Papers and Originals

Comparison of Cardiorespiratory Effects of Isoprenaline and Salbutamol in Patients with Bronchial Asthma

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Summary: The effects of isoprenaline and salbutamol administered orally, by inhalation, or by intravenous infusion were compared in 13 asthmatic patients. Bronchodilator activity was assessed by serial measurement of specific airways conductance (SGaw). Log-dose response curves were obtained for both drugs and showed them to be equipotent as bronchodilators. Cardiovascular effects were variable, but in general, isoprenaline caused greater rise in pulse rate and a greater change in blood pressure than the same dose of salbutamol.

Cardiorespiratory measurements during continuous intravenous infusion of increasing doses of both drugs suggested a greater effect of isoprenaline than the same dose of salbutamol on metabolic rate, pulmonary ventilation, pulmonary gas exchange, cardiac output, and heart rate. The effect of salbutamol on the heart rate was about 10 times less than that of isoprenaline but lasted longer.

Introduction

Pressurized aerosols containing adrenergic bronchodilator drugs are valuable in the treatment of many asthmatic patients. Since 1960, however, a definite rise in the death rate from asthma has occurred and has been correlated with the increasing use of such pressurized aerosols (Speizer *et al.*, 1968).

Sympathomimetic amines produce their bronchodilator effects by acting on beta adrenergic receptors in bronchial smooth muscle. Side-effects may be produced by their action on other beta receptors, especially in cardiac muscle and vascular smooth muscle. Recent work (Lands *et al.*, 1966; 1967; Furchgott, 1967) has shown that these receptors may be pharmacologically differentiated into beta₁ receptors in the heart and beta₂ receptors in bronchial and vascular smooth muscle. This has led to a search for selective beta stimulants which would act predominantly on bronchial—that is, beta₂—receptors. A selective action on beta₂ receptors has been found experimentally for isoetharine (Siegmund *et al.*, 1947) and orciprenaline (Englehardt *et al.*, 1961). The most recently developed selective beta₂ stimulant is salbutamol (A.H. 3365),

which is claimed to stimulate the beta₂ receptors in bronchial smooth muscle rather than those in vascular smooth muscle (Cullum *et al.*, 1969). Both orciprenaline and salbutamol are effective bronchodilators when given by mouth and have a longer action than isoprenaline. They are not metabolized by catechol-O-methyl transferase, but Davies *et al.* (1969) have shown that degradation by this enzyme does not account for the termination of effect of isoprenaline, so their prolonged action cannot be explained on this basis.

The purpose of this study was to compare the cardiorespiratory effects of salbutamol and isoprenaline in asthmatic patients in order to assess the possible advantages of using salbutamol in the treatment of asthma.

Patients

In the 13 patients selected for the studies (Table I) a diagnosis of bronchial asthma was based on a history of episodic wheeze and/or breathlessness with symptom-free

TABLE I.—Clinical Details of the 13 Patients with Bronchial Asthma

Case No.	Age and Sex	F.E.V. ₁ (L.)	V.C. (L.)	F.E.V. ₁ /V.C. (%)	Drug Therapy at Time of Studies	
					Corticosteroid	Adrenergic Bronchodilator*
1	41 F	1.0	2.8	36	Prednisolone 10 mg./day	Isoprenaline inhaler
2	41 F	1.0	2.2	45	Prednisolone 5 mg./day	Orciprenaline 20 mg. t.d.s. + Isoprenaline inhaler
3	55 F	1.2	2.4	50	Prednisolone 10 mg./day	Salbutamol inhaler
4	31 M	2.6	4.1	63	—	Salbutamol 2 mg. t.d.s. + inhaler
5	39 M	2.0	3.6	56	—	Salbutamol 4 mg. q.d.s.
6	46 M	0.8	2.4	33	—	Orciprenaline 20 mg. q.d.s.
7	31 M	3.4	4.9	69	—	—
8	22 F	2.3	3.5	66	—	—
9	63 F	0.5	1.5	33	Prednisolone 15 mg./day	Salbutamol 2 mg. t.d.s. + salbutamol inhaler
10	47 F	0.6	1.7	35	Prednisolone 12 mg./day	Orciprenaline inhaler
11	46 F	1.4	2.3	61	Prednisolone 5 mg./day	Orciprenaline 20 mg. t.d.s.
12	73 M	0.4	1.5	27	Prednisolone 10 mg./day	Orciprenaline 20 mg. q.d.s.
13	35 M	2.5	3.8	68	Betamethasone 0.25 mg./day	—

*No adrenergic bronchodilator was taken for 12 hours before the studies.

intervals (questions 16a and 16b in the M.R.C. questionnaire on respiratory symptoms 1966). The degree of variability of their airway obstruction was such that the forced expiratory volume in one second (F.E.V.₁) had been shown to fall by at least 50% during asthmatic attacks compared with the values during remission. All were breathless and wheezing and had pronounced airway obstruction on the days of the study. Eight of the patients were receiving corticosteroid treatment (Table I).

