Comparison of Two Oral Selective β_2-Adrenergic Stimulant Drugs in Bronchial Asthma

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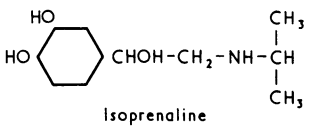
Summary

The effect of two oral selective β_2-stimulant drugs, salbutamol and terbutaline, on spirometry, arterial blood-gas tensions, pulse, and blood pressure was compared with placebo in a double-blind controlled trial in 12 asthmatic patients. Both drugs increased to forced vital capacity and the forced expiratory volume in 1 second equally for up to five hours, the maximal effect occurring at two to four hours. There was no significant change in arterial blood-gas tensions but both drugs increased pulse rate slightly. Tremor was the most common side effect. Terbutaline seems to be an effective alternative to salbutamol.

Introduction

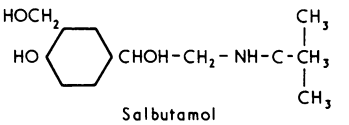
Adrenergic stimulant drugs are much used to reverse or diminish the widespread small airway obstruction which characterizes attacks of bronchial asthma. Until recently the drug most often used for this was isoprenaline given by aerosol inhalation.



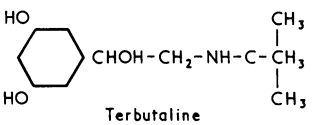
Isoprenaline

Isoprenaline has a comparatively short bronchodilator action because it is rapidly metabolized by the enzyme catechol-*o*-methyl transferase. Moreover, in addition to being a powerful stimulator of β_2-adrenergic receptors leading to bronchodilation it also stimulates β_1-receptors in the myocardium, leading to tachycardia and a rise in cardiac output (Aviado and Schmidt, 1957; Kelman *et al.*, 1969). Probably as a direct result of the cardiac effects hypoxaemia may become worse after isoprenaline even though airway obstruction is diminished, and where large doses are given, particularly when the patient is hypoxaemic, serious cardiac complications such as ventricular fibrillation or ventricular asystole may occur. The recent rise and decline in asthma mortality coincided with the widespread use of portable pressurized aerosols containing, most frequently, isoprenaline, and the downward trend in mortality is related to a reduction in the use of these aerosols and this drug (Inman and Adelstein, 1969). Clearly an alternative adrenergic stimulant drug to isoprenaline is needed. Fortunately, small chemical changes in the isoprenaline molecule have lead to a series of related compounds which have to a large extent overcome the disadvantages of isoprenaline. Substitution of other groups or rearrangements of existing groups in the benzene ring have rendered the compounds more resistant to the action of catechol-*o*-methyl transferase, thus prolonging their action, and changes in the side chain have increased their specificity for the β_2 or bronchial as opposed to the β_1 or cardiac receptors.

Two examples of selective β_2-stimulant drugs are salbutamol (Brittain *et al.*, 1968) and terbutaline. In animal



Salbutamol



Terbutaline

experiments both have been shown to act selectively on bronchial muscle and to have little or no effect on cardiac muscle. Clinically, salbutamol has been shown to lead to a satisfactory reduction in airway obstruction and lung hyperinflation in asthma, and there is usually no lowering of arterial oxygen tension or cardiovascular side effects (Palmer and Diament, 1969a, 1969b; Palmer *et al.*, 1970). So far the clinical effects of terbutaline have not been assessed, so we report here a comparison of salbutamol and terbutaline by mouth on spirometry, pulse rate and blood pressure, and arterial blood-gas tensions in the same asthmatic patients in a double-blind placebo controlled trial.

