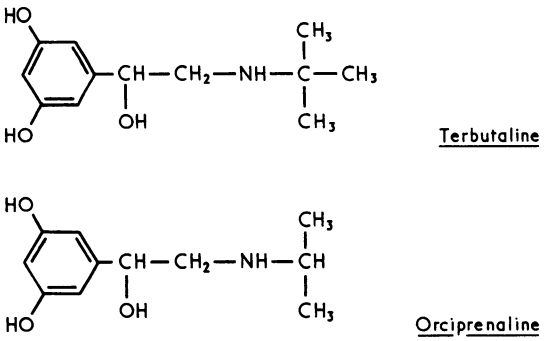

FIG. 1—Structural formulae of terbutaline and orciprenaline. Terbutaline differs from orciprenaline in having a tertiary butyl group at the nitrogen atom instead of an isopropyl group.

The ventilatory response was assessed by measurement of the forced expiratory volume in one second (FEV_1) before and at intervals after administration, a Vitalograph dry spirometer being used. Pretreatment spirometry was repeated at five-minute intervals until consecutive values differed by less than 10%. These final FEV_1 values represented the pretreatment values from which the response to the drug was calculated. The FEV_1 was measured at 15, 30, 45, and 60 minutes after oral administration, and thereafter half-hourly until 300 minutes. After subcutaneous administration measurements were made at 5, 15, 30, 45, and 60 minutes and thereafter half-hourly until 240 minutes. The absolute change in FEV_1 from the pretreatment value was calculated for each time interval. When the 10 patients had received all three presentations of the drug the means of the changes in FEV_1 for each time interval were calculated for each of the three presentations of the drug. The means of the maximal changes in FEV_1 occurring in individual patients were also calculated. When the pretreatment FEV_1 value differed markedly from that on other occasions the experiment was postponed, thus ensuring that the values were comparable on the three occasions of each drug presentation.

The cardiovascular response was assessed by the heart rate and blood pressure and by electrocardiography. Pretreatment measurements of heart rate and blood pressure were made every five minutes until consecutive values differed by less than 5%. After administration of the drug the measurements were made at the same intervals as for spirometry. The change in heart rate and blood pressure were calculated for each time interval, and the means of the changes were calculated for each drug presentation. The means of the maximal changes occurring in individual patients were also calculated. The blood pressure was measured by the East-Radcliffe Automatic Blood Pressure Recorder, which uses an inflatable cuff, in all patients except two in whom the instrument gave ill-defined readings, and in these the conventional auscultatory method was used. Electrocardiograms were obtained before treatment and, using standard lead II, repeated afterwards at the same time intervals as for spirometry. When certain abnormalities appeared 12-lead E.C.G.s were obtained for comparison with the 12 pretreatment leads.

Tests for toxicity were made before treatment; after the third treatment when given on consecutive days, or after 10 mg orally when given at weekly intervals; and about three weeks after the third treatment.

Patients were asked not to take bronchodilator drugs during the six hours before each experiment unless in need, but the need did not arise and no postponements were necessary on that account. Steps were also taken to ensure anticholinergic drugs were avoided.

TABLE I—*Clinical Details of Patients Receiving Terbutaline*

Case No.	Sex	Age	Other Conditions	On Long-term Corticosteroids	Other Drugs Taken at Time of Test
1	F.	44		+	
2	F.	67			
3	F.	53	Hypertension. Obesity		
4	M.	61		+	
5	M.	32			
6	F.	40	Obesity		
7	F.	41		+	Diazepam.
8	F.	40	Hypertension. Diabetes	+	Chlorpropamide. Polythiazide. Potassium chloride. Methyldopa. Norethisterone. Mestranol
9	F.	48		+	
10	M.	36	Diabetes		Chlorpropamide

Bronchodilator drugs were not used during the 6 hours preceding a test.

