Br. J. Pharmac. (1972), **45**, 574–583.

Actions of the sympathomimetic bronchodilator, rimiterol (R798), on the cardiovascular, respiratory and skeletal muscle systems of the anaesthetized cat

W. C. BOWMAN AND I. W. RODGER

Department of Pharmacology, University of Strathclyde, Glasgow G1 1XW

Summary

1. The actions of rimiterol [erythro(3,4-dihydroxyphenyl, 2-piperidyl methanol hydrobromide)], a new sympathomimetic bronchodilator, have been compared with those of salbutamol and laevoisoprenaline on the heart and lungs, and on contractions of the soleus muscle of cats under chloralose anaesthesia.

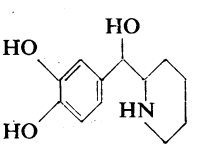
2. Rimiterol and salbutamol injected intravenously were about equipotent in all tests, and were about 8 times less potent than laevoisoprenaline both in opposing the bronchoconstrictor action of 5-hydroxytryptamine, and in decreasing the tension and degree of fusion of incomplete tetanic contractions of the cat soleus muscle. They were about 19 times less potent than laevoisoprenaline in increasing heart rate.

3. The effect on the soleus muscle is considered to be analogous to the muscle tremor that often occurs in man, and the results therefore suggest that systemic administration of bronchodilator doses of rimiterol, like salbutamol, may produce muscle tremor as an unwanted side-effect.

4. When equipotent doses to oppose 5-hydroxytryptamine-induced bronchospasm were compared, rimiterol and salbutamol produced less tachycardia than did laevoisoprenaline. In order to match the tachycardia produced by laevoisoprenaline, the doses of rimiterol or salbutamol had to be increased about two and a half times. This safety margin for salbutamol in the cat is considerably less than that reported by others for different species, which suggests that β_1- and β_2-adrenoceptors may be less clearly differentiated in the cat than they are in other laboratory animals.

Introduction

Rimiterol (R798) [erythro(3,4-dihydroxyphenyl, 2-piperidyl methanol hydrobromide)] is a new sympathomimetic bronchodilator recently described, under the code name WG253, by Griffin & Turner (1971), Turner & Griffin (1971), Laity (1971), and Carney, Daly, Lightowler & Pickering (1971).



Studies on animal tissues indicate that the compound has relatively more action on the bronchi (β_2-adrenoceptors) than on the heart (β_1-adrenoceptors). In man, when administered by aerosol, it gave longer protection against histamine-induced bronchospasm than did isoprenaline.

Some sympathomimetic bronchodilators have been found to produce muscle tremor as an unwanted side effect (Beumer, 1971 ; Legge, Gaddie & Palmer, 1971), and Bowman & Nott (1970) have suggested that the cat soleus muscle provides a useful model for detecting the likelihood of its occurrence. In the experiments described in this paper, the effects of rimiterol have been compared with those of laevoisoprenaline and salbutamol on the cardiovascular and respiratory systems and on the contractions of the soleus muscle of cats under chloralose anaesthesia.

Methods

The experiments were carried out on 33 cats of either sex anaesthetized with a mixture of chloralose (80 mg/kg) and sodium pentobarbitone (6 mg/kg) injected intraperitoneally. All records were made on a Grass 6-channel curvilinear polygraph (model 7WC 12PA). In all experiments, general arterial blood pressure was recorded from a femoral or a carotid artery by means of a Statham (model P23AC) pressure transducer.

Cardiovascular system

Left ventricular pressure, left ventricular dp/dt, heart rate, pulmonary artery pressure, and general arterial blood pressure were recorded simultaneously from open chest cats by a method similar to that described by McInnes & Parratt (1969). Left ventricular pressure was recorded by means of a Statham pressure transducer (model P23AC) attached to a needle cannula inserted into the left ventricle. This record was differentiated by means of a Grass (model 7P20) differentiator to give left ventricular dp/dt. Heart rate was recorded by means of a Grass (model 7P4C) tachograph triggered by the general arterial pulse. Pulmonary artery pressure was recorded by means of a Statham pressure transducer (model P23AC) attached to a needle cannula inserted into the pulmonary artery in the direction of blood flow.