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Each patient was told about the procedure of the study and gave his consent.

Methods. Study 1

Study 1 compared the bronchodilator and cardiovascular effects of inhaled isoprenaline and salbutamol.

(A) Bronchodilator Studies

Changes in specific airways conductance (SGaw) obtained with the body plethysmograph (Dubois *et al.*, 1956a, 1956b; Guyatt *et al.*, 1967, were used to indicate changes in airway obstruction. The two drugs were tested in the morning on separate days in an attempt to obtain comparable baseline values. Increasing doses of each drug were given to construct a dose response curve. The doses (10, 30, 100 and 500 μ g. of isoprenaline or salbutamol base) were chosen so that each dose was much larger than the dose which preceded it. This ensured that preceding doses made a relatively small contribution to the change in SGaw observed after a particular dose. The study utilized a series of aerosols which enabled each dose to be given as a single inhalation. The administration of drugs by aerosol introduces considerable inaccuracies in dose (Paterson *et al.*, 1968) but as this is a widely used method of administration in clinical practice it was employed in the present study.

Detailed Procedure

On the morning of the study the patients had taken no bronchodilator drugs. After resting for at least half an hour inspiratory airways conductance was measured in the body plethysmograph. (Each patient had become familiar with the apparatus on a previous occasion.) SGaw was calculated by dividing the airways conductance by the thoracic gas volume, which had been measured simultaneously. The mean of four readings was taken as the baseline value. A dose of 10 μ g. of one of the bronchodilator drugs was then administered as a single inhalation from a pressurized aerosol under close supervision. The patient then re-entered the body plethysmograph, and five minutes after inhalation four measurements of SGaw were made. The approximate change in SGaw was calculated by means of a specially designed slide rule. When an increase in SGaw of 20% or more was detected, further measurements were made 15 and 30 minutes after the inhalation and the remaining doses were then given. When there was a change of less than +20% in SGaw, however, the next dose (30 μ g.) was given immediately and the same procedure was followed until the full range of doses had been given.

On the second occasion the same procedure was adopted with the other drug. When the mean baseline SGaw on the first and second occasions were found to have been less than 40% different from their geometric mean the study was complete, but when the difference was greater a third study was arranged. On the third occasion the mean baseline SGaw was compared in turn with the baseline values of the two previous studies. When it proved to be less than 40% different from either one of these values the study proceeded with the bronchodilator *not* used in the study with the baseline SGaw value closest to that of the third occasion. When the baseline values were outside these limits further studies were arranged until finally, after four separate visits in some cases, data were available to allow comparison of the two drugs on occasions when baseline SGaw had been comparable (see Table II).

The means of four values of SGaw were calculated before the first dose was given (term B) and at 5, 15, and 30 minutes after each dose (term A). Changes in the logarithmic values of SGaw were used ($\log_{10}A - \log_{10}B$) since they express the

TABLE II.—Baseline Values for SGaw (sec/cm.H₂O) for each of the Paired Studies

Case No.	Isoprenaline baseline (mean of 4 readings)	Salbutamol baseline (mean of 4 readings)	Difference between mean baselines (% of geometric mean)
1	0.028	0.028	0
2	0.111	0.112	1
3	0.068	0.080	16
4	0.089	0.062	36
5	0.056	0.067	16
6	0.050	0.069	33

changes in SGaw as a proportion of the baseline value. Logarithmic values have the added advantage of approaching a normal distribution more nearly than do the absolute values (Guyatt and Alpers, 1968), and are therefore more acceptable for statistical purposes.

(B) Cardiovascular Studies

These studies were performed in the afternoon of the day when the bronchodilator effect of isoprenaline had been investigated. This arrangement avoided any confusion which might have resulted from the prolonged action of salbutamol (Choo-Kang *et al.*, 1969). At least two hours were allowed to elapse between the end of the morning and the start of the afternoon investigation.

The patients were studied in the supine position, but they were allowed to sit up briefly to take each inhalation. Blood pressure was measured with a sphygmomanometer, systolic and diastolic pressures being read at the levels of the first and fourth phase of the Korotkoff sounds. The heart rate was mentioned by an E.C.G.-triggered rate meter.