Results

VENTILATORY CHANGES

Pretreatment FEV_1 values and the expected values of each patient are shown in Table II. The mean pretreatment FEV_1 for each patient expressed as a percentage of the expected value gives an indication of the bronchospasm at the start of the experiments. The mean absolute changes in FEV_1 at each timed interval are shown for each of the three presentations of terbutaline in Fig. 2. After 10 mg four of the individual response curves showed plateaux, indicating that for these patients this dose was greater than the lowest dose required to achieve a maximal response. The means of the maximal

TABLE II—*Pretreatment FEV_1 Values*

Case No.	Pretreatment FEV_1				
	5 mg Orally	10 mg Orally	0·25 mg Subcut.	Mean	% Expected FEV_1
1 ..	1·39	1·31	1·12	1·27	67
2 ..	0·65	0·85	0·91	0·80	47
3 ..	0·98	1·25	1·03	1·09	52
4 ..	1·47	1·12	1·45	1·35	50
5 ..	2·38	2·30	2·32	2·33	69
6 ..	1·10	1·26	1·40	1·25	69
7 ..	1·85	1·80	2·10	1·92	80
8 ..	0·66	0·74	0·65	0·68	30
9 ..	1·73	1·79	1·58	1·70	73
10 ..	2·17	2·36	2·59	2·37	62
Mean ..	1·44	1·48	1·51		

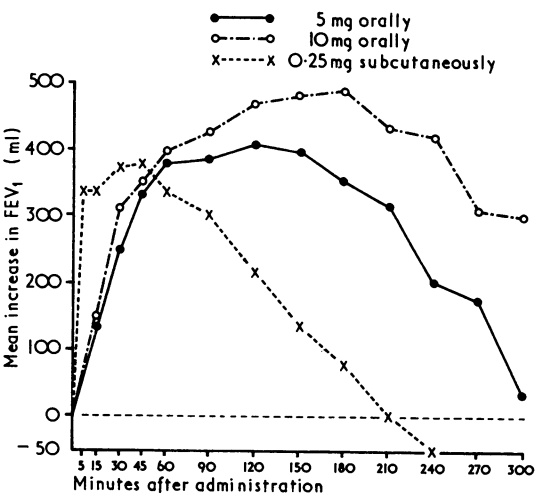

FIG. 2—Mean increase in FEV_1 at intervals after administration of terbutaline by oral and subcutaneous routes.

TABLE III—*Pretreatment FEV_1s, their Maximal and Integrated Increases, and the Significance of Differences between Results Obtained after Administration of 5 and 10 mg Orally and 0·25 mg Subcutaneously*

Measurement	Treatment Means			F Values for Treatments*	Significance of Differences between Treatments (†)	
	5 mg Orally A	10 mg Orally B	0·25 mg Subcut. C		5% Level	1% Level
Mean pretreatment FEV_1 (litres) ..	1·44	1·48	1·51	0·70‡	*A B C*	*A B C*
Mean maximal increase in FEV_1 (litres)	0·46	0·56	0·42	5·06§	*C A* B	*C A B*
Integrated increase in FEV_1 over 4 hours (litre-minutes) ..	71·0	88·4	47·3	8·11‖	C *A B*	*C A B*
Mean maximal increase in heart rate (per min) ..	18·8	34·6	12·5	12·87‖	*C A* B	*C A B*

*The F value measures overall differences between treatments. If there were no differences between treatments it would be distributed like Snedecor's F with (2·18) degrees of freedom.
†Lines join treatments which do not differ at given significance level.
‡$P > 0·05$.
§$0·05 > P > 0·01$.
‖$P < 0·01$.

increases in FEV_1 for each patient are shown in Table III. These values are slightly greater than those shown in Fig. 2 because the individual patient's maxima occurred at different times after administration. The maximal increases in FEV_1 after 5 and 10 mg orally differed significantly at the 5% level, but not at the 1% level.

A measure of the overall activity is the integrated increase, corresponding approximately to the area under the response curve. There was no significant difference at the 5% level between the integrated increases after 5 and 10 mg orally (Table III).