Airways resistance

The method used was adapted from that described by Amdur & Mead (1958) for the guinea-pig and modified by Apperley & Daly (1972). The trachea was cannulated and positive pressure, fixed volume, ventilation was applied from a Palmer Ideal Pump at a rate of 27 breaths/min and a stroke volume of 13 ml/kg body weight. A thin walled latex rubber balloon of 10 ml undistended volume attached to one end of a polythene tube (1 mm internal diameter) was inserted through the mouth into the lower third of the oesphagus. The volume of air in the balloon throughout each experiment was between 0·1 and 0·5 ml. The other end of the polythene tube was attached to a micromanometer (Mercury Electronics, model M6). An identical polythene tube was led from the side arm of the tracheal cannula into the same micromanometer. The output from the micromanometer was coupled to the pen recorder and corresponded to the transpulmonary pressure (TPP); i.e., the difference between the trachea pressure and the intraoesophageal pressure. [Intraoesophageal pressure corresponds closely to intrapleural pressure (Mead, 1961).]

Rate of air flow ($\dot{V}$) was recorded by means of a mesh screen pneumotachograph (Mercury Electronics, model F2—12 mm) connected to a second model M6 micromanometer. Electrical integration of the resulting signal by a Grass (model 7P 10A) integrator gave a measure of the tidal volume (V_T). All three parameters (TPP, $\dot{V}$ and V_T) were recorded simultaneously on three channels of the polygraph.

A constant submaximal degree of bronchoconstriction was produced about every 20 min by the intravenous injection of 1 to 10 μg/kg of 5-hydroxytryptamine. The dose of 5-hydroxytryptamine was chosen such that it was big enough to produce a considerable degree of bronchoconstriction but was insufficient to cause appreciable changes in blood pressure, heart rate or soleus muscle contractions. The effects of at least two control doses of 5-hydroxytryptamine were observed, and the sympathomimetic under test was then injected about 20 min later. The next dose of 5-hydroxytryptamine was injected at a time when the effect of the sympathomimetic had reached its maximum as judged by its effect on the soleus muscle contractions and on the heart rate. This was usually between 30 and 40 s after injection of the sympathomimetic amine. The intervals between successive injections of sympathomimetics were such that the responses to 5-hydroxytryptamine (given every 20 min) had returned to the control level. In each experiment, 4 or 5 doses of each of two sympathomimetics were administered.

In all experiments on the respiratory system, contractions of the soleus muscle were recorded simultaneously, and in some of them heart rate was also recorded.

Soleus muscle

The tendon of insertion of a soleus muscle was cut and attached to a Grass (model FT10C) force transducer. Subtetanic contractions of the soleus muscle were evoked by stimulating the soleus branch of the motor nerve at frequencies of 6–10 Hz (the frequency was constant in any one experiment) for 1 s every 10 seconds. The method was identical with that described by Bowman & Nott (1970). In some experiments, the relative potencies of the sympathomimetics were determined by the method of cumulative injection described by Nott & Raper (1972). In many experiments airways resistance and heart rate were recorded simultaneously with soleus muscle contractions.

Drugs were injected intravenously through a cannula in a brachial or a femoral vein.

The drugs used were: rimiterol hydrobromide (R798, formerly WG253) (3M-Riker), salbutamol (Allen & Hanbury), laevoisoprenaline bitartrate (Wyeth), bethanidine sulphate (Burroughs Wellcome), 5-hydroxytryptamine creatinine sulphate (5-HT, British Drug Houses), and (±)-propranolol (Imperial Chemical Industries). The doses quoted refer to the bases.

Results

Respiratory system

The doses of 5-hydroxytryptamine used produced a rapid increase in transpulmonary pressure coupled with a slight decrease in flow rate (Fig. 1). The effects reached their maxima within about 10 seconds. About 40 s after injection, 2 successive expirations were prevented by temporarily occluding the outflow to the pump so that hyperventilation occurred. This had the effect of rapidly ter-

