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THE HAEMODYNAMIC EFFECTS OF PROLONGED ORAL ADMINISTRATION OF OXYFEDRINE, A PARTIAL AGONIST AT β-ADRENOCEPTORS: COMPARISON WITH PROPRANOLOL

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1 Haemodynamic changes have been studied in cats after the chronic oral administration of oxyfedrine (14 mg/kg for 3-4 weeks) or of placebo (lactose). The initial part of the study was carried out under double-blind conditions. The arterial blood pressure was between 19 mmHg (diastolic) and 27 mmHg (systolic) higher in the oxyfedrine treated animals, but there were no differences between the two groups with regard to cardiac output, left ventricular dP/dt *max*, heart rate or systolic ejection time.

2 In cats similarly treated with propranolol (4 mg/kg) there was a slight (12%), but significant, reduction in cardiac output.

3 Isoprenaline dose-response curves were shifted to the right in the cats administered oxyfedrine as well as in those administered propranolol. The degree of shift was five-fold (positive chronotropic response) and 20-fold (decrease in diastolic blood pressure) in the oxyfedrine group and 10- and 80-fold, respectively, in the propranolol group.

4 In contrast to the partial blockade of the effects of isoprenaline, the haemodynamic response to oxyfedrine was largely unaltered, both in the cats pretreated with propranolol and in those pretreated with oxyfedrine. The pressor response to noradrenaline was potentiated in the cats pretreated with oxyfedrine.

5 These results provide an explanation for the anti-anginal action of oxyfedrine. Some degree of β-adrenoceptor blockade is achieved without a reduction in cardiac output or left ventricular dP/dt *max*. The relevance of these findings to the haemodynamic situation in angina is discussed.

Introduction

Oxyfedrine (L-3-methoxy-(1-hydroxy-1-phenyliso-propylamino)-propriophenone hydrochloride) is a partial agonist at β-adrenoceptors. It exerts sympathomimetic effects on atria, and on a variety of vascular and non-vascular smooth muscle preparations, in similar concentrations to those which antagonize the effects of β-adrenoceptor stimulants such as isoprenaline (Beckett & Foster, 1972, 1973; Mackenzie & Parratt, 1973; Sakai, Shiraki & Hashimoto, 1973). There is some evidence from double-blind trials that oxyfedrine is an effective anti-anginal drug (Greif & Liertzer, 1967; Stampfer, 1969; Marner, 1970; Raisp, 1970). The precise mechanism of action of oxyfedrine in this condition is not clear but the question arises as to whether, when given over a prolonged period, oxyfedrine loses its agonist properties whilst retaining its antagonist properties at β-adrenoceptor sites. It was to attempt to answer this question that the present experiments were performed in which oxyfedrine was administered orally to cats, over a period of 3-4 weeks, in a double-blind study. For comparison, the haemodynamic effects of the prolonged oral administration of propranolol were also examined.

Methods

Twenty-four cats of similar weight (2.5 ± 0.2 kg) were used for the main part of this study. Twelve were given capsules containing oxyfedrine (45 mg daily) and 12 matching placebo (lactose) capsules for a period of 3-4 weeks. The first part of the

study (six animals in each of the two groups) was carried out under double-blind conditions. The capsules were prepared by the Pharmaceutical Development Unit of Geigy Pharmaceuticals, Macclesfield, and the seal broken at the end of the experimental period when all the results were available. In view of the results obtained, a group of six cats (mean weight 2.6 kg) was given (±)-propranolol (as a commercially available tablet of 10 mg) daily for three weeks. All the animals were used 16 h after the administration of the last capsule or tablet.