Each drug was administered from the pressurized aerosols that were used in the SGaw studies. The same dosage schedule was used, except that in the absence of a response the administered dose was increased up to 2,000 μ g. in some cases. Isoprenaline was always given first because of its shorter duration of action. At least 20 minutes were allowed to elapse between the end of the isoprenaline and the start of the salbutamol studies.

Study 2

Study 2 sought the duration of the bronchodilatation resulting from inhaled or ingested salbutamol.

Two asthmatics (Cases 7 and 8) were given 100 μ g. of salbutamol by pressurized aerosol after steady baseline values for SGaw had been obtained over a 20-minute period. The measurements were repeated over the next three and a half hours in Case 7 and five hours in Case 8.

On a separate occasion the same patients swallowed 4 mg. tablets of salbutamol. SGaw and F.E.V.₁ and V.C. (measured with a McDermott bellows spirometer) were measured at intervals of 5 to 30 minutes for up to three and a half hours.

Study 3

Study 3 compared the cardiorespiratory effects of intravenous salbutamol and isoprenaline.

The five patients in this study were severe asthmatics (see Table V) who had been admitted to hospital with an exacerbation of their respiratory symptoms. All were receiving corticosteroid therapy. The patients were seated comfortably in the upright position in a padded dentist's chair, which was the only position they could tolerate for long periods.

A PE60 catheter 22 cm. long was introduced into the right brachial artery, the Seldinger percutaneous technique being used. Intravascular pressures were measured with a saline-filled variable inductance manometer (Elema), the calibration and linear response of which were checked before and after

each study. The reference point (at 0 mm.Hg) was taken as the sternal end of the fourth rib.

The respiratory circuit has been described elsewhere (Jones *et al.*, 1967). Expired air passed continuously through a Tissot spirometer which served as a mixing chamber except when it was used for timed gas collections. Expired gas sampled at the lips (tidal gas) or distal to the Tissot spirometer (mixed expired gas) was analysed by an infrared CO₂ meter (Godart URAS) and a paramagnetic O₂ meter (Servomex DCL). The E.C.G. was recorded continuously and the heart rate was recorded with an E.C.G.-triggered rate meter. Electrical signals from the Tissot potentiometer, CO₂ meter, O₂ meter, E.C.G., and arterial pressure manometer were displayed on a Mingograf direct-writing recorder. Arterial blood which had been drawn into heparinized glass syringes was analysed immediately for PCO₂ (Severinghaus electrode), PO₂ (Beckman macro-electrode), and total plasma CO₂ (Natelson, micro Van Slyke) from which bicarbonate concentration was calculated. The accuracy of these analyses has been reported (Jones *et al.*, 1967). Oxygenated mixed venous CO₂ tensions (PvCO₂) were measured by a rebreathing method (Jones *et al.*, 1967). From values of PvCO₂ and PaCO₂ the value of arteriovenous CO₂ content difference was obtained by using relationships developed by McHardy (1967). Cardiac output was calculated by an indirect Fick method for CO₂ (Higgs *et al.*, 1967).

The drugs were administered by infusion into a left antecubital fossa vein by means of a Harvard infusion pump.

Isoprenaline sulphate and salbutamol were dissolved in saline to provide solutions of 5 µg. of isoprenaline sulphate/ml. and 5 and 10 µg. of salbutamol/ml. Isoprenaline was infused in doses ranging from 0.005 to 0.095 µg. of isoprenaline base/kg./min., and salbutamol in doses ranging from 0.0001 to 0.31 µg. of base/kg./min. Blood pressure values were taken from the continuous record, and are the mean values for the last minute of each dose infused. They are set out in Table V, and because they were not obtained at the same time as those in Table IV (which are the mean values during the collection periods) they do not always exactly correspond.

Procedure

When the heart rate, blood pressure, mixed expired PCO₂ and PO₂ and end tidal CO₂ had become steady, expired gas and arterial blood were collected simultaneously for three minutes. Brachial artery pressures were recorded after flushing the catheter with heparinized saline immediately before and after the collection. Heart rate was recorded continuously throughout. PvCO₂ was measured immediately after the collection had ended.

The smallest dose of isoprenaline was then infused. When the heart rate had become steady, or if there was no change in heart rate after five minutes' infusion, a further collection was taken provided that the criteria of steady state were fulfilled (Jones *et al.*, 1967). After the collection had been made at the highest dose of isoprenaline the infusion was stopped. Sufficient time was allowed to elapse for the pulse rate to return to the baseline level. Salbutamol was then given and the same procedure was followed. These studies lasted up to six hours.

