Br. J. Pharmac. (1971), **43**, 624–638.

Comparison of the bronchodilator and cardiovascular actions of salbutamol, isoprenaline and orciprenaline in guinea-pigs and dogs

M. J. DALY, J. B. FARMER* AND G. P. LEVY

Department of Pharmacology, Allen & Hanburys Ltd., Ware, Herts.

Summary

1. Bronchodilator and cardiovascular actions of salbutamol and isoprenaline have been compared in guinea-pigs and dogs. Orciprenaline was also included in some experiments.

2. All three drugs antagonized acetylcholine-induced increases in pulmonary resistance. In addition they increased heart rate and decreased arterial blood pressure.

3. Compared with isoprenaline, salbutamol has relatively stronger actions on bronchial and vascular β-adrenoceptors than on cardiac β-adrenoceptors, on which its action is very weak. In contrast, orciprenaline has similar potencies on β-adrenoceptors in these three tissues.

4. The positive chronotropic potency of intravenously or orally administered salbutamol was increased in conscious dogs. These heart rate responses to salbutamol were probably mainly reflex in origin.

5. Salbutamol and orciprenaline were both longer acting than isoprenaline.

6. The results support the idea of two distinct groups of β-adrenoceptors. Salbutamol differentiates between bronchial and vascular β_2-adrenoceptors on the one hand and cardiac β_1-adrenoceptors on the other. Isoprenaline and orciprenaline do not differentiate between β_1- and β_2-adrenoceptors.

Introduction

Several aspects of the pharmacology of salbutamol have been described (Cullum, Farmer, Jack & Levy, 1969 ; Farmer & Levy, 1969 ; Fogelman & Grundy, 1970 ; Farmer, Kennedy, Levy & Marshall, 1970 ; Farmer, Levy & Marshall, 1970). In animals the predominant actions of the drug were mediated through stimulation of β-adrenoceptors, but salbutamol differed both qualitatively and quantitatively from the β-adrenoceptor stimulant isoprenaline, especially in its relatively high potency on tracheobronchial muscle and low potency on cardiac muscle. This selectivity of action was ascribed to differences in the nature of the β-adrenoceptors in the organs concerned. In man, salbutamol, given orally or by aerosol, is a potent and long acting bronchodilator agent in doses which have little cardiac stimulant effect (Choo-Kang, Simpson & Grant, 1969 ; Riding, Dinda & Chatterjee, 1970 ; Tattersfield & McNicol, 1969 ; Kamburoff & Prime, 1970).

* Present address: Department of Pharmacology, Fisons Limited, Loughborough, Leics.

This paper reports the results of a more detailed quantitative study of the bronchodilator and cardiovascular actions of salbutamol in anaesthetized guinea-pigs and dogs. Changes in pulmonary resistance and compliance have been used as sensitive indicators of lung function. Isoprenaline has been used as a reference drug in all experiments and orciprenaline included in some experiments for comparison. Differences in the profiles of action of these three drugs are discussed in relation to their receptor interactions and modes of inactivation.

Methods

Anaesthesia

Guinea-pigs of either sex weighing 300–520 g were anaesthetized with allobarbitone (Dial, Ciba), 135 mg/kg intraperitoneally, and artificially respired with room air using a stroke volume of 16 ml/kg.

Beagles of either sex weighing 7–12 kg were anaesthetized with pentobarbitone sodium, 35–40 mg/kg intravenously. Supplementary doses were given when necessary to maintain an adequate depth of anaesthesia. The dogs were artificially respired through a cuffed endotracheal tube using a stroke volume of 13 ml/kg. Three additional beagles were anaesthetized with a halothane/N_2O/O_2 mixture and made spinal by the method of Burn (1952).

Measurement of pulmonary resistance and compliance in anaesthetized guinea-pigs and dogs

Guinea-pigs

Pulmonary resistance and compliance were measured by the method described in detail by Diamond (1967, 1968) with the following modifications: intrapleural pressure was measured using the catheter system of Amdur & Mead (1958); airflow was measured using a Fleisch pneumotachograph, size 0000 and electrical integration of the flow signal was performed by a Sanborn 350–5000 respiratory preamplifier. Use of this amplifier facilitated display of pressure and flow signals on the x and y axis respectively of a Sanborn 780–6A oscilloscope. The resultant hysteresis loop was closed by subtracting a voltage proportional to lung volume from the pressure axis. The slope of the corrected loop is inversely proportional to the pulmonary resistance (Comroe, Botelho & Dubois, 1959). This system allowed continuous monitoring of pulmonary resistance throughout the course of the experiment. Permanent records of airflow, transpulmonary pressure and tidal volume were made using a Sanborn 7716A pen recorder, and pulmonary resistance and compliance calculated by the graphical method of Amdur & Mead (1958).

The potencies of the β-adrenoceptor stimulant drugs were assessed by measuring their effectiveness in preventing the increases in pulmonary resistance and decreases in pulmonary compliance induced by acetylcholine. A suitable submaximal dose of acetylcholine, selected in each experiment to give an increase in pulmonary resistance of approximately 3-fold, was administered intravenously at 5 min intervals until constant responses were obtained. The test drug was injected intravenously 1 min before the next dose of acetylcholine and doses of acetylcholine repeated subsequently at 5 min intervals until responses returned to normal. The responses were calculated as the percentage inhibition of the acetylcholine-induced pulmonary mechanical change. The maximum changes, which occurred invariably 1 min after

administration of test drug, were plotted against the log of the dose and ED50 values obtained from regression lines calculated by the method of least squares. This procedure differed slightly from that used in our previous experiments (Cullum *et al.*, 1969) in which *in vivo* bronchodilator potency was estimated 5 min after administration of test drugs.

Dogs

Pulmonary resistance and compliance were measured as described above for guinea-pigs with the following modifications: airflow was measured using a Fleisch pneumotachograph, size 0 and transpulmonary pressure was measured with an oesophageal balloon (Lulling, El Sayed & Lievens, 1967).