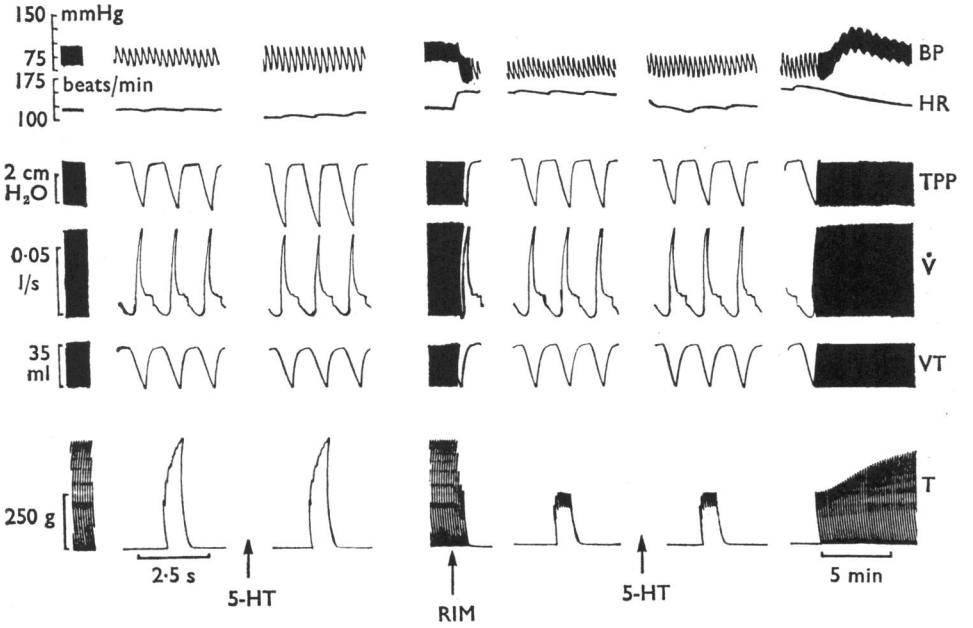


FIG. 1. Effects of rimiterol, from the top downwards, on general arterial blood pressure (BP), heart rate (HR), transpulmonary pressure (TPP), air flow ($\dot{V}$), tidal volume (VT), and incomplete tetanic contractions of the soleus muscle (T, 7 Hz for 1 s every 10 s). Only parts of the records are shown, some at a slow and some at a faster paper speed. 5-HT (8 μg/kg i.v.) produced a small increase in pulse pressure and a small decrease in heart rate. Transpulmonary pressure was increased and air flow slightly reduced. Tidal volume and soleus muscle contractions were unaffected. Twenty min later, rimiterol (RIM, 0·5 μg/kg i.v.) was injected in a dose just big enough to abolish the bronchoconstriction. Blood pressure fell, heart rate increased (by 35 beats/min) and soleus muscle contractions were decreased. The other parameters were unchanged. At the height of the effect of rimiterol on heart rate and soleus, the effects of 5-HT on transpulmonary pressure and air flow were abolished.

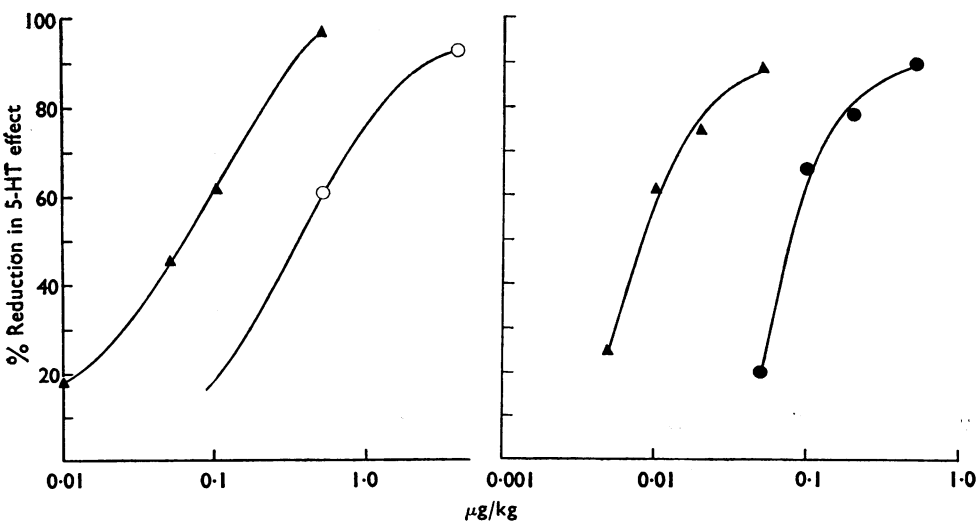


FIG. 2. Dose response curves from two typical experiments like that illustrated in Fig. 1 in which the effects of intravenous laevoisoprenaline (▲) were compared with those of salbutamol (○) and rimiterol (●) in reducing the bronchoconstriction produced by 5-HT. The responses are expressed as the percentage reduction of the degree of bronchoconstriction produced by 5-HT (10 μg/kg).

