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Mutual suppression of cardiovascular effects of some β-adrenoreceptor agonists in the cat

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Observations were made of the effects of adrenaline, isoprenaline and orciprenaline on the blood pressure, heart rate and configuration of the ECG in cats. The effects of single injections of these amines in producing a rise in heart rate and a fall in blood pressure were reduced during the intravenous infusion of any one of them: the pressor response to injected adrenaline was enhanced during an infusion. Combinations of these amines did not produce changes in the configuration of the ECG. These experiments were motivated by allegations of acute toxic effects on the cardiovascular system of large doses, or of combinations, of sympathomimetic bronchodilators in asthma. No evidence of deleterious effects of interactions was obtained.

IN the treatment of asthma, sympathomimetic amines are commonly employed in aerosol inhalers for their bronchodilator action, this being an effect on the β-adrenoreceptors of bronchial smooth muscle. The safety of these preparations has been questioned in a number of articles over the last few years because of deaths among asthma patients known to have been using metered aerosol sprays, particularly those containing adrenaline, isoprenaline or orciprenaline as the active component. It has been suggested that excess exposure to these amines (Greenberg & Pines, 1967), or their use in combinations (Anon., 1965), can result in untoward effects arising from their cardiac activity. Greenberg & Pines (1967) think that the amines may induce ventricular fibrillation, and other workers have suggested that they cause cardiac arrest and that this is the cause of death. The evidence for these assertions has included a number of ECG records showing patterns varying from ventricular tachycardia (Greenberg & Pines, 1967) to atrial flutter (Exon, 1967) in patients using sympathomimetic aerosols.

Although much work has been done on the blood pressure effects of large doses of these amines and on interactions between them, there has been little experimental work done on their cardiac effects. Therefore, experiments were made on cats to investigate the cardiovascular effects of interaction between three sympathomimetic amines commonly supplied as aerosol preparations, namely adrenaline, isoprenaline and orciprenaline.

Experimental

METHODS

Cats of either sex, weighing between 1·7 and 4·5 kg, were anaesthetized with chloralose (90 mg/kg) and pentobarbitone (5 mg/kg) given intraperitoneally. Blood pressure was monitored from the right femoral artery with a Statham strain gauge transducer. The heart rate was measured through a cardiotachometer coupler connected to needle electrodes inserted under the skin. Both blood pressure and heart rate were recorded on an Offner Dynograph. The electrocardiogram was recorded on a

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Phillips electrocardiograph using electrodes corresponding to standard human limb lead II. Intravenous injections were given into the right femoral vein in a volume of 0·1 ml and washed in with 0·1 ml/kg of 0·9% NaCl solution. The left femoral vein was cannulated for infusions from a Palmer motor-driven syringe at a constant rate of 0·2 ml/min.

The interval allowed to elapse before giving another injection after injecting adrenaline or isoprenaline was 7 min. However, after an orciprenaline injection, the interval before giving another injection was 15 min, since the increase in heart rate produced by this drug was long-lasting. Sometimes, the rate did not return to the previous level even within the 15 min period; despite this, the next injection was given. Control responses were not less reproducible when given during a sustained response to orciprenaline than when given after one of the other drugs.

Results

The first part of each experiment was devoted to obtaining the control response to injections of each of the sympathomimetic amines. The doses of injections of these drugs were chosen to produce definitely measurable increases in heart rate, of approximately equal magnitude from one experiment to another. Table 1 shows the heart rate increases produced by control injections of the three amines. The effect of adrenaline injections (0·1 to 1·0 μg/kg) on blood pressure varied, the response being purely depressor, biphasic with depressor and pressor components, or purely pressor. Isoprenaline (0·05 to 0·5 μg/kg) and orciprenaline (0·5 to 5·0 μg/kg) produced only a fall in blood pressure.

TABLE 1. EFFECT OF CONTROL INJECTIONS OF ADRENALINE, ISOPRENALINE AND ORCIPRENALINE ON HEART RATE.

Drug	No. of experiments	Mean heart rate increase (beats/min)	Standard error
Adrenaline (0·1–1·0 μg/kg)	25	22·8	±2·2
Isoprenaline (0·05–0·5 μg/kg)	20	31·3	±2·8
Orciprenaline (0·5–5·0 μg/kg)	26	20·3	±1·6

The initial rate of infusion chosen for adrenaline and orciprenaline was 0·1 μg/kg/min and for isoprenaline it was 0·05 μg/kg/min. The drugs had no effect on heart rate or blood pressure at these rates of infusion. If the response to control injections was unchanged during the infusion at the initial rate, the rate of infusion was increased until an effect was observed, but the rates were limited to the minimum that affected responses to injection since it was desired to minimize the effect of infusions themselves on heart rate and blood pressure.