Results: Study 1

(A) Bronchodilator effect of inhaled drugs

Effects of the two bronchodilators on SGaw are shown in Fig. 1. Baseline values for SGaw and values at various times after inhalation were the mean of four readings. The standard deviation of these individual readings about their means was averaged for all the observations on all six patients; a value of $\pm 5.8\%$ was obtained.

The comparability of baseline values before each drug was given is shown in Table II. The difference between baseline values ranged from 0 to 36% of the geometric means. In three

patients the baseline value was higher before salbutamol, and in one it was higher before isoprenaline. In three patients isoprenaline appeared to be the more effective bronchodilator and in the other three salbutamol appeared to have the advantage. The two drugs obviously have very similar bronchodilator activity when given in equal doses.

In Fig. 2 the log-dose response curve of isoprenaline and that of salbutamol are compared. On the "response" axis is plotted the maximum change in log SGaw after each dose. In view of the different durations of action of the two drugs, the change in SGaw after each dose of isoprenaline was considered to be the result of that dose alone, whereas the change after each dose of salbutamol was considered to be the cumulative effect of all the doses given up to that time, though the step-wise gradation of doses chosen was large enough to reduce this effect to a minimum. The mean log-dose response of the two drugs were compared. There was no significant difference between their slopes ($P=0.4$) or their intercepts ($P=0.15$).

FIG. 1.—Effect of isoprenaline and salbutamol on SGaw in Cases 1-6.

FIG. 2.—Comparison of log-dose response curves of isoprenaline and salbutamol in Cases 1-6.

(B) Cardiovascular Effect of Inhaled Drugs

The results are set out in Table III. The values are the changes in heart rate and blood pressure for each dose from the baseline reading immediately before the dose was given. The values given are those obtained at the moment of maximum change or one minute after the inhalation. Isoprenaline increased the heart by 10 more beats/minute in Case, 3, 4, and 5. Increase in pulse pressure was noted only in Case 4. Salbutamol produced a similar rise in heart rate in Cases 1 and 2. There was a slight increase in pulse pressure in Case 1, but changes in blood pressure caused by either drug in this study were minimal.

TABLE III.—Response of Pulse Rate and Blood Pressure to Inhaled Isoprenaline and Salbutamol (Study 1)

Case No.		Isoprenaline							Salbutamol						
		10 µg.	30 µg.	100 µg.	500 µg.	1,000 µg.	1,500 µg.	2,000 µg.	10 µg.	30 µg.	100 µg.	500 µg.	1,000 µg.	1,500 µg.	2,000 µg.
1	{	Δ P. Δ B.P.		0 -2/-2	+6 -4/+2	0 +8/-2	0 0		+6 +2/0	+10 +6/0	+6 0/-2	+4 +4/-8			
2	{	Δ P. Δ B.P.	0 -4/-2	+1 -8/+6	+1 -2/-2	0 -4/+4	+9 +4/+2	+9 -4/+2			0 -6/0	0 -4/-4		+14 -6/0	
3	{	Δ P. Δ B.P.			+9 -4/+4	+9 0	+26 +2/+2				0 -2/-2		+1 0/-2		
4	{	Δ P. Δ B.P.	+4 0	+14 +10/0	+14 +10/0	+23 +10/0	+21 +10/-5	+14 +10/-10		0 0	0 0/-5	0 0	+7 0	+4 0/-5	+6 -5/-5
5	{	Δ P. Δ B.P.	0 -2/0	+4 -4/+4	+3 -4/0	+3 +16/+4	+2 -2/+6		+12 +2/+12		+1 -2/+4	0 +2/-4			+8 -8/-4
6	{	Δ P. Δ B.P.	0 0	0 -2/+4	0 -2/0	0 -2/+4	0 0	0 0			0 0/-4		0 +2/+2		+6 +2/+4

Δ P. = Change in pulse rate (beats/min.).
Δ B.P. = Change in blood pressure (mm.Hg).

Study 2

Values for changes in SGaw in Cases 7 and 8 after 100 µg. of inhaled and 4mg. of ingested salbutamol are plotted in Fig 3.

FIG. 3.—Response to salbutamol in Cases 7 and 8.

After inhalation maximal changes in SGaw were observed at 20 and 60 minutes. There was little apparent diminution in this effect even after six hours.

After ingestion definite increases in SGaw were detected at 20 minutes and 10 minutes. After reaching maximal levels at 60. minutes in both cases there was a gradual decline.