minating the action of 5-hydroxytryptamine. In effect, 5-hydroxytryptamine prolonged the expiratory phase of breathing by virtue of its bronchoconstrictor action. In assessing the bronchodilator activity of the sympathomimetics, the increase in airways resistance produced by 5-hydroxytryptamine in their presence was expressed as a percentage reduction of that produced by 5-hydroxytryptamine alone. The increases in airways resistance were calculated from the flow rate and the transpulmonary pressure at isovolumic points as described by Amdur & Mead (1958). Figure 1 illustrates the reduction in the bronchoconstrictor effects of 5-hydroxytryptamine produced by a dose of rimiterol, and the graphs of Fig. 2 illustrate dose-response curves for rimiterol and laevoisoprenaline, and salbutamol and laevoisoprenaline, from typical experiments. The dose-response curves in all experiments were close to parallel. Salbutamol and rimiterol were approximately equipotent, and at the 50% level, ranged from 6–10 times less potent than laevoisoprenaline on a weight basis (calculated as bases). The design of these experiments did not allow accurate determination of the duration of the bronchodilator effects of the amines, except that the effects of salbutamol were clearly longer lasting than those of laevoisoprenaline and rimiterol.

Effective bronchodilator doses of all three sympathomimetics always decreased the tension and fusion of incomplete tetanic contractions of the soleus muscle. Figure 1 also illustrates the effect of rimiterol on the soleus muscle. In 4 experiments, heart rate was recorded simultaneously with bronchodilator as well as soleus muscle effects. The largest doses of sympathomimetics used abolished the bronchoconstrictor effects of 5-hydroxytryptamine but were not great enough to produce the maximum increases in heart rate, and therefore could not be compared at the 50% level. In 2 of these experiments, salbutamol (2·0 and 4·0 μg/kg) in doses that caused 90% inhibition of bronchoconstriction, caused increases in heart rate of 42 and 61 beats/minute. The corresponding bronchodilator doses of laevoisoprenaline (0·20 and 0·50 μg/kg) in the same experiments produced increases of 51 and 72 beats/minute. The comparable figures for rimiterol (0·5 and 5·0 μg/kg), in the other two experiments, were 38 and 45 beats/min and for laevoisoprenaline (0·05 and 0·3 μg/kg), 56 and 58 beats/minute.

Cardiovascular system

All three sympathomimetic amines lowered general arterial blood pressure, slightly increased pulmonary artery pressure, increased heart rate, and increased left ventricular pressure and positive dp/dt. Quantitative comparisons were made only on heart rate. The graphs of Fig. 3 illustrate typical cumulative dose-response curves plotted from an experiment in which laevoisoprenaline was compared with rimiterol and with salbutamol on heart rate. In all experiments, the drugs produced the same maximum effects, the heart rate increasing by 80–220 beats/min in different experiments, and the dose-response curves were close to parallel for all three drugs. At the 50% of maximum effect level, on a weight basis, rimiterol was from 12–30 (mean $\pm$ S.E., $20{\cdot}7 \pm 2{\cdot}3$) times less potent than laevoisoprenaline, and salbutamol from 10–22 (mean $\pm$ S.E., $18{\cdot}2 \pm 2{\cdot}1$) times less potent than laevoisoprenaline. Any difference between the potencies of salbutamol and rimiterol was not significant ($0{\cdot}30 > P > 0{\cdot}25$). After cumulative addition to produce the maximum effects on heart rate, half recovery with laevoisoprenaline occurred in 3 to 4 minutes. The effects of rimiterol took 2 to 4 times longer and those of salbutamol more than 20 times longer to decay to half recovery (Fig. 3).