CARDIOVASCULAR CHANGES

Heart Rate.—The mean changes in heart rate are shown in Fig. 3. Patients differed markedly in responsiveness. Thus the heart rate of Case 1 fell initially, that of Case 4 remained almost without change, while Case 9 was highly responsive and achieved larger increases with all three drug presentations than the other patients. The times of maximal change in heart rate were about the same as those for maximal ventilatory increase. The means of the individual maximal increases in heart rate were 18·8 after 5 mg and 34·6 after 10 mg orally; after 0·25 mg subcutaneously it was 12·5.

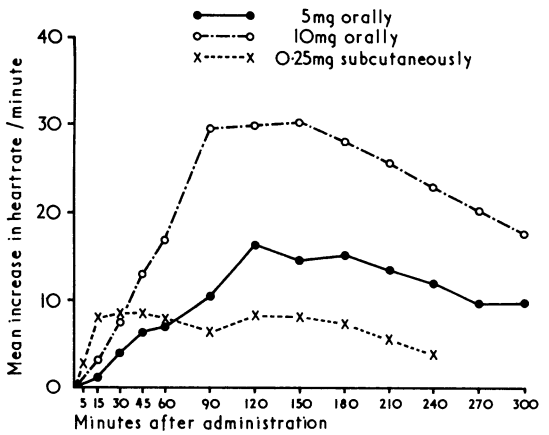

FIG. 3—Mean increase in heart rate at intervals after administration of terbutaline by oral and subcutaneous routes.

Blood Pressure.—The mean changes in systolic and diastolic blood pressures were small (Fig. 4). Apart from small initial rises in systolic pressure with 5 mg orally and 0·25 mg subcutaneously, the general trend was a modest fall which affected the diastolic more than the systolic and was dose-related. The untreated hypertensive patient (Case 3) sustained greater falls than the other patients, but these falls were all within the therapeutic range. The B.P. of the other hypertensive patient (Case 8), who was being treated with methyldopa and polythiazide, underwent modest rises. In no instance was there a rise or fall in blood pressure to cause the slightest concern.

ELECTROCARDIOGRAPHIC CHANGES

Reduced amplitude (depression) of the T wave often occurred; the incidence was as follows: 5 mg orally, five patients; 10 mg orally, eight patients; 0·25 mg subcutaneously, eight patients. The onset and duration of T wave depression corresponded generally with the onset and duration of ventilatory and heart rate changes, but individually there was little correspondence. Thus some patients with T depression had no tachycardia, and vice versa. The degree of depression amounted to flattening in seven instances. T-wave inversion occurred only in one patient (Case 9), who had diabetes and treated hypertension, and it occurred with all three drug presentations.

A trough-like depression of the QRS baseline was observed several times. This is not seen in ischaemic heart disease, and its possible significance is discussed later. Depression of the ST interval did not occur, except as part of the above-mentioned phenomenon. No arrhythmias occurred after administration of the drug. On the contrary, one patient (Case 10) had atrial ectopics, one in six beats, before administration, which ceased with the tachycardia.