The cardiovascular responses induced by injections of the three amines were unchanged during saline infusions (0·2 ml/min) in 3 control studies. During infusions of adrenaline (0·1 to 0·5 μg/kg/min), isoprenaline (0·05 to 1·0 μg/kg/min), or orciprenaline (0·05 to 0·5 μg/kg/min), the tachycardia and depressor effects obtained with single injections of the amines were significantly reduced. Figs 1–3 illustrate the effects of infusions on the

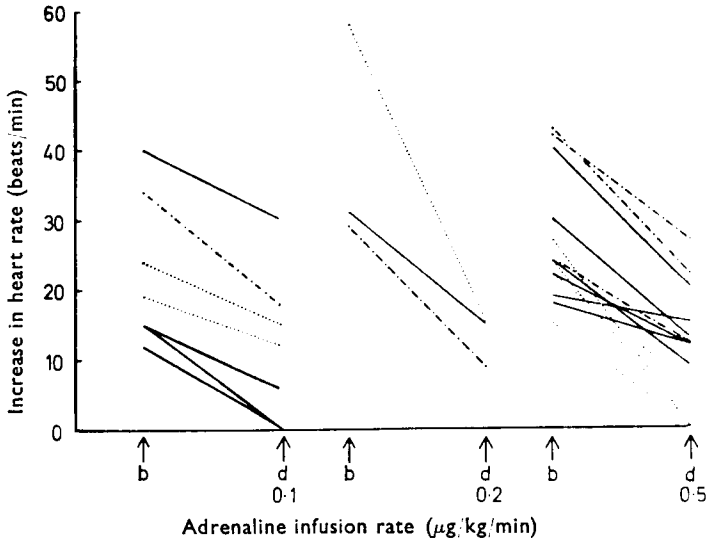

FIG. 1. Reduction in tachycardia in response to injections of adrenaline (· · · · · ·), isoprenaline (·–·–·) and orciprenaline (———) produced by infusions of adrenaline at 0·1, 0·2 and 0·5 μg/kg/min. The control responses to the amines are indicated by b, and the responses during the infusions by d.

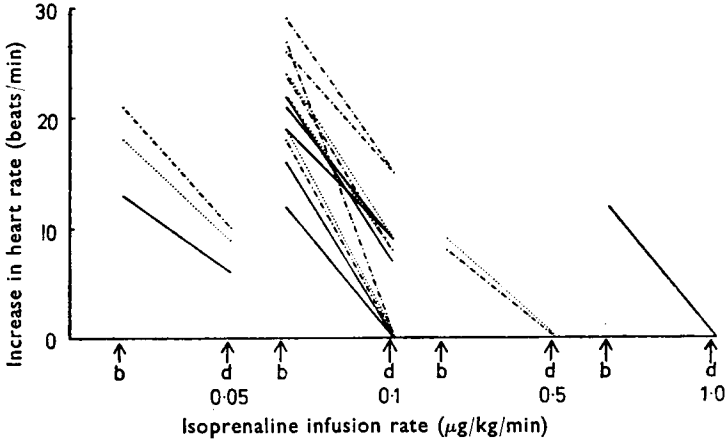

FIG. 2. Reduction in tachycardia in response to injections of adrenaline (· · · · · ·), isoprenaline (·–·–·) and orciprenaline (———) produced by infusions of isoprenaline at 0·05, 0·1, 0·5 and 1·0 μg/kg/min. The control responses to the amines are indicated by b, and the responses during the infusions by d.

tachycardia produced by injections of the three amines. The onset of this antagonism was fairly rapid (5–10 min), and a partial or complete return of the responses to control levels was often observed after the infusion was terminated (Fig. 5).