Before ingestion initial values for F.E.V.₁/V.C. in Cases 7 and 8 were 3.2/4.9 and 2.3/3.5 l. respectively Maximum values of 4.1/5.3 l. were obtained one and a half hours after ingestion in Case 7, and 3.1/3.75 l. after one hour in Case 8. Values had fallen to 3.4/5.0 and 2.8/3.7 l. respectively four hours after ingestion.

The results suggest that at these doses salbutamol has, if anything, a more prolonged bronchodilator action when inhaled than when taken orally.

Study 3

The results of this study in Cases 9 to 13 are presented in Tables IV, V, and VI and Fig. 4.

Metabolic Rate.—Oxygen intake increased during infusion of isoprenaline in Cases 10 and 11 and fell slightly in the other two. During salbutamol infusion oxygen intake increased only in Case 11, and here the effect was less pronounced than with the comparable dose of isoprenaline.

Pulmonary Ventilation.—In most cases total expired ventilation increased during the infusions of either drug. In Cases 10 and 11 this effect was greater with isoprenaline than with a

comparable or larger dose of salbutamol. Arterial PCO₂ (Paco₂) fell from normal or low values in the patients whose total ventilation increased, indicating a level of alveolar ventilation in excess of metabolic requirements. This was particularly so in Case 11, whose Paco₂ fell from 31 to 22 mm.Hg during isoprenaline infusion. Physiological dead space:tidal volume ratio (V_D/V_T) was high in Cases 11 and 12 before infusion and there was little change with either drug.

Pulmonary Gas Exchange.—Arterial Po₂ (Pao₂) was low (range 70.5-73.5 mm.Hg) in all cases before infusion began. In one patient only (Case 9) Pao₂ fell during isoprenaline infusion from 73.5 to 61.5 mm.Hg, but there was no fall with even 13 times the dose of salbutamol. In most of the other patients Pao₂ increased (by up to 10.5 mm.Hg) with increasing alveolar ventilation during the infusions of both drugs.

Circulatory Effect (Tables IV, V, and VI).—As judged by the change in heart rate with increasing doses, both drugs have an appreciable effect on the cardiovascular system. Isoprenaline was about 10 times as active as salbutamol (Fig. 4).

FIG. 4.—Effect of isoprenaline and salbutamol on pulse rate in Cases 9-12.

Neither drug produced a consistent change in systolic, diastolic, or mean blood pressures. The values set out in Table VI are derived from the baseline reading and the response obtained in the last minute of infusion of the highest dose of each drug. Cardiac output values (Table V) are not available for all infused doses. Isoprenaline consistently increased cardiac output (by 1.5-3.5 l./min.) in Cases 10, 11, and 12. Salbutamol had little effect on the cardiac output in Cases 10, 11, and 12.

Discussion

The apparent effectiveness of a bronchodilator drug depends on the degree of airway obstruction present before it is administered (Hume and Jones, 1960; Pain and Read, 1963). In asthmatic patients the great variation in airway obstruction from day to day and during the course of a single day (Minette, 1964) makes the valid comparison of bronchodilator

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drugs extremely difficult. In this study, changes in SGaw produced by the two drugs were considered to be comparable only when the percentage difference between the baselines on the two occasions was less than 40% of their geometric mean.

Estimation of SGaw by means of the body plethysmograph was chosen as a measure of airway obstruction because of its sensitivity in detecting small changes, because it is less dependent on the patient's effort, and less exhausting than measurements of F.E.V.₁ when frequently repeated, and does not require the patient to take deep breaths which may alter airway dynamics (Nadel and Tierney, 1961).

The comparison of arbitrarily selected single doses of two drugs presupposes that the dose-response curves of the two drugs have the same form and intercept. Since we were in no position to make this assumption increasing doses of the drugs were given and dose-response curves were constructed.

