

Comparison of cardiorespiratory effects of terbutaline and salbutamol aerosols in patients with reversible airways obstruction

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Harris, L. (1973). Thorax, 28, 592-595. Comparison of cardiorespiratory effects of terbutaline and salbutamol aerosols in patients with reversible airways obstruction. The effects of pressurized aerosol administration of terbutaline were compared with those of salbutamol in 14 patients with at least 20% reversibility of airways obstruction. The two drugs were found to be equipotent bronchodilators in the dosage used. Salbutamol was found to produce significant increases in minute ventilation, physiological dead space/tidal volume ratio, and ventilatory equivalent for oxygen, with significant falls in arterial oxygen tension and heart rate. Terbutaline did not induce significant changes in any of these variables. These results suggest that terbutaline is less likely than salbutamol to have an adverse effect upon ventilation-perfusion relationships.

Among the newer β -adrenergic stimulating bronchodilators, terbutaline (Carlström, 1970) and salbutamol (Lewis, 1971) have been shown to be relatively selective β -2 stimulators.

The oral preparations of these two drugs have been compared by Legge, Gaddie, and Palmer (1971), who found no significant difference between them. Freedman (1972) demonstrated that 100 μ g salbutamol and 250 μ g terbutaline by aerosol administration had an equipotent bronchodilating effect without any clinically important side effects.

The present study is a more detailed comparison of cardiorespiratory variables following the administration of the two substances by pressurized aerosol in twice the dosages used by Freedman.

MATERIAL

Fourteen volunteers were studied as outpatients. All were men (age 35-65, mean 55.5) shown repeatedly to have reversibility of airways obstruction by at least 20% increase in forced expiratory volume in 1 second (FEV₁) after administration of a bronchodilator. All had previously taken part in similar studies. Comparisons were acceptable only if FEV₁ values after placebo agreed within 10% on the test days. Initially, 18 patients were entered for the trial but 4 were excluded from future study because of wide fluctuations in baseline FEV₁ measurements on the test days.

METHODS

The study was designed as a 'within-patient' trial. Each patient attended at the same time on the same day of the week on two successive weeks. At each visit baseline measurements were made 30 minutes after two inhalations from an aerosol device containing only propellant ('placebo'). Measurements were then repeated 30 minutes after two inhalations of either terbutaline or salbutamol ('active'). The order for allocation of active aerosol was randomized. At the conclusion of the trial it was found that eight patients had used terbutaline on the first visit and six had used salbutamol first. Placebo and active aerosols were indistinguishable to the patients, although the operator was aware that placebo was being used for baseline measurements. The use of propellant alone in this way compensates for any placebo effect of using an aerosol device and for any possible effect of the propellant itself. Prior to each study day the patients abstained from all their usual therapy for at least 12 hours (including corticosteroid in three patients). The dosage delivered by two activations of the aerosol devices was 500 μ g terbutaline and 200 μ g salbutamol respectively. Measurements were made at 30 minutes because previous reports (Kennedy and Simpson, 1969; Legge *et al.*, 1971) have shown that both drugs can be expected to produce maximum bronchodilatation at that time, and possible adverse effects not persisting for 30 minutes are unlikely to be clinically important.

The aerosol was, on every occasion, manipulated by the investigator personally. The FEV₁ was taken as the best of three attempts on a Vitalograph spirometer. Values were corrected to body temperature and pressure, saturated (BTPS).

Minute ventilation was measured as inspiratory volume (\dot{V}_I) over a 5-minute period with a Parkinson-Cowan dry gas meter, and respiratory frequency (f) was recorded simultaneously. \dot{V}_I was converted to expiratory volume (\dot{V}_E) by the formula $\dot{V}_E = \dot{V}_I \times F_{IN_2} / F_{EN_2}$ and corrected to BTPS. The patients were allowed to get used to the noseclip and mouthpiece, and measurements were recorded only after \dot{V}_I had become stabilized over a period of at least 3 minutes. Expired air was collected for 5 minutes in a 100 litre Douglas bag using a low-resistance one-way valve and was analysed for CO₂ and O₂. Nitrogen was calculated as $100 - FE_{O_2} - FE_{CO_2}$. Oxygen was measured with a Servomex paramagnetic O₂ analyser calibrated with oxygen-free nitrogen and room air. Carbon dioxide was measured with an Hilger-IRD infrared CO₂ analyser calibrated with gases of known CO₂ and O₂ content. Calibration gases were analysed for CO₂ with a modified Haldane apparatus. Oxygen consumption (\dot{V}_{O_2}) and carbon dioxide output (\dot{V}_{CO_2}) were then calculated with correction to STPD.