Measurement of blood pressure, heart rate and cardiac output in anaesthetized and spinal dogs

Arterial blood pressure (1 mmHg≡1·333 mbar) was measured from a cannula in the right femoral artery and the pulse pressure used to trigger a Neilson instantaneous ratemeter for a continuous record of heart rate. Cardiac output (minus coronary flow) was measured with a probe of an electromagnetic flowmeter (M.4000, Statham Instruments, Inc.) placed around the ascending aorta. Drugs were injected intravenously through a cannula in the right femoral vein.

In preliminary experiments an interaction was observed between the vasodepressor responses to isoprenaline and salbutamol, the extent of which depended upon the interval between successive doses, the number of doses administered and the magnitude of the responses obtained. In the present experiments, therefore, a dosing-interval of 60 min was used, the total number of doses in each experiment was restricted to six and no attempt was made to obtain maximum responses. Approximately equipotent vasodepressor doses of isoprenaline and salbutamol were administered alternately, beginning with doses selected for each drug to produce near-threshold responses and using 10-fold increases in dose in each case.

Measurement of blood flow to hind limbs of anaesthetized dogs

In some experiments the skin of the right hind limb was separated from the underlying tissues as far as the ankle and then sewn back into position. In other experiments the unskinned limb was used. The right external iliac artery was exposed through a lower abdominal incision and an electromagnetic flow probe applied approximately 3 cm below the aortic junction. The internal iliac, deep circumflex and deep femoral arteries were tied off. A fine polythene cannula for injection of drugs was inserted retrogradely into the deep femoral artery so that its tip lay at the junction with the external iliac artery. A tourniquet was applied to the limb just above the paw. This, together with the skinning procedure, was designed to restrict blood flow mainly to the muscles of the limb. Arterial blood pressure was recorded from a carotid artery and heart rate derived from the pulse pressure as described above. Intravenous injections were made through a cannula in a jugular vein.

Measurement of blood flow to heads of anaesthetized dogs

An electromagnetic flow probe was placed around the right common carotid artery in the lower neck. The left common carotid artery and left and right vertebral

arteries were tied off. A small side branch of the right common carotid artery distal to the flow probe was cannulated for injection of drugs.

In the blood flow experiments the volume of the intra-arterial injections was not greater than 0·1 ml. Control injections of 0·9% w/v saline, 0·1 ml, were given throughout each experiment. Results from isolated experiments in which saline itself caused significant increases in flow were rejected.

Permanent records of arterial blood pressure, heart rate and blood flow were made on a Devices M.8 recorder.

Measurement of systolic blood pressure and heart rate in conscious dogs

Oral administration

Systolic blood pressure and heart rate were measured in beagles equipped with exteriorized carotid arteries. Readings were made daily at 10.00, 12.00, 14.00 and 16.00 hours. Isoprenaline and salbutamol were administered in gelatin capsules at 11.00 hours.

Intravenous administration

Beagle dogs were trained to lie quietly and the E.C.G. recorded from plate electrodes attached to the limbs. The QRS complex was used to trigger a Neilson instantaneous ratemeter to give a continuous record of heart rate. Isoprenaline and salbutamol were injected through a polythene cannula implanted in a jugular vein.

Quantitative analysis

Values quoted in the text are means with 95% confidence intervals in parentheses. Differences were taken to be significant when $P<0{\cdot}05$.

Drugs

Solutions were made up each day in 0·9% w/v saline containing 10^{-5} g/ml ascorbic acid, stored on ice and protected from light. The following drugs were used: acetylcholine chloride (B.D.H.); isoprenaline sulphate (Burroughs Wellcome); orciprenaline sulphate (Boehringer Ingelheim); salbutamol base or sulphate (Allen and Hanburys). Doses in the text refer to the appropriate free base.

Results

Bronchodilator activity in guinea-pigs and dogs

Mean values for pulmonary resistance and compliance were 155·1 (144·7–165·5) cm H_2O l^{-1} s^{-1} and 0·700 (0·551–0·849) ml cm H_2O^{-1} respectively in sixteen guinea-pigs; and 5·40 (4·12–6·68) cm H_2O l^{-1} s^{-1} and 24·66 (19·12–30·20) ml cm H_2O^{-1} respectively in fourteen dogs. Isoprenaline, salbutamol and orciprenaline decreased resistance and increased compliance in both species but these changes were small and not always dose related. The drugs were therefore assessed by their effectiveness in preventing acetylcholine-induced increases in resistance and decreases in compliance. Acetylcholine was used because of its potent but short lasting bronchoconstrictor action (Colebatch, Olsen & Nadel, 1966). The primary aim of these

experiments was to assess the relative activities of the drugs on pulmonary resistance since the cause of changes in pulmonary compliance is less clear (Colebatch *et al.*, 1966 ; Diamond, 1968).

The results obtained are summarized in Table 1 and were similar in guinea-pig and dog. All three drugs antagonized the changes in pulmonary resistance and compliance produced by acetylcholine. Relative potencies on the two parameters were similar. Salbutamol and orciprenaline were significantly less potent than isoprenaline in these experiments. In the guinea-pig the duration of activity was short (5–10 min) for all three drugs but in the dog salbutamol and orciprenaline each had a longer duration of action (20–30 min) than isoprenaline (5–10 min).

Cardiovascular activity in anaesthetized and spinal dogs

Anaesthetized dog

Intravenous administration of isoprenaline, 0·01–1 μg/kg, salbutamol, 0·1–10 μg/kg or orciprenaline, 0·1–10 μg/kg, lowered arterial blood pressure and increased heart rate and cardiac output. Results for isoprenaline and salbutamol are summarized in Fig. 1 and part of one experiment is illustrated in Fig. 2.