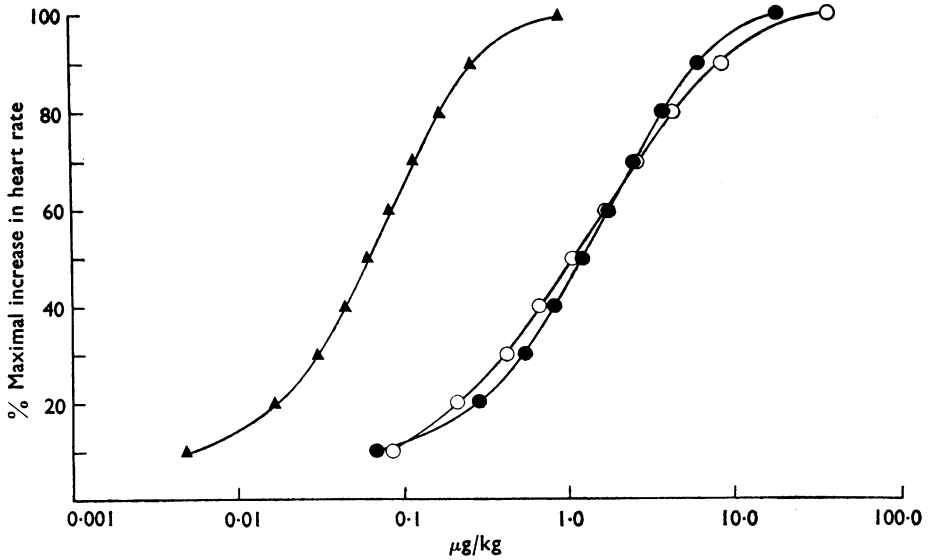


FIG. 3. Cumulative dose response curves from a typical experiment in which the effects of intravenous laevoisoprenaline (▲), rimiterol (●) and salbutamol (○) on heart rate were compared. The responses are expressed as the percentage of the maximal increase in heart rate. In this experiment, resting heart rate varied from 108 to 130 beats/min; and this increased to maxima of 190 to 212 beats/min after cumulative injection of the drugs.

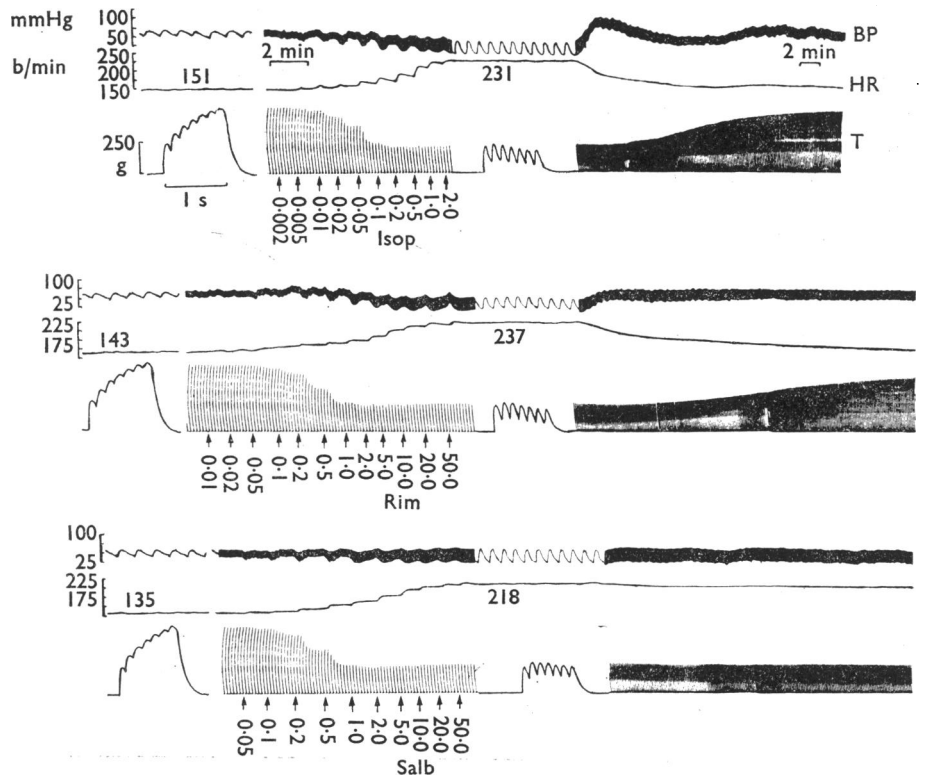


FIG. 4. Effects of laevoisoprenaline (Isop), rimiterol (Rim), and salbutamol (Salb) on general arterial blood pressure (BP), heart rate (HR), and incomplete tetanic contractions of the soleus muscle (T, 7 Hz for 1 s every 10 s). All records are from the same experiment. For each record, the paper speed was increased at two points to show the degree of fusion of the soleus contraction, and was decreased after the maximum effects were produced to show the extent of recovery. The blood pressure was low in this animal as a result of deep anaesthesia. The numbers on the heart rate record are the resting and the maximum heart rates in beats/minute. The doses in μg/kg injected intravenously (not the cumulative doses) are given under the soleus muscle records.

In 2 cats, the relative potencies were redetermined after bilateral vagotomy and the intravenous injection of bethanidine (2–6 mg/kg) in doses sufficient to abolish the carotid occlusion reflex. The potencies of the drugs before and after these procedures were unchanged. In 2 further experiments, additional chloralose was administered to lower the systolic blood pressure to around 75 mmHg. Under these conditions, the drugs produced little further lowering of blood pressure. The relative potencies of the amines in increasing heart rate still fell within the ranges quoted above.