Patients and Methods

Twelve asthmatic patients (seven women and five men) were investigated. All bronchodilator drugs were stopped for 12 hours beforehand. The nature of the experiment was explained to them and all gave their consent. Their mean age was 41·7 (range 23-58) years, height 164·6 (range 152-175) cm, and weight 69·9 (range 51-85) kg. They all had a long history of attacks of airway obstruction which was usually well reversed by bronchodilator drugs. Six had positive scratch tests to various allergens and all had sputum and/or blood eosinophilia. They attended the laboratory on three consecutive days and arterial blood-gas tensions, dynamic lung volumes, pulse, and blood pressure were measured before and at intervals up to six hours after 5 mg of salbutamol, 5 mg of terbutaline, or placebo by mouth, the order of the drugs being allocated at random. Blood samples were obtained in a heparin-lubricated syringe from the radial artery when the patient was breathing air, and Pa_{O_2} and Pa_{CO_2} were measured in duplicate with electrodes manufactured by Radiometer, Copenhagen. The standard deviation for a single measurement in our hands was 1·14 mm Hg for the oxygen electrode and 1·02 mm Hg for the carbon dioxide electrode. Forced expiratory spirograms were obtained and from the best of three attempts the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1) were measured. The measurements were recorded in litres A.T.P.S. (ambient temperature and pressure saturated with water vapour).

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Results

The means (with standard error) of the spirometer findings, arterial blood-gas tensions, pulse rate, and blood pressure before and after the drugs and placebo are shown in Table I and in the Chart. At the beginning of the experiment the FVC and FEV_1 were reduced and there was hypoxaemia without hypercapnia—findings typical of asthma of moderate severity. After salbutamol and terbutaline there were significant rises in FEV_1, the effect being maximal at two to four hours and persisting for at least five hours. A significant rise in FVC was seen after salbutamol but not after terbutaline. There were slight mean rises in Pa_{O_2} after both drugs but these did not reach significant levels. The Pa_{CO_2} showed no significant change. While there was no significant change in pulse rate after the drugs there was a significant fall after the

TABLE I—*Effect of Salbutamol, Terbutaline, and Placebo on Mean (Standard Error) Dynamic Lung Volumes (Litres A.T.P.S.), Arterial Blood-gas Tensions (mm Hg), Pulse Rate, and Blood Pressure (mm Hg) in 12 Asthmatic Subjects*