Salbutamol was less potent than isoprenaline on all three parameters but its low positive chronotropic potency was particularly marked. In the dose range tested, the slope of the regression line relating increase in heart rate to dose was flatter for salbutamol than for isoprenaline and it is not possible therefore to give a single estimate of relative potency. In five experiments, comparison of the doses to increase heart rate by five and ten beats/min showed salbutamol to be respectively 112 (22–556) times and 575 (330–10,040) times less potent than isoprenaline.

TABLE 1. *Potencies of isoprenaline, salbutamol and orciprenaline given intravenously in preventing acetylcholine-induced bronchospasm*

Species	Drug	No. of animals	Dose (μg/kg) (95% confidence limits) to produce 50% inhibition of acetylcholine effect on		Mean dose ratio (95% confidence limits)	
			Pulmonary resistance	Pulmonary compliance	Pulmonary resistance	Pulmonary compliance
Guinea-pig	Isoprenaline	5	0·45 (0·16–1·29)	0·73 (0·23–2·38)	1	1
	Salbutamol	6	2·09 (0·87–5·05)	4·15 (1·35–12·8)	4·64* (1·46–14·8)	5·67* (1·43–22·4)
	Orciprenaline	5	12·8 (5·03–32·6)	29·0 (10·4–80·7)	28·5* (8·80–92·2)	39·6* (10·8–144·8)
Dog	Isoprenaline	6	0·69 (0·21–2·26)	0·77 (0·26–2·27)	1	1
	Salbutamol	4	8·55 (4·66–15·7)	9·46 (4·78–18·75)	12·45* (3·92–39·5)	12·25* (4·13–36·3)
	Orciprenaline	4	12·1 (4·34–33·65)	19·7 (6·97–55·85)	17·6* (4·79–64·6)	25·53* (7·5–86·9)

* Significantly different from isoprenaline ($P<0·05$). Salbutamol was significantly more potent than orciprenaline in the guinea-pig ($P<0·05$) but not in the dog.

In contrast, the slopes of the regression lines for the vasodepressor actions of the two drugs were not significantly different. Salbutamol was 10·8 (6·3–18·4) times less potent than isoprenaline in decreasing diastolic blood pressure.

Increases in cardiac output with salbutamol appeared to be related more closely to the vasodepressor responses than to the positive chronotropic responses. Thus, vasodepressor responses to the smallest dose of salbutamol tested (0·1 μg/kg) were accompanied by increases in cardiac output without any change in heart rate. In five experiments, salbutamol was 11·2 (5·5–22·6) times less potent than isoprenaline in increasing cardiac output, which is close to the vasodepressor potency ratio obtained for these two drugs.

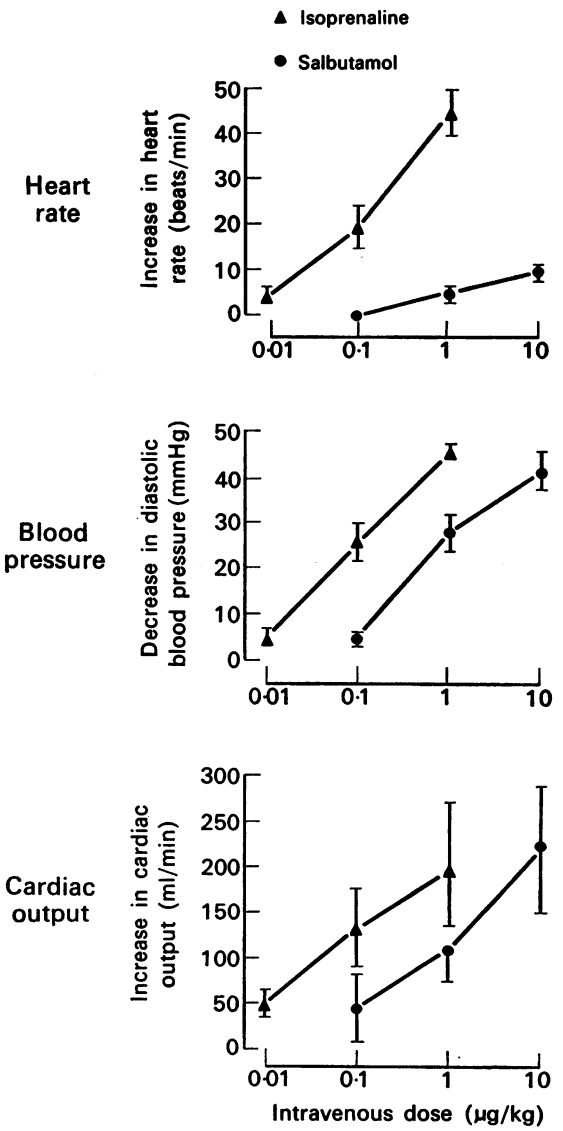

FIG. 1. Actions of intravenously administered isoprenaline and salbutamol on the cardiovascular system of the anaesthetized dog. Each point is the mean ± S.E.M. of five observations.

In all these experiments salbutamol was 2–3 times longer acting than isoprenaline.

Orciprenaline resembled salbutamol in its long duration of action but was otherwise qualitatively similar to isoprenaline. Figure 2 shows that approximately equipotent vasodepressor doses of orciprenaline and isoprenaline produced similar increases in heart rate. In three experiments in which a direct comparison with isoprenaline was made the following mean dose ratios for orciprenaline were obtained (isoprenaline=1): decrease in diastolic blood pressure, 13 (range 12–15); increase in heart rate, 10 (range 7–12).