In most of our patients SGaw had not returned to its initial baseline value many hours after the last dose of bronchodilator drug had been inhaled, so the testing of the two drugs on the same day was not attempted. It is important to note that this failure to return to baseline after bronchodilation does not necessarily imply a prolonged action of the drug. It is a common clinical experience that many asthmatics who awaken with symptoms of pronounced airway obstruction are relieved by a single inhalation of isoprenaline and remain symptom-free for the rest of the day. This can scarcely reflect a persisting pharmacological action of isoprenaline. Ideally each different dose of both drugs would have been tested on different days, but this was not practicable. As a compromise, a series of increasing doses of one drug was given on each occasion. The steps taken to ensure the comparability of baseline SGaw have been described above. The

TABLE IV.—Cardiorespiratory Effects of Salbutamol and Isoprenaline Infusions (Study 3)

Case No.	Drug Dose (µg. base/kg./min.)	VO ₂ (ml./min.) (S.T.P.D.)	VE (l./min.) (B.T.P.S.)	f (br./min.)	Paco ₂ (mm.Hg)	V _D /V _T	PaO ₂ (mm.Hg)	PA-aO ₂ (mm.Hg)	Q _{Va} /Q _t (%)	Q _t (l./min.)	H.R.* (beats/min.)	B.P.* (mm.Hg)
9	Baseline 1	215	6.8	13	35	0.22	73.5	33	16	5.5	94	176/112
	Isoprenaline 0.007	200	8.0	15	27	0.23	62.5	52.5			103	167/103
	" 0.018	190	6.2	16	32.5	0.26	61.5	42			125	179/103
	Baseline 2	200	6.0	13	31.5	0.24	65.5	38.5			90	166/108
	Salbutamol 0.0089	170	5.5	12	33	0.24	68.5	37.5			96	170/114
	" 0.024	160	5.3	12	32.5	0.22	72.5	35.5			102	174/114
	" 0.240	200	10.3	20	27.5	0.29	67.5	51			128	183/119
	Baseline 1	245	7.3	15	41	0.33	73.5	24	10	3.5	82	171/103
	Isoprenaline 0.024	240	8.1	19	40	0.23	77.5	30	11	4	100	154/91
	" 0.047	245	8.3	22	40	0.26	76.5	29	15	5	114	160/91
	" 0.095	280	10.2	20	37	0.24	82.5	28.5	10	5.5	134	150/98
	Baseline 2	235	7.7	18	41	0.25	79	26.5	12	4	82	178/108
10	Salbutamol 0.0313	195	6.2	18	41	0.20	76.5	28	11	3	76	181/102
	" 0.0625	190	6.6	19	40.5	0.22	77.5	30	12	3.5	81	182/105
	" 0.1250	185	6.1	17	40.5	0.20	78	29	13	3.5	89	175/99
	" 0.3125	195	6.6	17	40	0.23	78	29.5	13	3.5	100	171/97
	Baseline 1	265	11.7	22	31	0.43	71.5	38.5	13	4	82	137/82
	Isoprenaline 0.002	240	12.5	24	28.5	0.41	73	44	11	3.5	87	138/85
	" 0.022	290	17.1	25	24.5	0.44	78	44	8	5	104	153/90
	" 0.054	360	21.7	27	22	0.43	78.5	45.5	7	5.5	112	150/85
	Baseline 2	240	12.3	21	26	0.42	76	41.5	9	3.5	86	156/83
	Salbutamol 0.0001	280	14.7	27	26.5	0.43	73.5	43.5	11	4	94	147/88
	" 0.036	290	19.5	27	22	0.44	80.5	45.5	6	3.5	95	141/86
	" 0.059	295	17.9	29	22	0.40	78	46.5	6	3.5	97	148/82
11	" 0.138	320	17.1	26	22.5	0.40	74.5	46	7	4	97	147/78
	Baseline 1	400	22.1	20	31.5	0.55	70.5	37	10	5.5	78	130/77
	Isoprenaline 0.013	385	22.8	19	32	0.59	70	36	14	8	77	124/75
	" 0.031	360	22.5	21	30	0.57	70.5	39	14	7.5	82	98/63
	" 0.052	370	26.9	22	25.5	0.54	80.5	36.5	11	9	108	113/68
	Baseline 2	280	14.3	18	33	0.56	52.5	48			75	111/68
	Salbutamol 0.006	270	14.3	22	39	0.58	57.5	40.5			66	94/60
	" 0.010	245	13.8	18	38.5	0.57	57	44.5	41	6	65	113/68
	" 0.025	245	15.0	21	37	0.57	63	41.5	40	7.5	64	103/62
	Baseline 1	400	22.1	20	31.5	0.55	70.5	37	10	5.5	78	130/77
	Isoprenaline 0.013	385	22.8	19	32	0.59	70	36	14	8	77	124/75
	" 0.031	360	22.5	21	30	0.57	70.5	39	14	7.5	82	98/63
12	" 0.052	370	26.9	22	25.5	0.54	80.5	36.5	11	9	108	113/68
	Baseline 2	280	14.3	18	33	0.56	52.5	48			75	111/68
	Salbutamol 0.006	270	14.3	22	39	0.58	57.5	40.5			66	94/60
	" 0.010	245	13.8	18	38.5	0.57	57	44.5	41	6	65	113/68
	" 0.025	245	15.0	21	37	0.57	63	41.5	40	7.5	64	103/62
	Baseline 1	400	22.1	20	31.5	0.55	70.5	37	10	5.5	78	130/77
	Isoprenaline 0.013	385	22.8	19	32	0.59	70	36	14	8	77	124/75
	" 0.031	360	22.5	21	30	0.57	70.5	39	14	7.5	82	98/63
	" 0.052	370	26.9	22	25.5	0.54	80.5	36.5	11	9	108	113/68
	Baseline 2	280	14.3	18	33	0.56	52.5	48			75	111/68
	Salbutamol 0.006	270	14.3	22	39	0.58	57.5	40.5			66	94/60
	" 0.010	245	13.8	18	38.5	0.57	57	44.5	41	6	65	113/68
	" 0.025	245	15.0	21	37	0.57	63	41.5	40	7.5	64	103/62