The cats were anaesthetized with sodium pentobarbitone (30 mg/kg by intraperitoneal injection). They breathed spontaneously, and the corneal and tracheal reflexes were present. The electrocardiogram (ECG) was recorded from limb electrodes. Polyethylene catheters were then placed in the left femoral vein, the right atrium (by way of the right external jugular vein) and the aortic arch (by way of the right common carotid artery in the neck). This latter catheter was used for blood sampling and for blood pressure measurement with a capacitance transducer (Elema Schönander EMT 3, range 0-300 mmHg; 1 mmHg = 1.333 mbar), which was calibrated before each experiment against a mercury column. Blood pressure and the ECG were recorded on an ink-jet writing recorder (Elema Schönander Mingograph 81). Heart rate was calculated from the ECG and systolic ejection time (in ms) from the beginning of the upstroke of the central aortic pulse to the trough of the incisural notch, with a paper speed of 250 mm/second. Cardiac output was measured, in duplicate, by thermodilution. A 36 swg copper-constantan thermocouple, sheathed in polyethylene tubing, was inserted by way of the left femoral artery into the upper portion of the abdominal aorta. The thermojunction itself was pushed beyond the tubing for a distance of 20-25 mm such that it lay free in the aortic stream. The reference junction of this thermocouple was inserted about 50 mm into the rectum and lay alongside a direct recording thermocouple (Ellab, Copenhagen). This enabled the aortic blood temperature to be recorded with an accuracy of at least 0.01°C. For the measurement of cardiac output, 1.8 ml of 0.9% w/v NaCl solution at room temperature (16-23°C) was injected rapidly into the right atrium and the output from the thermocouple circuit fed directly into a Kipp and Zonen BD5 recorder (50 μV for a full scale of 20 cm = 1.25°C). The paper speed was 200 mm/minute. The area under the thermodilution curve was calculated by the method of Williams, O'Donovan & Wood (1966) and the cardiac output calculated by a modification of the formula described by Evonuk, Imig, Greenfield & Eckstein (1961). The difference between consecutive cardiac output measurements obtained by this method was 5.4 ± 0.9% (26 estimations).

A blood sample (2.0 ml) was taken anaerobically from the arterial catheter and analysed for oxygen and carbon dioxide tensions, and pH, with appropriate electrode systems (Radiometer, Copenhagen). The pH electrode was calibrated with standard buffers and the oxygen and carbon dioxide electrodes with gas mixtures, the oxygen and carbon dioxide concentrations of which had been measured with a modified Lloyd-Haldane apparatus. Oxygen and carbon dioxide tensions (mmHg) and pH were corrected for any temperature difference between the electrode systems (usually 37.3°C) and the animal's mid-oesophageal (or blood) temperature by means of the blood gas calculator described by Severinghaus (1966). This was also used to calculate base-excess and blood bicarbonate. Arterial lactate was measured by the Hohorst enzymatic method using a Boehringer test combination for L-lactate and, by courtesy of Dr B. Furman, plasma glucose was measured by the glucose oxidase method using a Beckman analyser.

(±)-Isoprenaline was injected intravenously in these spontaneously breathing cats in doses of 10, 20, 40, 80, 100, 200, 400 and 800 ng(base)/kg and dose-response curves constructed with respect to increased heart rate and decreased diastolic blood pressure. The pressor responses to intravenous (−)-noradrenaline (20, 50, 100, 200 and 500 ng(base)/kg) were also assessed.

The cats were then artificially respired with room air by means of a Palmer pump (rate 20/min; stroke volume 40-60 ml), the thorax opened, and catheters placed in the pulmonary artery and left ventricle as previously described (Parratt, 1973). Left ventricular pressure, left ventricular end-diastolic pressure (LVEDP), LV dP/dt, pulmonary artery pressure, systemic arterial pressure and the electrocardiogram were recorded before, and at various times after, the intravenous injection of oxyfedrine (Ildamen, Chemiewerk-Homburg) in doses of 0.25, 0.5 and 1.0 mg/kg as outlined by Moore & Parratt (1972). At the end of the experiments the hearts were removed, trimmed, and weighed. The heart weight was expressed as a % of the total body weight.

Results

Effect of prolonged treatment with oxyfedrine and propranolol on body and heart weights

All, except one, of the cats given oxyfedrine for 3-4 weeks lost weight over the period of

treatment. The mean weight of the cats before treatment began, but after one or two weeks' acclimatization in the animal house, was 3.02 kg. The weight loss over the experimental period varied between 0.10 and 0.65 kg (with a mean of 0.40 kg, i.e. 13%). The weight loss in the cats treated with propranolol was similar, varying between 0.2 and 0.6 kg (with a mean of 0.32 kg, or 12%). Cats fed with placebo capsules neither gained, nor lost weight over the four week period (mean increase in body weight 0.05 kg).

There was no difference, at the end of the experimental period, between the heart weights of the oxyfedrine treated cats and the placebo group. The values were 0.38 ± 0.03% of body weight (2.48 ± 0.32 kg) in the oxyfedrine treated group and 0.39 ± 0.02% of body weight (2.45 ± 0.22 kg) in the placebo group.