Spinal dog

Responses to isoprenaline, 0·01–1 μg/kg and salbutamol, 0·1–10 μg/kg, in spinal dogs were essentially similar to those in anaesthetized animals. However, since heart rate, cardiac output and arterial blood pressure were relatively low in spinal animals, increases in heart rate and cardiac output were larger and decreases in blood pressure smaller than in anaesthetized animals. One of three experiments in which intravenously administered isoprenaline and salbutamol were compared directly in the spinal dog is illustrated in Fig. 3. Since decreases in blood pressure were small, vasodepressor potencies were not calculated. In the dose range studied, the slopes of the regression lines for increase in heart rate and cardiac output were flatter for salbutamol than for isoprenaline. In three experiments, comparison of

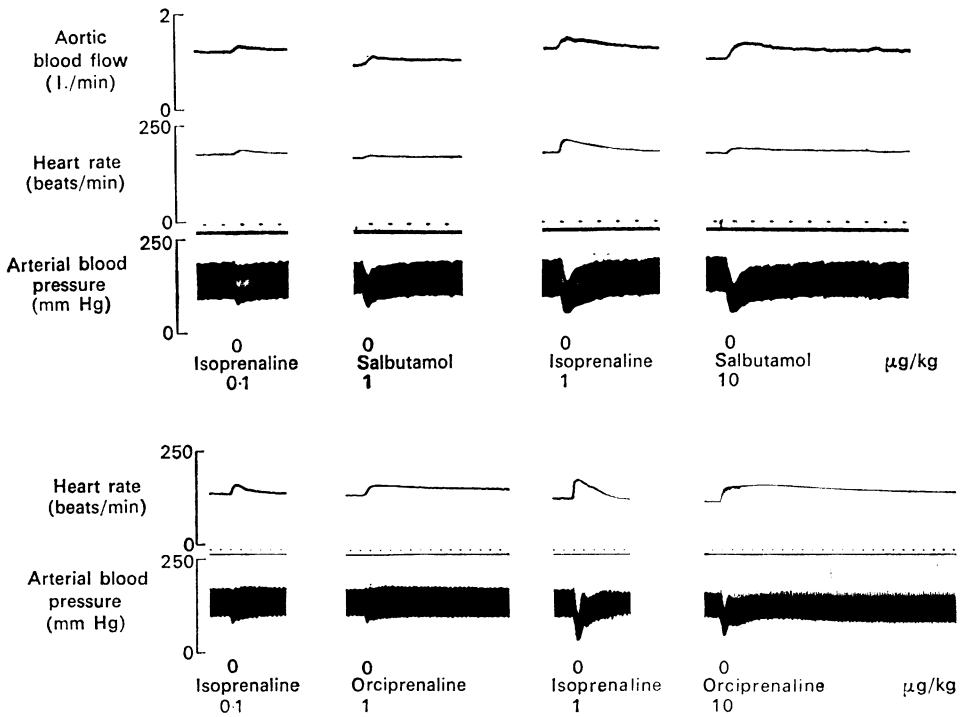

FIG. 2. Anaesthetized dog, upper 10 kg, lower 9 kg. Comparison of the cardiovascular actions of intravenously administered isoprenaline and salbutamol (upper) and isoprenaline and orciprenaline (lower). Note the low positive chronotropic response to salbutamol compared with isoprenaline in doses which cause similar falls in arterial blood pressure. Orciprenaline lacks the selectivity of action of salbutamol. Both salbutamol and orciprenaline are longer acting than isoprenaline. Time marker in both experiments, 1 minute.

the mean doses to increase heart rate by twenty and forty beats/min showed salbutamol to be respectively 285 (range 115–707) times and 792 (256–2,456) times less potent than isoprenaline ; and comparison of the mean doses to increase cardiac output by 100 and 200 ml/min showed salbutamol to be respectively 65 (range 43–100) times and 269 (135–537) times less potent than isoprenaline.

Regional blood flow in anaesthetized dogs

Hind limb

Intra-arterial injections of isoprenaline, 0·001–0·1 μg/kg, salbutamol, 0·001–0·2 μg/kg or orciprenaline, 0·1–5 μg/kg, produced short-lasting increases in blood flow to the hind limb. In the dose-ranges used these responses were not accompanied by changes in arterial blood pressure or heart rate. Results in the skinned limb did not differ significantly from those obtained in the unskinned limb. Part of an experiment in which isoprenaline and salbutamol were compared directly is illustrated