Effect of adrenaline infusions. Fig. 4 illustrates the effect of an infusion

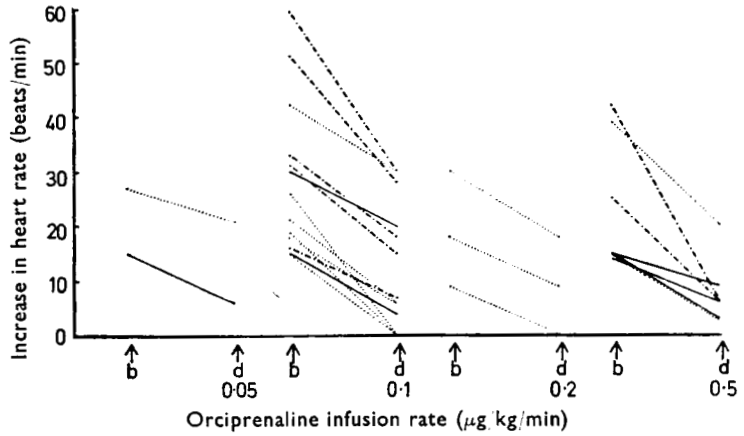

FIG. 3. Reduction in tachycardia in response to injections of adrenaline (· · · · · ·) isoprenaline (—·—·—) and orciprenaline (———) produced by infusions of orciprenaline at 0·05, 0·1, 0·2 and 0·5 μg/kg/min. The control responses to the amines are indicated by b, and the responses during the infusions by d.

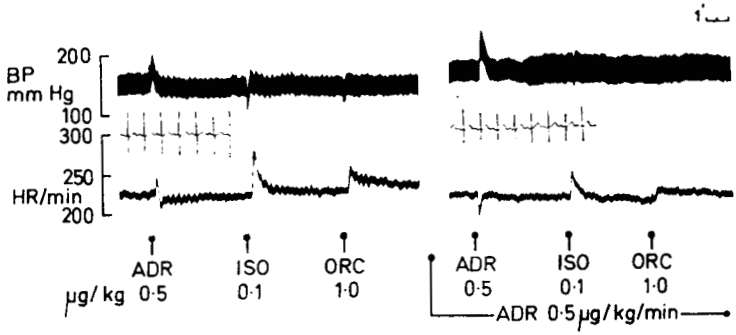

FIG. 4. Antagonism of responses to injected adrenaline (ADR), isoprenaline (ISO) and orciprenaline (ORC), during infusion of adrenaline in a chloralose anaesthetized cat (3·7 kg). The upper tracing is arterial blood pressure (BP), the lower is heart rate (HR). Intravenous injections are indicated by the arrows, and intravenous infusion by the horizontal line. The portions of ECG record were taken during the control period and during the infusion, in each case before injections were given.

of adrenaline on responses to single injections of adrenaline, isoprenaline and orciprenaline. During adrenaline infusions, the depressor component of the response to adrenaline was abolished and the pressor component was variably enhanced. The tachycardia previously obtained with injections of adrenaline was converted to reflex bradycardia in 4 of 10 experiments, and reduced by more than 40% in the remaining experiments. Depressor effects of isoprenaline (0·1 to 0·2 μg/kg) were less effectively blocked than were those of adrenaline. In 3 experiments, a complete block of isoprenaline vasodepression was seen during adrenaline infusions, with more than 40% antagonism in three others. The tachycardia produced by isoprenaline was reduced by 40 to 60% in each case. Infusions

of adrenaline reduced the depressor effects of orciprenaline injections more readily than those of isoprenaline, complete antagonism of the effect of orciprenaline being obtained in 9 of 12 experiments, with more than 50% reduction in the remaining three instances. The tachycardia in response to orciprenaline was abolished in 3 cats, reduced by 30 to 80% in 7 cats, and no effect was observed in the other two.

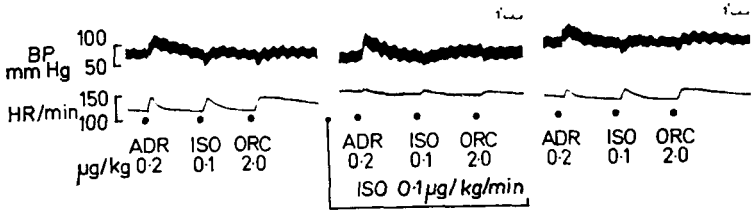

FIG. 5. Antagonism of responses to injected adrenaline (ADR), isoprenaline (ISO) and orciprenaline (ORC) during an infusion of isoprenaline in a chloralose anaesthetized cat (1·7 kg). The upper tracing is arterial blood pressure (BP), the lower is heart rate (HR). Intravenous injections are indicated by the arrows and intravenous infusion by the horizontal line.

Effect of isoprenaline infusions. Infusions of isoprenaline had a similar effect to those of adrenaline in modifying the responses to injections of the three amines, as shown in Fig. 5. The effects of adrenaline on heart rate were reduced to 50% of the preinfusion levels. The antagonism of depressor responses to isoprenaline was greater than 40% in 7 experiments, and the tachycardia produced by isoprenaline was reduced by more than 50%. Isoprenaline infusions even more readily antagonized orciprenaline depressor effects, producing 75 to 100% antagonism in 5 cats, with a 50 to 60% decrease in the cardiac response.