Soleus muscle

All three amines decreased the tension and fusion of incomplete tetanic contractions of the soleus muscle. Figure 4 illustrates an experiment in which each amine was injected cumulatively until the maximal effects on the soleus muscle and on heart rate were achieved. The maxima were the same for all three drugs (decreases in tension of 45–60% in different experiments). Figure 5 illustrates typical cumulative dose-response curves for the effect on the soleus muscle. For a given submaximal effect on the soleus muscle, the effects of rimiterol and of salbutamol on heart rate were relatively weaker than those of laevoisoprenaline. The dose of laevoisoprenaline necessary to produce 50% of the maximum increase in heart rate was about 3 times greater than the dose to produce 50% of the maximum depression of the soleus. For salbutamol and rimiterol this ratio was about 8 (compare the graphs of Figs. 3 and 5 which are from the same experiment). The relative potencies of the drugs in depressing soleus muscle contractions were closely similar to those obtained when their effects on the bronchi were studied. Rimiterol was 5–10 (mean $\pm$ S.E., 7·5 $\pm$ 2·2) times and salbutamol 6–10 (mean $\pm$ S.E.,

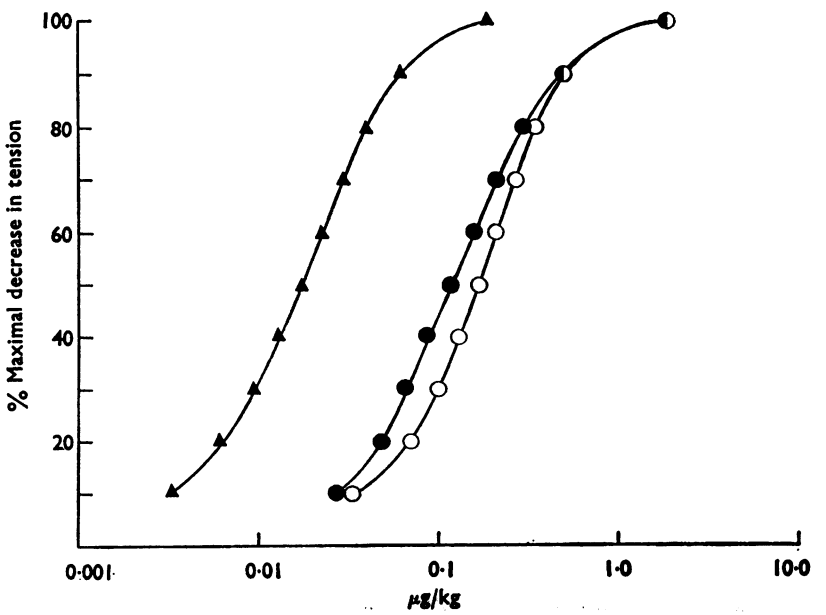


FIG. 5. Cumulative dose-response curves, from a typical experiment in which the effects of intravenous laevoisoprenaline (▲), rimiterol (●) and salbutamol (○) on incomplete tetanic contractions of the soleus muscle were compared. The responses are expressed as the percentage of the maximal depression of contractions. In this experiment the amines produced a maximal decrease in tension of 58%.

8·0 ± 2·3) times less potent than laevoisoprenaline on a weight basis. There was no significant difference between the potencies of rimiterol and salbutamol ($0{\cdot}95 > P > 0{\cdot}90$). Apperley & Daly (1972) have recently reported ratios of potency for laevoisoprenaline and salbutamol similar to those found in the present experiments on the bronchi and soleus muscle of the cat.

After a single dose of laevoisoprenaline just sufficient to produce the maximal depression of soleus contractions, half recovery occurred in 3 to 5 minutes. Rimiterol was 1·5 to 3 times longer lasting. The duration of action of salbutamol also fell within this range, but in any one cat was always slightly longer lasting in its effects than rimiterol.

In experiments, such as that illustrated in Fig. 4 in which the amines were injected cumulatively to produce the maximum effect on heart rate, that is, in doses far in excess of those necessary to produce the maximum effects on the soleus, striking differences in duration of action were evident. The effects of laevoisoprenaline and of rimiterol maintained the same relationship as that with single doses. However, after salbutamol, no sign of recovery of soleus contractions was seen throughout the remainder of the experiment (up to 8 h), although propranolol (0·2 mg/kg) given at any time during this prolonged effect, restored the contractions to the control level within 5 minutes.