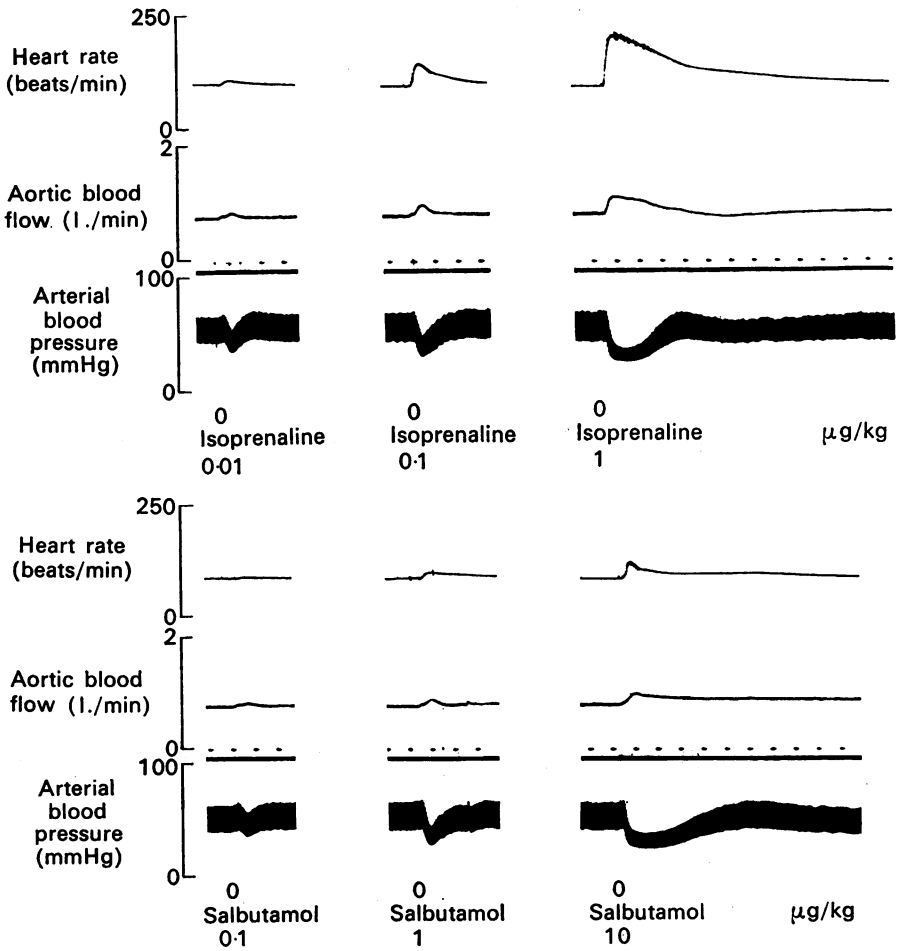

FIG. 3. Spinal dog, 8 kg. Comparison of cardiovascular actions of intravenously administered isoprenaline and salbutamol. Note low positive chronotropic potency of salbutamol. Time marker, 1 minute.

in Fig. 4. In six experiments (three in skinned and three in unskinned hind limbs) salbutamol was 3·17 (1·98–5·05) times less potent than isoprenaline in increasing hind limb blood flow. Similarly, in three experiments in unskinned hind limbs orciprenaline was an average of 33 (range 25–36) times less potent than isoprenaline.

Head

In each of two experiments salbutamol was 5 times less active than isoprenaline in increasing carotid blood flow after intra-arterial injection.

Systolic blood pressure and heart rate in conscious dogs

Oral administration

The most usual effect on systolic blood pressure of both isoprenaline, 0·1–5 mg/kg, and salbutamol, 0·001–0·05 mg/kg, was a decrease 1 h after administration but the changes were small and not dose related.

Both drugs caused dose dependent increases in heart rate although responses to isoprenaline varied more than to salbutamol. Maximum increases with both drugs

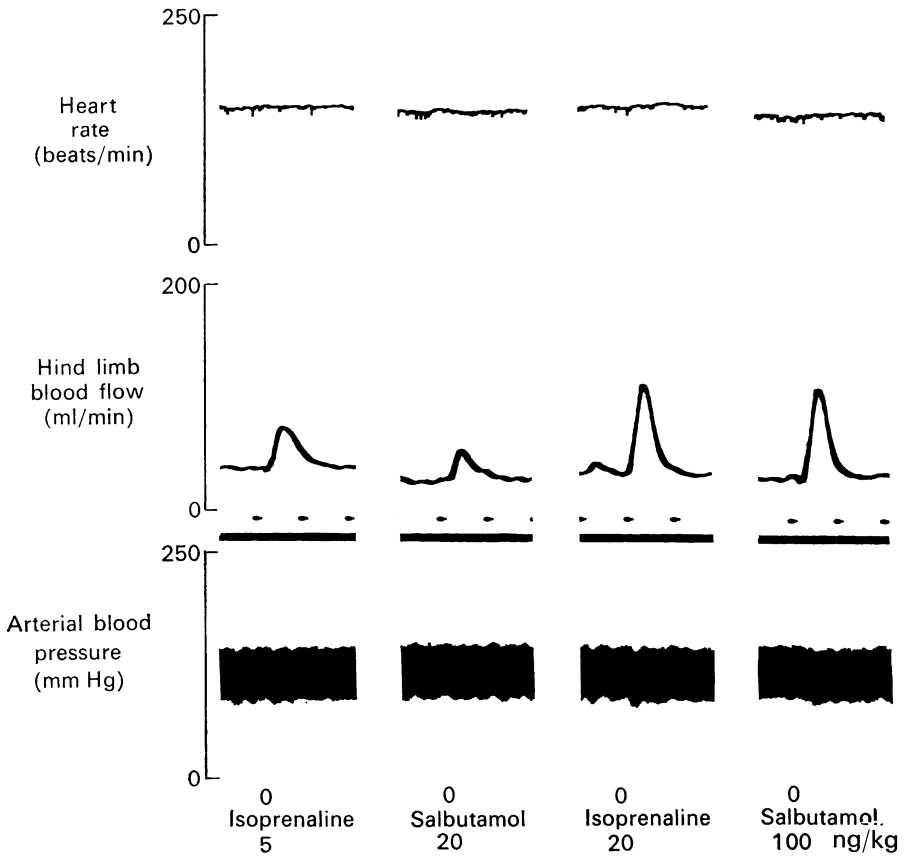

FIG. 4. Anaesthetized dog, 8 kg. Records of heart rate, blood flow through the right external iliac artery and arterial blood pressure. Increases in blood flow produced by injection into the artery of isoprenaline and salbutamol. Time marker, 1 minute.

occurred 1 h after dosing but responses to salbutamol frequently lasted for more than 5 h whereas those to isoprenaline returned to normal within this period. The positive chronotropic potencies of the two drugs are compared in Fig. 5. Salbutamol was approximately 60 times more potent than isoprenaline in increasing heart rate after oral administration. The slopes of the two curves were similar but the maximum response to isoprenaline was greater than to salbutamol.

Intravenous administration

Isoprenaline, 0·03–0·3 μg/kg and salbutamol, 0·1–3 μg/kg, caused dose-related increases in heart rate when given intravenously. In two experiments salbutamol was 7 times and 10 times less potent than isoprenaline and some 5 times longer acting.

Discussion

Diamond (1968) emphasized that pulmonary resistance values depend directly on the calibre of the airways so that their magnitude is very sensitive to changes in the smooth muscle tone of the tracheobronchial tree. The effectiveness of salbutamol in preventing increases in pulmonary resistance caused by acetylcholine suggests that its major action in the lung, like those of isoprenaline and orciprenaline, is to increase airways diameter.