As the subjects were volunteer outpatients and were required to attend on at least two occasions, it was decided to avoid arterial cannulation and cardiac catheterization because of the potential risk associated with these procedures.

Oxygenated mixed venous PCO₂ was measured by a 'trial and error' rebreathing equilibration method using CO₂/O₂ mixtures of known composition until an acceptable plateau was obtained on the rapid CO₂ analyser tracing (Hackney, Sears, and Collier, 1958). Blood gases and hydrogen ion concentration were measured on an IL blood gas analyser incorporating a Severinghaus type PCO₂ microelectrode and a Clark type PO₂ microelectrode. Samples were taken from the hyperaemic earlobe into heparinized capillary tubes and analysed promptly. The earlobe was rendered hyperaemic by vigorous massage for 3 minutes with a cream containing thurfyl nicotinate. Langlands and Wallace (1965) have reported a close correspondence between the results obtained from gas analysis of blood from the hyperaemic earlobe and that taken from the brachial artery, and MacIntyre, Norman and Smith (1968) have confirmed these findings with the technique used in the present study. Godfrey, Wozniak, Courtenay-Evans and Samuels (1971) have also confirmed the reliability of the method and have suggested correction factors. They state that no correction is required for PO₂ but recommend a correction factor of 0.65 mmHg to be added to the earlobe PCO₂. This correction factor has been applied to the earlobe PCO₂ measurements in this study. Physiological dead space tidal volume ratio was calculated from the formula, $V_D/V_E = 1 - (PE_{CO_2}/PaCO_2)$ with correction for valve box dead space of 35 ml. Cardiac output was derived from the

Fick principle; that is $\dot{Q}_T = \dot{V}_{CO_2} / C\dot{V}_{CO_2} - Ca_{CO_2}$ with appropriate temperature and pressure corrections. Blood CO₂ contents were derived from the tables of McHardy (1967). Alveolar oxygen tension (P_{AO_2}) was calculated from the formula, $PaO_2 = PIO_2 - PaCO_2/R(PaCO_2/R \times F_{IO_2} (1-R))$. The alveolar-arterial oxygen tension gradient ($A-ADO_2$) was then obtained by subtraction.

RESULTS

Mean values (\pm SEM) after placebo and after active aerosols are shown in the Table. Base line values after placebo for each variable show no significant differences on each of the two test days. Results were analysed by *t* test.

VENTILATION AND GAS EXCHANGE The increase in FEV₁ (+37%) after active aerosol was identical for both groups and highly significant ($P < 0.001$). \dot{V}_E was significantly increased after salbutamol ($P < 0.01$). V_D/V_E was also increased after salbutamol whereas it was decreased after terbutaline, the difference between the means being significant ($P < 0.01$). There were no significant changes in f , \dot{V}_{O_2} or \dot{V}_{CO_2} with either drug, but there was a significant increase in \dot{V}_E/\dot{V}_{O_2} after salbutamol ($P < 0.05$).

BLOOD GASES Neither active aerosol produced any significant change in PCO₂. Terbutaline did not produce any significant change in PO₂ but salbutamol produced a significant fall in PO₂ ($P < 0.05$). Examination of individual PO₂ changes showed that three patients had falls greater than 5 mmHg after salbutamol (-13, -10, -9) and two had such falls after terbutaline (-9, -7). The patient with the lowest PO₂ showed a fall of 4.5 mmHg (from 50 to 45.5) with salbutamol but a rise of 6 mmHg (from 54 to 60) with terbutaline. There were no significant differences in $A-ADO_2$ with either drug.

CARDIAC OUTPUT Accepting the well-known limitations of the indirect Fick CO₂ method, the use of which in similar patients with increased metabolic rates is supported by Warell *et al.* (1970), there was no evidence of any change in cardiac output with either drug. The absence of significant changes in blood pressure and heart rate after terbutaline and in blood pressure with reduced heart rate ($P < 0.05$) after salbutamol are consistent with the cardiac output findings.