Effect of orciprenaline infusions. In one experiment, an infusion of orciprenaline converted the response to adrenaline from tachycardia to a reflex bradycardia, and in 8 other experiments there was a reduction in tachycardia of greater than 28%. The antagonism of vasodepressor effects of isoprenaline varied from zero to 50% in 8 experiments; the accompanying heart rate increases were reduced to 50 to 80% of the control value. Orciprenaline infusions resulted in a decrease in the chronotropic response induced by single injections of the same amine from 30 to 60%, but the depressor effects were variably affected, no antagonism being observed in 3 cats, whereas in 2 others there was complete abolition of the response. The results from one experiment are illustrated in Fig. 6.

OBSERVATIONS ON THE CONFIGURATION OF THE ECG

Infusions of the three sympathomimetics sometimes produced changes in the configuration of the T-wave, varying from depression to enhancement, but effects were inconstant in both occurrence and duration. When an infusion produced a decrease in the positive chronotropic response to the injection of an amine, the effect of the injection of that amine on the T-wave was also reduced. In only one experiment was an arrhythmia

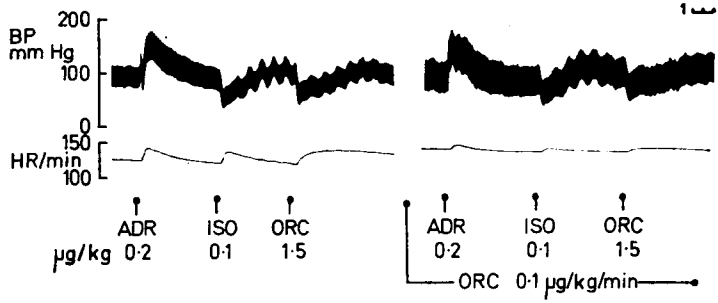

FIG. 6. Antagonism of responses to injected adrenaline (ADR), isoprenaline (ISO) and orciprenaline (ORC) during infusion of orciprenaline in a chloralose anaesthetized cat (2·8 kg). The upper tracing is arterial blood pressure (BP), the lower is heart rate (HR). Intravenous injections are indicated by the arrows and intravenous infusion by the horizontal line.

observed during an infusion, and this occurred when the positive chronotropic effect of adrenaline had been so effectively antagonized that the normal response of tachycardia was converted to a reflex bradycardia.

Discussion

These experiments demonstrate that in normal cats the interaction between adrenaline, isoprenaline and orciprenaline results in antagonism rather than potentiation of cardiovascular effects attributable to actions on β-adrenoreceptors. During infusions of the amines, the animal shows decreased sensitivity to cardiac and depressor effects of single injections of any one amine. Vasodepressor effects were more readily antagonized than were the positive chronotropic effects, particularly those induced by injections of orciprenaline, and some effect on heart rate generally persisted with injections of isoprenaline and orciprenaline although their effects were usually diminished. Reflex bradycardia was often seen when the depressor component of an adrenaline response was abolished during an infusion and the pressor effect of adrenaline was thereby increased. Reversal of the blood pressure effects of isoprenaline and orciprenaline was not observed, although this has been shown for isoprenaline by Gutman & Beyth (1964) and Beyth & Gutman (1965) using infusion concentrations of adrenaline and isoprenaline comparable to ours. Butterworth (1963) demonstrated that large doses ('priming doses') of isoprenaline blocked the depressor effects of smaller doses, and caused the appearance of pressor activity to subsequent administrations of the large dose.

Thus our experimental observations give no evidence of cardiovascular toxicity arising from the interactions of the amines. It has been suggested that the pathological changes associated with asthma may cause untoward drug effects. Lockett (1965) showed that when the heart is fatigued or under strain, it is more subject to arrhythmias precipitated by catecholamines, and Kerr (1967) considered that this may apply when the myocardium is anoxic. However, as has been pointed out (Herxheimer, 1965;

Kennedy, 1965), Lockett's observations with the heart-lung preparation may not be a true reflection of the behaviour of the human heart in the asthmatic state.

However, not enough is known of the effects of sympathomimetic drugs in the conditions associated with asthma. The possibility of reversal or blockade of the effects of sympathomimetic amines on the bronchi after giving large doses has not apparently been reported.

Our experiments have been concerned only with the possibility of the acute cardiovascular toxicity of sympathomimetic amines. The effect of long term therapy with sympathomimetic amines requires careful consideration, bearing in mind the possible development of changes in myocardial reactivity or tolerance to bronchodilator efficacy.

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