We find salbutamol to be respectively 5 times and 13 times less potent than isoprenaline in preventing acetylcholine-induced increases in pulmonary resistance after intravenous administration to guinea-pigs and dogs, values which correspond to those obtained after intravenous administration to anaesthetized cats (Fogelman & Grundy, 1970) and *in vitro* on tracheobronchial muscle of guinea-pig and man

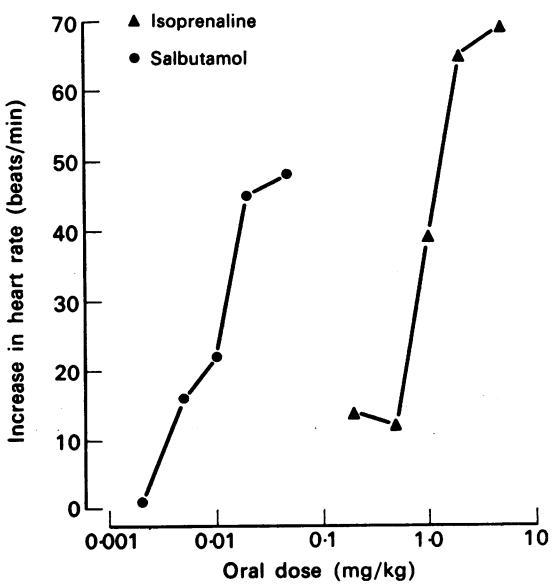

FIG. 5. Conscious dog. Comparison of the effects of orally administered isoprenaline and salbutamol on heart rate. Each point is the mean of the maximum increases in heart rate obtained in four dogs.

(Farmer, Kennedy, *et al.*, 1970 ; Hedges & Turner, 1969). However, when administered orally or by aerosol to animals (Cullum *et al.*, 1969) or to man (Choo-Kang *et al.*, 1969 ; Riding *et al.*, 1970 ; Tattersfield & McNicol, 1969 ; Kamburoff & Prime, 1970) salbutamol has a potency equal to or greater than that of isoprenaline. This enhanced potency of salbutamol by the two latter routes of administration most likely reflects a relatively greater rate of inactivation of isoprenaline. After intravenous injection little or no inactivation of either drug will occur before reaching the lungs since the route is *via* the right heart directly into the pulmonary circulation. When given orally, however, isoprenaline is almost completely inactivated by sulphatase enzymes in the intestinal flora or gut wall or, subsequently, by the enzyme catechol-*o*-methyl transferase (COMT) in the liver (Conway, Minatoya, Lands & Shekosky, 1968 ; Morgan, Sandler, Davies, Conolly, Paterson & Dollery, 1969). Salbutamol has high activity orally because it is not a substrate for either of these enzymes (Martin, Hobson, Page & Harrison, 1971). By aerosol, isoprenaline is well absorbed from the buccal cavity and respiratory tract, and is rapidly inactivated by uptake into tissues (Gryglewski & Vane, 1970) and subsequently intracellular metabolism to '3-*o*-methyl isoprenaline' by COMT. This rapid removal of isoprenaline both before and upon reaching its site of action will reduce its peak potency and duration of action. The weak β-adrenoceptor blocking activity of the metabolite '3-*o*-methyl isoprenaline' (Paterson, Conolly, Davies & Dollery, 1968) may further reduce the bronchodilator action of isoprenaline. In contrast, the activity of salbutamol in aerosol form is maintained because it is only slowly absorbed from the airways (Kennedy & Simpson, 1969) and is not degraded by COMT (Martin *et al.*, 1971).

The low cardiac stimulant potency of salbutamol in spinal and anaesthetized dogs confirms previous *in vivo* and *in vitro* results (Cullum *et al.*, 1969 ; Farmer, Kennedy *et al.*, 1970 ; Fogelman & Grundy, 1970). The spinal animal should provide the more precise estimate of direct cardiac stimulant potency because of the absence of a reflex component to the tachycardia in response to the concomitant decrease in arterial blood pressure. Since the relative potencies are, in fact, similar, the contribution of such a reflex tachycardia to the observed response in the anaesthetized animal presumably is minor. Dunlop & Shanks (1968) reached similar conclusions for isoprenaline in barbitone or chloralose-anaesthetized dogs. This lack of reflex tachycardia can be attributed to the anaesthetic used. Barbiturates depress the compensatory reflexes which normally would act in the presence of hypotension, firstly by their central action (Strobel & Wollman, 1969) and secondly by a peripheral blockade of the vagus nerve (Linegar, Dille & Koppanyi, 1936). In conscious dogs, compensatory reflexes are fully functional and a considerable proportion of the increase in heart rate produced by isoprenaline was shown to be mediated reflexly in response to the fall in arterial pressure by inhibition of cardiac vagal activity (Dunlop & Shanks, 1968). The pronounced increase in the positive chronotropic activity of intravenously or orally administered salbutamol in conscious dogs is probably of similar origin. Thus, it is likely that a major proportion of the tachycardia observed in these animals arises as a reflex response to the fall in arterial pressure, only a minor proportion resulting from a direct action of the drug on the sino-auricular node.