Haemodynamic and metabolic effects of prolonged oral treatment with oxyfedrine: comparison with the placebo group

Spontaneously breathing cats. The mean respiratory rate in these anaesthetized and spontaneously breathing cats was similar in the two groups (oxyfedrine and placebo) being 25 and 24/min respectively. There were no differences between the two groups with respect to arterial oxygen tension (94 ± 3 mmHg in both groups), carbon dioxide tension (27 ± 2 in the placebo group and 28 ± 2 mmHg in the oxyfedrine group), pH (7.317 ± 0.011 and 7.335 ± 0.020 units respectively), plasma glucose (106 ± 6 and 111 ± 8 mg/100 ml respectively) or in arterial lactate (6.7 ± 0.9 and 5.3 ± 0.6 mg/100 ml). The relatively low value for P_{CO_2} is similar to that obtained in previous studies in both conscious cats and in anaesthetized but spontaneously breathing cats (Dejours & Lacaisse, 1971; Parratt, 1973). It reflects the relatively small buffering capacity of the blood in this species (Fink & Schoolman, 1963). The calculated blood bicarbonate for the control (placebo) cats was a mean of 14.3 mEq/l and for the oxyfedrine-treated cats a mean of 15.5 mEq/litre.

The resting haemodynamic values for the two groups are shown in Table 1. There was no significant difference between the two groups with respect to resting heart rate, systolic ejection time, the PR interval, nor in cardiac output (389 ± 15 ml/min in the placebo group and 401 ± 24 ml/min in the oxyfedrine-treated group). However, the systemic blood pressure was significantly higher (by a mean of 19 mmHg diastolic and 27 mmHg systolic) in the cats treated with oxyfedrine.

It was clear from the results of isoprenaline administration that prolonged treatment with oxyfedrine resulted in partial blockade of β-adrenoceptors both in the heart (β_1) and peripheral vascular bed (β_2). The log dose-response curves were shifted to the right in a parallel manner following prolonged oxyfedrine treatment (Figures 1 and 2). About 20 times as much isoprenaline was required to reduce diastolic blood pressure by 10-30 mmHg in these animals compared with the animals given lactose; with regard to the increase in heart rate the ratio was between 4 and 5. In contrast, the pressor response to the intravenous administration of noradrenaline was significantly potentiated (Figure 3). For example, a dose of 100 ng/kg raised the blood pressure in the control (placebo) animals by 27 ±6 mmHg (systolic) and by 13 ± 4 mmHg (diastolic). In the oxyfedrine-treated animals the same dose of noradrenaline raised the pressure by 44 ± 2 mmHg (systolic) and by 30 ± 3 mmHg (diastolic; $P < 0.001$).

Table 1 Haemodynamic parameters of cats following the prolonged oral administration of lactose (controls), oxyfedrine or propranolol

	Control	*Oxyfedrine-treated*	*Propranolol-treated*
Heart rate (beats/min)	189 ± 8	204 ± 5	194 ± 4
Systolic blood pressure (mmHg)	151 ± 5	178 ± 5*	152 ± 7
Diastolic blood pressure (mmHg)	116 ± 5	135 ± 4***	114 ± 10
PR interval (ms)	68 ± 2	62 ± 1	74 ± 5
Systolic ejection time (ms)	128 ± 6	120 ± 3	142 ± 9
Cardiac output (ml kg^{-1} min^{-1})	161 ± 6	168 ± 8	138 ± 5**
Stroke volume (ml/beat)	2.0 ± 0.1	1.9 ± 0.1	1.7 ± 0.2

Values are mean ± s.e. and were obtained from spontaneously breathing, close-chest animals.
Significantly different from control * $P < 0.005$; ** $P < 0.01$; *** $P < 0.02$.

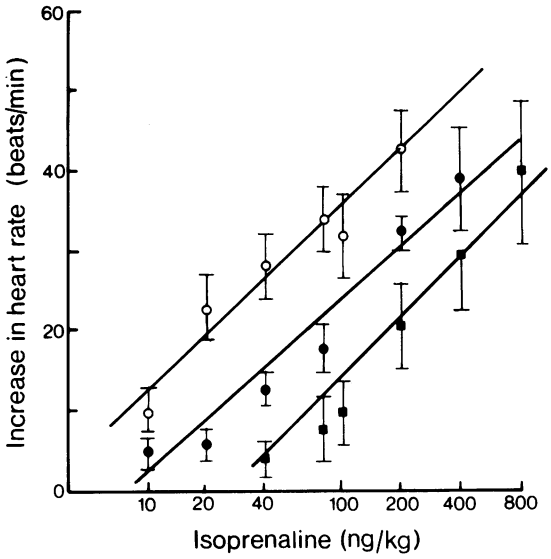

Fig. 1 The effect of isoprenaline on heart rate (beats/min as change from the control levels) in cats treated for 3-4 weeks with oxyfedrine (●), propranolol (■) or placebo (lactose; ○). Values are means ± s.e.