	Basal	30 min	60 min	120 min	180 min	240 min	300 min	360 min
Salbutamol								
FEV_1 (l. A.T.P.S.)	1·48 (0·19)	1·84* (0·22)	2·01* (0·24)	2·09* (0·25)	2·09* (0·23)	1·96* (0·24)	1·77† (0·23)	1·70 (0·23)
FVC (l. A.T.P.S.)	2·78 (0·29)	3·07† (0·31)	3·12† (0·30)	3·17† (0·30)	3·26† (0·29)	3·09 (0·32)	2·93 (0·30)	2·91 (0·30)
Pa_{O_2} (mm Hg)	73·83 (1·58)			76·88 (2·79)				
Pa_{CO_2} (mm Hg)	38·38 (0·93)			38·88 (0·88)				
Pulse rate	86·0 (4·57)	83·3 (4·69)	86·3 (3·96)	84·7 (3·70)	87·3 (4·3)	86·8 (4·65)	85·7 (4·56)	83·7 (5·25)
Systolic B.P.	124·8 (3·89)	125·0 (3·90)	125·6 (3·68)	124·9 (3·91)	122·1 (3·64)	120·8† (3·84)	121·2† (4·0)	121·7 (4·2)
Diastolic B.P.	80·75 (3·86)	79·42 (3·71)	79·42 (3·63)	80·33 (3·69)	79·0 (3·46)	76·5 (3·88)	79·92 (3·85)	78·0 (4·2)
Terbutaline								
FEV_1 (l. A.T.P.S.)	1·56 (0·19)	1·89† (0·18)	2·01† (0·20)	2·08† (0·21)	2·10† (0·20)	2·09† (0·21)	1·96† (0·22)	1·76 (0·21)
FVC (l. A.T.P.S.)	2·83 (0·27)	3·1 (0·26)	3·16 (0·28)	3·23 (0·28)	3·18 (0·27)	3·21 (0·28)	3·08 (0·30)	2·99 (0·28)
Pa_{O_2} (mm Hg)	73·42 (2·14)			75·25 (2·49)				
Pa_{CO_2} (mm Hg)	37·83 (0·97)			37·96 (0·93)				
Pulse rate	82·7 (5·05)	80·0 (4·43)	82·7 (4·69)	83·4 (4·51)	84·0 (4·55)	86·2 (4·83)	84·3 (4·53)	83·7 (4·76)
Systolic B.P.	120·8 (3·23)	123·3 (3·35)	124·7 (3·50)	124·0 (2·9)	122·3 (3·12)	124·1 (3·72)	123·7 (2·95)	121·4 (3·28)
Diastolic B.P.	78·83 (3·91)	78·92 (3·62)	79·08 (3·67)	79·17 (3·43)	78·75 (3·51)	77·33 (3·85)	78·33 (3·55)	76·75 (3·52)
Placebo								
FEV_1 (l. A.T.P.S.)	1·51 (0·17)	1·64 (0·17)	1·66 (0·18)	1·63 (0·21)	1·72 (0·20)	1·59 (0·23)	1·55 (0·22)	1·58 (0·22)
FVC (l. A.T.P.S.)	2·77 (0·22)	2·88 (0·25)	2·90 (0·24)	2·87 (0·28)	2·91 (0·28)	2·77 (0·30)	2·75 (0·30)	2·78 (0·28)
Pa_{O_2} (mm Hg)	73·96 (2·68)			74·92 (2·51)				
Pa_{CO_2} (mm Hg)	38·33 (1·04)			39·13 (0·98)				
Pulse rate	86·3 (5·3)	80·4† (4·32)	77·8† (4·18)	78·5† (4·94)	77·4† (2·21)	78·2† (4·08)	78·7 (4·06)	79·3 (4·06)
Systolic B.P.	125·0 (3·91)	123·2 (2·96)	123·7 (3·17)	123·1 (2·85)	124·5 (3·03)	122·6 (3·39)	122·0 (3·19)	122·0 (3·52)
Diastolic B.P.	80·5 (3·34)	79·17 (3·40)	78·17 (3·69)	79·42 (3·39)	80·08 (3·23)	78·58 (3·53)	78·42 (3·56)	78·17 (3·37)

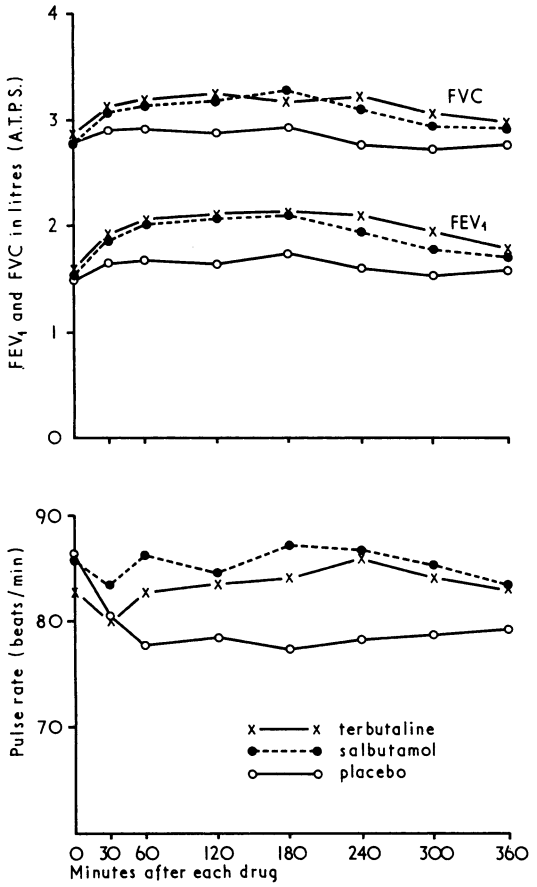
*Highly significant. †Significant.