The ability of salbutamol to increase cardiac output in anaesthetized dogs is, at first sight, greater than expected, in view of its low positive chronotropic potency,

TABLE 2. *Dose ratios for salbutamol and orciprenaline relative to isoprenaline (=1) on the preparations used*

Preparation and response measured	Route of administration	Receptor classification	Salbutamol		Orciprenaline	
			Mean dose ratio	n	Mean dose ratio	n
Anaesthetized guinea-pig						
Inhibition of acetylcholine-induced increase in pulmonary resistance	Intravenous	β_2	4·64 (1·46–14·8)	6	28·5 (8·80–92·2)	5
Anaesthetized dog						
Inhibition of acetylcholine-induced increase in pulmonary resistance	Intravenous	β_2	12·45 (3·92–39·5)	4	17·6 (4·79–64·6)	4
Fall in blood pressure	Intravenous	β_2	10·8 (6·3–18·4)	5	13 (range 12–15)	3
Increase in blood flow to:						
Head	Intra-arterial	β_2	3·17 (1·98–5·05)	6	33 (range 25–36)	3
Hind-limb	Intra-arterial	β_2	5	2	NT	
Increase in cardiac output	Intravenous	—	11·2 (5·5–22·6)	5	NT	
Positive chronotropic effect	Intravenous	β_1	At five beats/min 112 (22–556)	5	10 (range 7–12)	3
			At ten beats/min 575 (330–10,040)	5		
Spinal dog						
Positive chronotropic effect	Intravenous	β_1	At twenty beats/min 285 (range 115–707)	3	NT	
			At forty beats/min 792 (range 256–2,456)	3		
Increase in cardiac output	Intravenous	—	At 100 ml/min 65 (range 43–100)	3	NT	
			At 200 ml/min 269 (range 135–537)	3		
Conscious dog						
Positive chronotropic effect	Intravenous	—	7–10	2	NT	
Positive chronotropic effect	Oral	—	0·017	4	NT	

n, Number of determinations; NT, Not tested; figures in parentheses are 95% confidence limits unless otherwise stated.

but this apparent discrepancy can be explained if the increase is attributed primarily to peripheral vasodilatation. The vasodilator action of isoprenaline is restricted mainly to precapillary resistance vessels, for example in skeletal muscle and intestine, with relatively little effect on venous capacitance vessels (Mellander & Johansson, 1968). This profile should be shared by salbutamol because it is thought to arise from a sparser distribution of β-adrenoceptors on the venous than arterial side of vascular beds (Mellander & Johansson, 1968). It is likely that selective arterial dilatation would produce an increase in venous return and a consequent increase in cardiac output. This proposal is consistent with the very close correlation which was found for the relative potencies of isoprenaline and salbutamol in decreasing arterial blood pressure and increasing cardiac output. The increased venous return with isoprenaline can be dealt with, at least in part, by the accompanying increase in heart rate. Increases in heart rate with salbutamol were small in the dose range used and an increased venous return must, therefore, produce an increase in cardiac filling and emptying. Analysis of aortic flow and heart rate records shows that estimated stroke volume did increase after salbutamol but usually either decreased or remained unchanged after isoprenaline. Cardiac output increases with salbutamol in man were also attributed primarily to an action of the drug on peripheral vascular smooth muscle (Gibson & Coltart, 1971). In spinal dogs vasomotor tone has been abolished and there is a consequent high degree of peripheral vasodilatation. In these preparations, salbutamol was much less effective than isoprenaline in increasing cardiac output. It appears, therefore, that, in contrast to anaesthetized dogs, increases in cardiac output in spinal dogs result mainly from the direct effects of the two drugs on the heart.

The selective stimulant actions of salbutamol were explained previously (Cullum *et al.*, 1969; Farmer, Kennedy *et al.*, 1970; Farmer *et al.*, 1970) on the basis of Lands and coworkers' idea that β-adrenoceptors comprise two subgroups, termed β_1 and β_2 (Lands, Arnold, McAuliff, Luduena & Brown, 1967; Lands, Luduena & Buzzo, 1967). The present results, which are summarized in Table 2, confirm those of previous studies (Cullum *et al.*, 1969; Fogelman & Grundy, 1970) in showing salbutamol to have high potency on bronchial β_2-adrenoceptors but exceptionally low potency on cardiac β_1-adrenoceptors. These results also show that the potency of salbutamol relative to isoprenaline was similar on bronchial and vascular β_2-adrenoceptors. The low vasodepressor potency of salbutamol found previously (Cullum *et al.*, 1969) was attributed to possible differences in the nature of these receptors, but is more likely to have resulted from the interaction found subsequently to be associated with vasodepressor responses (see **Methods**).

Orciprenaline has similar potencies on both β_1- and β_2-adrenoceptors and so, apart from its long duration of action, resembles isoprenaline rather than salbutamol. This lack of selectivity confirms our previous findings (Farmer *et al.*, 1970) and those of other workers (Shanks, Brick, Hutchinson & Roddie, 1967; O'Donnell, 1970). The lower incidence of cardiovascular side-effects with orciprenaline than with isoprenaline by aerosol administration to man (Holmes, 1968) may result, therefore, from a slower absorption from the respiratory tract rather than from a pharmacological differentiation between β-adrenoceptors.

We wish to thank Mrs. D. Worgan, Miss A. Stocks and Mr. G. Apperley for technical assistance and Mr. A. Davey for help with statistics.

REFERENCES

AMDUR, M. O. & MEAD, J. (1958). Mechanics of respiration in unanaesthetized guinea-pigs. *Am. J. Physiol.*, **192**, 364–368.

BURN, J. H. (1952). *Practical Pharmacology*, pp. 35–37. Oxford: Blackwell.

CHOO-KANG, Y. F. J., SIMPSON, W. T. & GRANT, I. W. B. (1969). Controlled comparison of the bronchodilator effects of three β-adrenergic stimulant drugs administered by inhalation to patients with asthma. *Br. med. J.*, **2**, 287–289.

COLEBATCH, H. J. M., OLSEN, C. R. & NADEL, J. A. (1966). Effect of histamine, serotonin and acetylcholine on the peripheral airways. *J. appl. Physiol.*, **21**, 217–226.

COMROE, J. H., BOTELHO, Stella Y. & DUBOIS, A. B. (1959). Design of a body plethysmograph for studying cardiopulmonary physiology. *J. appl. Physiol.*, **14**, 439–444.

CONWAY, W. D., MINATOYA, H., LANDS, A. M. & SHEKOSKY, J. M. (1968). Absorption and elimination profile of isoproterenol III. The metabolic fate of dl-isoproterenol-7-^{3}H in the dog. *J. Pharm. Sci.*, **57**, 1135–1141.