Discussion

The results showed that rimiterol, like isoprenaline, salbutamol and other β-adrenoceptor agonists (Bowman & Zaimis, 1958 ; Bowman & Nott, 1969 ; 1970), produces a decrease in the tension and degree of fusion of incomplete tetanic contractions of the slow-contracting cat soleus muscle. Other β-adrenoceptor agonists have been shown to produce a similar effect on the slow-contracting units in human muscles (Marsden & Meadows, 1970). In a voluntary contraction, the various muscle units within a muscle contract asynchronously and intermittently at subtetanic frequencies, but the pattern of activity is so integrated at central level that the algebraic sum of the contractions and relaxations of the units gives an almost smooth contraction from the whole muscle. A decrease, produced by β-adrenoceptor agonists, in the fusion of the slow units within a muscle, like that produced on the cat soleus, might be expected to produce the type of enhanced physiological tremor that has become an increasingly observed side-effect of sympathomimetic bronchodilators, especially when administered systemically. All the β-adrenoceptor agonists so far examined have affected the cat soleus muscle in this way in intravenous doses that are similar to or even smaller than those required to produce bronchodilatation. This indicates that the β-adrenoceptors in the soleus muscle closely resemble those in the bronchi, and it may therefore prove impossible to produce a sympathomimetic bronchodilator which does not occasionally cause muscle tremor as an unwanted side effect when administered systemically. Muscle tremor is said to diminish with repeated use of a bronchodilator. A possible explanation of the disappearance of this side effect is that the central nervous system learns to combat it by adjusting the frequency of discharge of nerve impulses to the muscles in an appropriate way. There is no evidence of tachyphylaxis in the effect on the cat soleus muscle, when doses are given at regular intervals throughout a prolonged experiment.

In these experiments on the cat, rimiterol and salbutamol were about equipotent in their effects on lungs, heart and muscle. Salbutamol, however, was always

longer lasting in its effects and the difference in duration of action was particularly marked when the drugs were given cumulatively to produce maximal effects. The different durations of action are probably largely due to different methods and rates of metabolism. Rimiterol is likely to be a substance for catechol-*O*-methyl transferase, whereas salbutamol is known not to be (Cullum, Farmer, Jack & Levy, 1969).

Salbutamol and rimiterol were about 8 times less potent than laevoisoprenaline in preventing 5-hydroxytryptamine-induced bronchospasm, and about 20 times less potent than laevoisoprenaline in stimulating the heart. Numerous experiments in this laboratory have shown that (±)-isoprenaline is about half as potent as laevoisoprenaline in all its effects, so that, in comparison with (±)-isoprenaline, salbutamol and rimiterol in the cat are about 4 times less potent on the bronchi and 10 times less potent on the heart. Thus at equipotent bronchodilator doses, salbutamol and rimiterol would be less active than (±)-isoprenaline in stimulating the heart, and in order to produce the same degree of cardiac stimulation as that produced by (±)-isoprenaline, the dose of salbutamol or rimiterol would have to be increased about two and a half times. The potencies of the sympathomimetic amines were not changed by vagotomy, by lowering the blood pressure so that their depressor effects were reduced, or by the administration of bethanidine in doses sufficient to block the carotid occlusion reflex. Their stimulant effects on the heart therefore appeared to be direct, and not the result of a reflex inhibition of vagal tone or of a reflex increase in sympathetic drive consequent upon the fall in blood pressure. Daly, Farmer & Levy (1971) reached similar conclusions with regard to isoprenaline and salbutamol.

The safety margin between bronchial and cardiac effects for salbutamol and rimiterol indicates a clear advantage of these drugs over isoprenaline. However, the safety margin for salbutamol found here in the cat is surprisingly small in comparison with that reported for other species by Cullum *et al.* (1969) and Daly *et al.* (1971). It may be that β_1- and β_2-adrenoceptors in the cat are less clearly differentiated than they apparently are in some other species. In the absence of detailed clinical trials in which the relative potencies of the drugs on the different organ systems in man are compared after systemic administration, it is not possible to decide to what extent the cat is a suitable test animal for determining degrees of selectivity of drugs for β-adrenoceptors in different human organs. Furthermore, it is not known to what extent 5-hydroxytryptamine-induced bronchoconstriction is a suitable model for asthma. β-Adrenoceptor agonists, as well as directly dilating the bronchi, have been shown to inhibit the release of endogenous bronchoconstrictor substances from the lung (Assem & Schild, 1969; Kaliner, La Raia, Orange & Austen, 1971). This additional effect probably plays a part in the relief of asthmatic symptoms, but is irrelevant to the antagonism of bronchoconstriction induced by 5-hydroxytryptamine. Calculation of the increases in airways resistance produced by 5-hydroxytryptamine in different cats showed that comparable degrees of bronchoconstriction were produced. However, this degree of bronchoconstriction, which was limited by the desire to avoid cardiovascular effects of 5-hydroxytryptamine, was entirely arbitrary. With smaller degrees of bronchoconstriction, the safety margin between bronchodilation and tachycardia would be widened for all the drugs, whereas with more severe bronchoconstriction, the doses needed to dilate the bronchi would presumably be larger and then more closely approach those that stimulate the heart. A long duration of action may

then constitute a disadvantage because once the dose level to affect the heart is reached, the tachycardia produced is prolonged.