T A B L E

	FEV ₁ (litres) BTPS	f (cycles/ min)	V _E (litres/min) BTPS	V _D /V _E (%)	V _E /V _{O₂} (litres/ litre)	V _{O₂} (ml/min) STPD	VCO ₂ (ml/min) STPD	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	A-aDO ₂ (mmHg)	QT (litres/ min)	Heart Rate (cycles/ min)	BP (mmHg)		
													Systolic	Diastolic	
Salbutamol															
Placebo	0.98 (±0.06)	19.7 (±1.60)	10.74 (±0.43)	32.00 (±2.20)	38.9 (±2.85)	277.8 (±18.31)	307.1 (±19.00)	40.32 (±1.13)	71.86 (±2.52)	44.8 (±2.72)	7.37 (±0.68)	81.4 (±2.64)	130.3 (±4.55)	78.6 (±2.79)	
Active	1.34 (±0.09)	21.8 (±1.67)	11.83 (±0.51)	36.9 (±1.93)	43.9 (±3.85)	267.6 (±14.34)	298.6 (±13.87)	38.93 (±1.22)	68.75 (±3.01)	47.8 (±2.58)	6.96 (±0.85)	75.9 (±2.11)	125.9 (±5.57)	77.9 (±3.35)	
Change	+0.365** (±0.05)	+2.1 (±1.13)	+1.09** (±0.31)	+4.9* (±2.33)	+5.0* (±2.09)	-10.2 (±14.25)	-8.5 (±15.79)	-1.39 (±1.56)	-3.11* (±1.33)	+3.0 (±2.08)	-0.41 (±0.93)	-5.5* (±1.85)	-4.4 (±2.79)	-0.7 (±1.73)	
Terbutaline															
Placebo	0.98 (±0.05)	20.1 (±1.05)	11.47 (±0.43)	38.1 (±2.71)	40.4 (±2.23)	272.9 (±15.12)	288.6 (±11.27)	39.86 (±1.52)	70.69 (±2.44)	45.6 (±2.51)	7.04 (±2.34)	81.1 (±2.57)	128.6 (±4.56)	75.9 (±2.48)	
Active	1.34 (±0.09)	21.8 (±1.88)	11.70 (±0.54)	36.4 (±1.98)	40.6 (±2.37)	273.1 (±11.95)	283.6 (±11.13)	37.54 (±1.24)	69.39 (±1.70)	47.7 (±1.75)	5.57 (±0.36)	76.3 (±3.59)	125.4 (±3.34)	77.0 (±2.97)	
Change	0.36** (±0.05)	+1.0 (±1.28)	+0.23 (±0.33)	+1.7 (±1.71)	+0.3 (±0.17)	+0.2 (±0.02)	-5.0 (±7.74)	-2.32 (±1.13)	-1.30 (±1.77)	+2.1 (±2.33)	-1.47 (±0.68)	-4.8 (±2.31)	-3.2 (±2.73)	+1.1 (±2.00)	

* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001
 Mean values (±SEM) and mean changes (±SEM) for forced expiratory volume in 1 second (FEV₁), respiratory rate (f), volume of expired air in litres per minute (V_E), physiological dead space ventilation ratio (V_D/V_E), oxygen ventilation equivalent (V_E/V_{O₂}), oxygen uptake (V_{O₂}), carbon dioxide uptake (VCO₂), arterial carbon dioxide tension (PaCO₂), arterial oxygen tension (PaO₂), alveolar-arterial oxygen difference (A-aDO₂), cardiac output (QT), heart rate, and systolic and diastolic blood pressure in 14 male patients with reversible airways obstruction.

DISCUSSION

The results confirm that pressurized aerosol administration of terbutaline is as effective in producing bronchodilatation as is salbutamol. In the dosage used (salbutamol 200 μg , terbutaline 500 μg) they were equipotent and both show a wide dissociation between β_1 (cardiac) and β_2 (bronchial) effects. No side effects were noted in this dosage.

In general, the two drugs have much the same effects on most cardiorespiratory variables except that there appears to be an increase in 'wasted' ventilation after salbutamol, as shown by the increase in V_D/V_E and $V_E/\dot{V}O_2$.

In addition, terbutaline seems to be less likely to produce increased hypoxaemia on the basis of group mean changes. However, two patients showed falls in P_{O_2} greater than 5 mmHg with terbutaline compared with three such falls after salbutamol, indicating that neither drug is entirely free from this hazard. Nevertheless, at the lowest P_{O_2} , which is where the real danger lies, salbutamol caused a fall whereas terbutaline produced a rise.

The literature concerning increased hypoxaemia induced by β -adrenergic stimulating drugs has been previously reviewed by the author (Harris, 1970, 1972), who suggested that it is the β_2 pulmonary vasodilator effect which is responsible by interfering with the homeostatic mechanism whereby blood flow is reduced to underventilated areas. This concept appears to be substantiated by the absence of change in cardiac output in the present study.

Having now reached the state of obtaining potent β -adrenergic stimulating bronchodilators with wide separation of β_1 and β_2 effects, the next stage of development might be the separation of the β_2 bronchodilator and vasodilator effects (in which case the latter might become known as β_3 effect).

The results presented suggest that terbutaline and salbutamol are equally effective bronchodilators when administered by pressurized aerosol, without cardiac effects, in the dosage used, and that terbutaline is less likely than salbutamol to cause increased hypoxaemia.

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