* Mean values during three min. collections of blood and expired gas.

VO₂ (ml./min.) (S.T.P.D.)

VE (l./min.) (B.T.P.S.)

f (br./min.)

V_D/V_T

PA-aO₂ (mm.Hg)

= Oxygen uptake.

= Total expired ventilation.

= Respiratory frequency.

= Physiological dead space: tidal volume ratio.

= Alveolar to arterial PO₂ difference.

Q_{Va}/Q_t

Q_t (l./min.)

H.R. (beats/min.)

B.P. (mm.Hg)

= Pulmonary venous admixture (% of cardiac output).

= Cardiac output.

= Heart rate.

= Brachial artery pressure.

TABLE V.—Cardiovascular Effects of Infused Isoprenaline and Salbutamol (Study 3)

Case No.	Isoprenaline Dose infused (µg. base/Kg./min.)						Salbutamol Dose infused (µg. base/Kg./min.)					
9	Baseline	0.007	0.009	0.018			Baseline	0.009	0.024	0.060	0.120	0.240
	P.	88	105	105	122		P.	92	96	98	102	105
	B.P.	167/110	160/98	168/103	179/103		B.P.	156/106	170/114	174/114	176/118	173/116
10	Baseline	0.005	0.009	0.024	0.047	0.095	Baseline	0.006	0.0125	0.0313	0.0625	0.1250
	P.	75	77	75	95	105	P.	70	70	70	72	77
	B.P.	171/103	162/102	169/99	154/91	160/91	B.P.	178/108	175/112	178/112	181/102	182/105
11	Baseline	0.002	0.012	0.022	0.054		Baseline	0.0001	0.036	0.059	0.138	
	P.	82	82	87	104	112	P.	86	86	94	95	97
	B.P.	147/88	141/86	148/82	147/78	142/84	B.P.	137/82	138/85	153/90	150/85	156/83
12	Baseline	0.006	0.010	0.025			Baseline	0.013	0.031	0.052		
	P.	70	74	81	104		P.	72	61	64	63	
	B.P.	130/77	124/75	98/62	112/68		B.P.	111/68	94/60	112/68	103/62	
13	Baseline	0.005	0.009	0.022	0.039		Baseline	0.011	0.029	0.052	0.072	0.130
	P.	72	78	76	96	118	P.	75	75	77	79	85
	B.P.	130/95	138/92	144/96	158/90	156/90	B.P.	126/100	130/100	130/98	128/100	130/98

P = Maximum pulse rate. B.P. = Blood pressure. Q_T = Cardiac output (litres/minute).

TABLE VI.—Maximum Alteration in Blood Pressure as Percentage of Baseline Produced by Infusion of (maximum) Doses of Both Drugs Expressed as $\mu\text{g. base/kg./min.}$

Case No.	Pressure	Isoprenaline	Maximum Dose	Salbutamol	Maximum Dose
9	Systolic	+10%	0.018	+17%	0.240
	Diastolic	—6%		+12%	
	Mean	—0%		+20%	
10	Systolic	—12%	0.095	—4%	0.313
	Diastolic	—5%		—10%	
	Mean	—9%		—7%	
11	Systolic	—3%	0.054	+14%	0.138
	Diastolic	—5%		+1%	
	Mean	—5%		+7%	
12	Systolic	—14%	0.025	—7%	0.052
	Diastolic	—11%		—9%	
	Mean	—13%		—7%	
13	Systolic	+20%	0.039	+10%	0.260
	Diastolic	—5%		—12%	
	Mean	+5%		—4%	

results obtained under these conditions indicate that the bronchodilator effects of isoprenaline and salbutamol are very similar and that the log-dose response curves of the two drugs are virtually identical.