We are grateful to Mr. J. Houston for technical assistance and to Allen & Hanburys Ltd., British Drug Houses Ltd., Burroughs Wellcome & Co. Ltd., Imperial Chemical Industries Ltd., 3M-Riker Ltd., and John Wyeth and Brother Ltd., for generous gifts of drugs. We are indebted to the Wellcome Foundation for a grant towards apparatus. One of us (I. W. Rodger) was in receipt of a Medical Research Council Scholarship.

REFERENCES

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

APPERLEY, G. H. & DALY, M. J. (1972). Simultaneous measurement of skeletal muscle, pulmonary mechanical and vascular responses to bronchodilators in the cat. *J. Pharm. Pharmac.*, **24**, 152–153.

ASSEM, E. S. K. & SCHILD, H. O. (1969). Inhibition by sympathetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature*, **224**, 1028–1029.

BEUMER, H. M. (1971). Comparative studies of the protective effect of Alupent and Th1165a against histamine in man. *Respiration*, **28**, 148–157.

BOWMAN, W. C. & NOTT, M. W. (1969). Actions of sympathomimetic amines and their antagonists on skeletal muscle. *Pharmac. Rev.*, **21**, 27–72.

BOWMAN, W. C. & NOTT, M. W. (1970). Actions of some sympathomimetic bronchodilator and β-adrenoceptor blocking drugs on contractions of the cat soleus muscle. *Br. J. Pharmac.*, **38**, 37–49.

BOWMAN, W. C. & ZAIMIS, E. (1958). The effects of adrenaline, noradrenaline and isoprenaline on skeletal muscle contractions in the cat. *J. Physiol. (Lond.)*, **144**, 92–107.

CARNEY, I., DALY, M. J., LIGHTOWLER, J. E. & PICKERING, R. W. (1971). The comparative pharmacology of WG253 (Rimiterol hydrobromide), a new bronchodilator. *Archs int. Pharmacodyn. Thér.*, **194**, 334–345.

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

DALY, M. J., FARMER, J. B. & LEVY, J. P. (1971). Comparison of the bronchodilator and cardiovascular actions of salbutamol, isoprenaline and orciprenaline in guinea-pigs and dogs. *Br. J. Pharmac.*, **43**, 624–638.

GRIFFIN, J. P. & TURNER, P. (1971). Preliminary studies of a new bronchodilator (WG253) in man. *J. Clin. Pharmac.*, **11**, 280–287.

KALINER, M. A., LA RAIA, P. J., ORANGE, R. P. & AUSTEN, K. F. (1971). Cyclic 3-5-adenosine monophosphate and modulation of the immunologic release of histamine and slow reacting substance of anaphyllaxis in human lung. International Conference on Physiology and Pharmacology of Cyclic AMP. Milan, Italy, July, 1971. Abstracts of Lectures.

LAITY, J. L. M. (1971). A comparison of the effects of isoprenaline, WG253 and salbutamol on the tension and rate of rabbit isolated atria. *J. Pharm. Pharmac.*, **23**, 633–634.

LEGGE, J. S., GADDIE, J. & PALMER, K. N. V. (1971). Comparison of two oral selective β_2-adrenergic stimulant drugs in bronchial asthma. *Br. med. J.*, **1**, 637–639.

MARSDEN, C. D. & MEADOWS, J. C. (1970). The effects of adrenaline on the contraction of human muscle. *J. Physiol. Lond.*, **207**, 429–448.

MCINNES, L. & PARRATT, J. R. (1969). Studies on the mode of action of hexobendine, a prospective anti-anginal drug. *Br. J. Pharmac.*, **37**, 272–282.

MEAD, J. (1961). Mechanical properties of lungs. *Physiol. Rev.*, **41**, 281–329.

NOTT, M. W. & RAPER, C. (1972). The use of cumulative dose-response curves in potency comparisons of sympathomimetic amines on the cat soleus muscle. *Br. J. Pharmac.*, **44**, 589–591.

TURNER, P. & GRIFFIN, J. P. (1971). Antagonism of acetylcholine-induced bronchospasm by WG253, a new sympathomimetic amine. *J. Pharm. Pharmac.*, **23**, 632.

(Received March 22, 1972)