TABLE II—*Comparison between the Mean Change (with Standard Error) during the Whole Trial in Dynamic Lung Volumes (l. A.T.P.S.), Arterial Blood-gas Tensions (mm Hg), Pulse Rate and Blood Pressure (mm Hg) in 12 Asthmatic Subjects after Salbutamol, Terbutaline, and Placebo*

	FEV_1	FVC	Pa_{O_2}	Pa_{CO_2}	Pulse Rate	Systolic B.P.	Diastolic B.P.
Salbutamol *v* placebo	+0·333* (0·07)	+0·235† (0·09)	+2·09 (1·56)	−0·29 (0·34)	+7·98* (1·64)	+0·44 (1·95)	+0·43 (1·52)
Terbutaline *v* placebo	+0·317† (0·12)	+0·247 (0·17)	+0·88 (1·75)	−0·67 (0·56)	+8·27* (1·79)	+4·71 (2·45)	+1·10 (1·70)
Salbutamol *v* terbutaline	+0·016 (0·08)	−0·012 (0·14)	+1·21 (1·30)	−0·38 (0·60)	−1·04 (1·12)	−4·27† (1·75)	−0·68 (1·14)

*Differences highly significant.
†Differences significant.
Other differences not significant.

+Drug effect greater than placebo or salbutamol effect greater than terbutaline.
−Drug effect less than placebo, salbutamol effect less than terbutaline.



Changes in dynamic lung volumes and pulse rate with salbutamol, terbutaline, and placebo.

placebo, indicating that both drugs increase pulse rate somewhat. There was no increase in systolic or diastolic blood pressure.

In Table II the mean change in the measurements is shown for the whole period of the trial. While the rise in the spirometric measurements was greater with salbutamol versus placebo than with terbutaline versus placebo the difference between salbutamol and terbutaline did not reach significant levels. There was a highly significant increase in pulse rate after both drugs. The apparent rise in systolic blood pressure after terbutaline is most likely due to the lower control readings before this drug compared with salbutamol and placebo. The incidence of side-effects is shown in Table III. Fine finger tremor was the most common, occurring in four patients after salbutamol and in five after terbutaline. Only one patient, however, experienced this side effect on both drugs. Two patients, one on each of the active drugs, complained of palpitation and one on terbutaline noted sweating.

TABLE III—*Side Effects with Salbutamol, Terbutaline, and Placebo*

	Tremor	Palpitation	Sweating	Headache
Salbutamol	4	1	0	0
Terbutaline	5	1	1	1
Placebo	0	0	0	1

Discussion

This trial shows that salbutamol and terbutaline are potent long-acting bronchodilator drugs when given orally. The reduction in airway obstruction as shown by the rise in FEV_1 appeared to be somewhat greater after 5 mg of salbutamol than after 5 mg of terbutaline. As the mean increase in FEV_1 obtained during the whole period of the trial did not differ significantly as between salbutamol and terbutaline we consider they are probably equally active in the relief of asthmatic airway obstruction and that terbutaline may be used as a satisfactory alternative to salbutamol. Both drugs caused slight tachycardia but there was no change in systolic or diastolic blood pressure. The cardiac effects did not lead to a fall in Pa_{O_2}, in fact it rose slightly after both drugs, though the rise was not statistically significant. There was no change in the level of alveolar ventilation and therefore in the Pa_{CO_2}. Fine finger tremor was the commonest side effect occurring in about a third of the patients having either drug. This was usually not troublesome at rest but became evident during fine co-ordinated movements such as writing or sewing. As only one patient developed this symptom on both drugs it seems likely that where tremor occurs with one drug the other can be used as an alternative.

Our clinical experience subsequent to the completion of this trial is that reducing the dose usually results in the disappearance or a noticeable reduction of the tremor without significantly reducing the bronchodilator effect. The dose used in the trial was 5 mg, the dose now recommended for salbutamol is 2-4 mg three times a day, so that in practice tremor should be an infrequent limiting factor to the use of these drugs.

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