CULLUM, Valerie, A., FARMER, J. B., JACK, D. & LEVY, G. P. (1969). Salbutamol: a new, selective β-adrenoceptive receptor stimulant. *Br. J. Pharmac.*, **35**, 141–151.

DIAMOND, L. (1967). Utilization of changes in pulmonary resistance for the evaluation of bronchodilator drugs. *Archs int. Pharmacodyn.*, **168**, 239–250.

DIAMOND, L. (1968). Bronchodilatory and cardiovascular effects of metaproterenol. *J. Pharm. Sci.* **57**, 971–975.

DUNLOP, D. & SHANKS, R. G. (1968). Selective blockade of adrenoceptive β-receptors in the heart. *Br. J. Pharmac. Chemother.*, **32**, 201–218.

FARMER, J. B., KENNEDY, I., LEVY, G. P. & MARSHALL, R. J. (1970). A comparison of the β-adrenoceptor stimulant properties of isoprenaline with those of orciprenaline, salbutamol, soterenol and trimetoquinol on isolated atria and trachea of the guinea-pig. *J. Pharm. Pharmac.*, **22**, 61–63.

FARMER, J. B. & LEVY, G. P. (1969). Comparative β-adrenoceptive stimulant properties of salbutamol (AH 3365), orciprenaline and soterenol (MJ 1992). *Br. J. Pharmac.*, **35**, 358*P*–359*P*.

FARMER, J. B., LEVY, G. P. & MARSHALL, R. J. (1970). A comparison of the β-adrenoceptor stimulant properties of salbutamol, orciprenaline and soterenol with those of isoprenaline. *J. Pharm. Pharmac.*, **22**, 945–946.

FOGELMAN, F. & GRUNDY, H. F. (1970). A comparison of the cardiovascular actions of AQ 110 with those of isoprenaline and salbutamol. *Br. J. Pharmac.*, **38**, 416–432.

GIBSON, D. G. & COLTART, D. J. (1971). Haemodynamic effects of intravenous salbutamol in patients with mitral valve disease—comparison with isoprenaline and atropine. *Post-grad. med. J. Suppl.*, **46**, 40–44.

GRYGLEWSKI, R. & VANE, J. R. (1970). The inactivation of noradrenaline and isoprenaline in dogs. *Br. J. Pharmac.*, **39**, 573–584.

HEDGES, Annmarie & TURNER, P. (1969). β-Receptors in human isolated smooth muscle. *Br. J. Pharmac.*, **37**, 547*P*–548*P*.

HOLMES, T. H. (1968). A comparative clinical trial of metaproterenol and isoproterenol as bronchodilator aerosols. *Clin. Pharmac. Ther.*, **9**, 615–624.

KAMBUROFF, P. L. & PRIME, F. J. (1970). Oral and inhaled salbutamol as a bronchodilator. *Br. J. Dis. Chest*, **64**, 46–54.

KENNEDY, M. S. C. & SIMPSON, W. T. (1969). Human pharmacological and clinical studies on salbutamol: a specific β-adrenergic bronchodilator. *Br. J. Dis. Chest.*, **63**, 165–174.

LANDS, A. M., ARNOLD, A., MCAULIFF, J. P., LUDUENA, F. P. & BROWN, T. G. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature, Lond.*, **214**, 597–598.

LANDS, A. M., LUDUENA, F. P. & BUZZO, H. J. (1967). Differentiation of receptors responsive to isoproterenol. *Life Sci.*, **6**, 2241–2249.

LINEGAR, C. R., DILLE, J. M. & KOPPANYI, T. (1936). Studies on barbiturates XVIII. Analysis of a peripheral action of barbiturates. *J. Pharmac. exp. Ther.*, **58**, 128–134.

LULLING, J., EL SAYED, F. & LIEVENS, P. (1967). Ventilatory mechanics in the dog. Its application to quantitative study of bronchomotor active drugs. *Med. Pharmac. exp.*, **16**, 481–495.

MARTIN, L. E., HOBSON, J. C., PAGE, Jean A. & HARRISON, C. (1971). Metabolic studies of salbutamol-^{3}H, a new bronchodilator, in rat, rabbit, dog and man. *Eur. J. Pharmac.*, **14**, 183–199.

MELLANDER, S. & JOHANSSON, B. (1968). Control of resistance, exchange and capacitance functions in the peripheral circulation. *Pharmac. Rev.*, **20**, 117–196.

MORGAN, C. Diana, SANDLER, M., DAVIES, D. S., CONOLLY, M., PATERSON, J. W. & DOLLERY, C. T. (1969). The metabolic fate of Dl-(7-^{3}H) isoprenaline in man and dog. *Biochem. J.*, **114**, 8*P*.

O'DONNELL, Stella R. (1970). A selective β-adrenoceptor stimulant (Th 1165a) related to orciprenaline. *Eur. J. Pharmac.*, **12**, 35–43.

PATERSON, J. W., CONOLLY, M. E., DAVIES, D. S. & DOLLERY, C. T. (1968). Isoprenaline resistance and the use of pressurized aerosols in asthma. *Lancet*, **ii**, 426–429.

RIDING, W. D., DINDA, P. & CHATTERJEE, S. S. (1970). The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. *Br. J. Dis. Chest.*, **64**, 37–45.

SHANKS, R. G., BRICK, I., HUTCHINSON, D. & RODDIE, I. C. (1967). Stimulation of adrenergic β-receptors by orciprenaline. *Br. med. J.*, **1**, 610–612.

STROBEL, G. E. & WOLLMAN, H. (1969). Pharmacology of anaesthetic agents. *Fedn Proc.*, **28**, 1386–1403.

TATTERSFIELD, Anne E. & MCNICOL, M. W. (1969). Salbutamol and isoproterenol. A double-blind trial to compare bronchodilator and cardiovascular activity. *New Engl. J. Med.*, **281**, 1323–1326.

(*Received March*, 1, 1971)