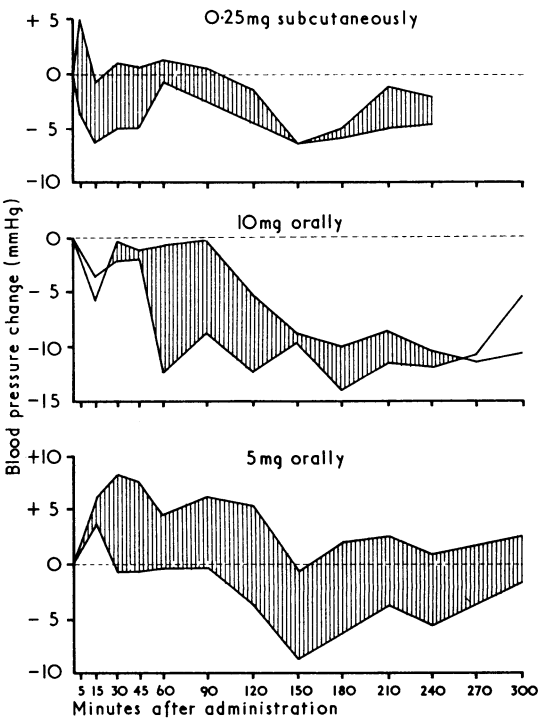

FIG. 4—Mean changes in systolic and diastolic blood pressure after administration of terbutaline. The changes after 5 and 10 mg orally and 0·25 mg subcutaneously are shown separately. Where the diastolic pressure rises less or falls more than the systolic, the area is hatched; this shows the increase in pulse pressure.

TOXICITY TESTS

One patient (Case 5) had glycosuria five hours after 10 mg of terbutaline orally. Otherwise, all tests were normal and there was no evidence of cardiac, hepatic, renal, or haematological damage.

SUBJECTIVE SIDE EFFECTS

These were too trivial to provoke spontaneous comment by any patient. On being questioned, a few noticed tremor, and this was sometimes seen on the E.C.G. tracings around 60 to 120 minutes. No patient was aware of palpitations. None had headache or feelings of anxiety. By contrast, three patients slept for long periods.

Discussion

Terbutaline is a potent bronchodilator with prolonged activity. The mean maximal FEV_1 increase after 5 mg orally was 82% of the increase after 10 mg, indicating little ventilatory advantage with the double dose. Comparison of the integrated increase yielded similar results. Furthermore, the response curves of four of the patients showed plateaux after taking 10 mg. In these four cases the dose was greater than the smallest amount needed to obtain the full effect. The mean maximal increase in heart rate after 5 mg was 54% that which occurred with 10 mg. It follows that a 10 mg dose achieves little ventilatory advantage over 5 mg at the cost of a disproportionately large increase in heart rate. It seems that an oral dose greater than 5 mg would not often be required and that a suitable presentation might be about half that amount.

The observed changes in heart rate show that terbutaline in clinical doses exerts some activity on β_1-receptors. Mean maximal increases in heart rate were 19 per minute after 5 mg orally and 35 per minute after 10 mg. This is in contrast to the results of other workers who obtained much smaller responses (Mattila and Muittari, 1969; Formgren, 1971; Fagerberg and Tegner, personal communication; Bernstein *et al.* 1971). These authors report rises in heart rate of only 0 to 6 per minute after 5 mg orally and of 5 to 9·3 per minute after 10 mg. The greater tachycardia in the present series may have been due in part to the mode of administration, which favoured rapid absorption—namely, fragmentation of the tablets and ingestion with a relatively large volume of water on a probably empty stomach. But this could not account for the tachycardia continuing, and, furthermore, after subcutaneous injection of 0·25 mg the increase was 12·5 per minute whereas Arner (1970) obtained an increase of 3 to 4. It seems the patients in the present series may have been unduly sensitive to the cardiovascular action of the drug.

Little has been published about E.C.G. changes after administration of drugs with predominantly β-adrenergic activity, Littman *et al.* (1950-1) described a trough-like depression of the QRS baseline after 0·25 mg of isoprenaline given subcutaneously, which was similar to that observed in our cases. They suggested that it was due to augmentation of the atrial T wave. This phenomenon is not characteristic of myocardial ischaemia, and it may be a specific response to β-adrenergic activity. Its clinical significance is obscure and it is currently the subject of further study.

Riding *et al.* (1970) described depression of the ST segment and depression or inversion of the T wave after inhalation of isoprenaline aerosols. There were no instances of ST depression after terbutaline, except as part of the trough-like depression of the QRS baseline previously referred to. Some degree of T-wave depression occurred with many of the patients, and inversion occurred with one patient. The significance of this is not clear, and it would be premature to ascribe it to ischaemia in the present state of knowledge of E.C.G. changes after administration of β-adrenergic drugs. In my experience T-wave depression is common after administration of sympathomimetic bronchodilators.

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