It is important to note that in some patients studied the linear increase in bronchodilatation was maintained up to the maximum dose of both drugs. The doses needed to produce maximum bronchodilatation in all patients were not established. Nevertheless, it is felt that this kind of study, which compares similar doses and starts from comparable baselines, is more informative than those in which fixed arbitrary and often dissimilar doses of isoprenaline and salbutamol are compared without any reference to baseline values.

The apparently prolonged bronchodilator effect of inhaled salbutamol reported by Choo-Kang *et al.* (1969) is confirmed by our measurements of SGaw in Cases 7 and 8. Oral salbutamol appeared to be as effective a bronchodilator as the aerosol in the doses used in the same two subjects, but its action was less prolonged than that of the inhaled drug. Published metabolic studies are incomplete (Kennedy and Simpson, 1969). They indicate that after oral administration peak plasma levels occur within one to three hours. Within four hours 49 to 56% of the administered dose has been excreted in the urine. By 24 hours 90 to 95% of the administered dose appears in the urine. Within four hours after inhalation only 28 to 34% of the dose has been excreted in the urine and subsequent excretion is slower than after oral administration. It is possible that this reflects slow absorption from the airways. This could explain the prolonged bronchodilator effect reported.

The cardiovascular responses to inhaled isoprenaline and salbutamol were extremely variable. Neither drug in this study produced a striking alteration in blood pressure. Isoprenaline increased the heart rate more than 10% above baseline in Cases 2, 3, 4, and 5. The average increase after inhalation of 100 $\mu\text{g.}$ was 10 beats/min. Salbutamol increased the heart rate by only 14 beats/min. in Case 2 at a dose of 1,500 $\mu\text{g.}$ The average increase after 200 $\mu\text{g.}$ in three patients was 7 beats/min.

It is known that the response to isoprenaline in aerosol form is very variable, presumably because a large and in-constant proportion of the dose is swallowed and inactivated by conjugation in the gut wall (Davies *et al.*, 1969) rather than being inhaled. It should be noted that any salbutamol which is swallowed will not be inactivated in this way and may continue to exert a pharmacological effect. After the inhalation of salbutamol in Case 2 (total dose 2.6 mg.) and in two other patients (not included in this study) who inhaled cumulative doses of 1.6 and 3.1 mg. an increase in heart rate of 15–25 beats/min. was observed, which returned to normal after 40 to 60 minutes.

The results of the cardiorespiratory measurements made during infusion of isoprenaline and salbutamol suggest that at the same dose level salbutamol has less effect on the meta-

bolic rate, pulmonary ventilation, pulmonary gas exchange, and cardiac output than isoprenaline. The indirect CO_2 Fick method for measuring cardiac output is not reliable in truly resting subjects whose CO_2 output (VCO_2) and veno-arterial PCO_2 difference (PV-aCO_2) are low. Its use in the study was justified by the increased metabolic rate in most of our subjects, but the results should be regarded as approximations. The values in Table IV were corrected to the nearest 0.5 litre. Palmer and Diament (1969) found no difference between the average PaO_2 and PCO_2 measured before and five minutes after inhalation of 200 $\mu\text{g.}$ of salbutamol, but made no comparison with isoprenaline in the same patients. Among our four patients who received the infusions of the two drugs only one showed a fall in PaO_2 (of 12 mm.Hg) after isoprenaline. The remainder rose by 5–10 mm.Hg and none showed any significant change after salbutamol.

In this study isoprenaline had a greater chronotropic effect on the heart than the same doses of salbutamol, being on average 10 times (range 8 to 13) more potent in this respect. Isoprenaline produced a modest fall in diastolic pressure in all patients (range 5 to 11%). The systolic pressure, however, fell in three, but rose in two (range —12% to +20%). Salbutamol lowered the diastolic pressure in three patients (range —10% to —12%) while the change in systolic pressure ranged from —7% to +17%. The maximum doses of salbutamol infused were in all except Case 9 roughly two to three times greater than the maximum doses of isoprenaline.

This study indicates that the effects of salbutamol on the cardiovascular system are less than those of isoprenaline, though not negligible. It is felt that as the bronchodilator activity of the two drugs is so similar, observations on cardiovascular side-effects must necessarily be made by comparing the actions of identical doses of both compounds and, ideally, administering the drug by a more reproducible method than inhalation from a pressurized aerosol.

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