Open-chest cats

The haemodynamic effects of intravenously administered oxyfedrine in the placebo group were similar to those described by Moore & Parratt (1972). There were increases in heart rate, left ventricular d*P*/d*t* *max*, slight (but significant) increases in pulmonary arterial pressure and cardiac output, and reductions in systemic blood pressure and systolic ejection time. These haemodynamic effects (which result mainly from β-adrenoceptor stimulation) were also seen in the cats treated for 3-4 weeks with oxyfedrine (Table 2). It was clear that prolonged oxyfedrine treatment did not reduce cardiac output, or the maximum rate of pressure development within the left ventricle, nor did it reduce the increased contractility which results from the acute administration of oxyfedrine itself.

Effects of prolonged oral treatment with propranolol

Spontaneously breathing cats. After anaesthesia, the values for arterial oxygen tension (85 ± 5 mmHg), carbon dioxide tension (22 ± 3 mmHg), pH (7.331 ± 0.026 units), lactate (5.9 ± 0.5 mg/100 ml) and plasma glucose (117 ± 23 mg/100 ml) were not significantly different from those obtained in the placebo (or oxyfedrine)-treated

Table 2 Haemodynamic effects of oxyfedrine (0.25 and 0.5 mg/kg intravenously) in placebo (lactose) treated cats and in cats treated for 3-4 weeks with oxyfedrine

	Placebo-treated			*Oxyfedrine-treated*		
		Change after oxyfedrine			*Change after oxyfedrine*	
		0.25	0.5 mg/kg		0.25	0.5 mg/kg
LV d*P*/d*t* *max* (mmHg s^{-1})	3347 ± 378	+1274 ± 268	+1928 ± 273	3228 ± 306	+1420 ± 375	+1440 ± 350
Heart rate (beats/min)	180 ± 8	−33 ± 6	+26 ± 7	196 ± 7	+18 ± 5	+25 ± 4
Systolic ejection time (ms)	134 ± 11	−23 ± 7	−17*	128 ± 6	−10 ± 3	−13 ± 3
Systolic blood pressure (mmHg)	126 ± 4	−2 ± 1	−2 ± 1	132 ± 9	−4 ± 2	−4 ± 1
Diastolic blood pressure (mmHg)	86 ± 2	−6 ± 1	−12 ± 3	93 ± 9	−4 ± 2	−7 ± 1
Cardiac output (ml kg^{-1} min^{-1})	133 ± 3	+13 ± 8	+6 ± 4	123 ± 9	+9 ± 6	+11 ± 1

Values are means ± s.e. (6-10 experiments) and were obtained after thoracotomy
* Two experiments only.

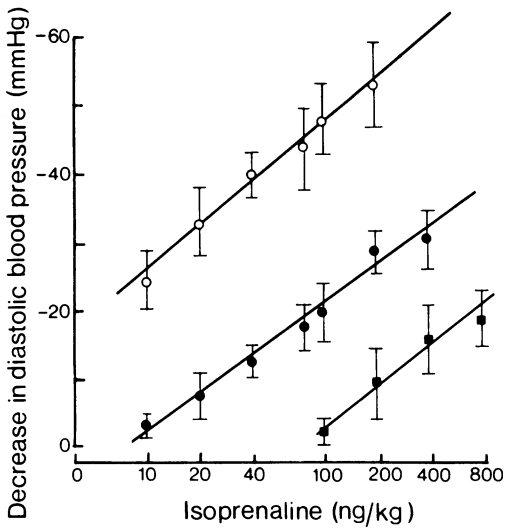

Fig. 2 The effect of isoprenaline on diastolic blood pressure (mmHg, as change from control levels) in cats treated for 3-4 weeks with oxyfedrine (●), propranolol (■), or placebo (lactose; ○). Values are means ± s.e.

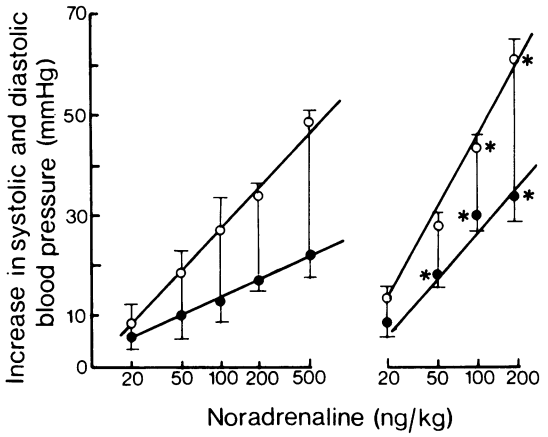

Fig. 3 The effect of noradrenaline on systolic (○) and diastolic (●) blood pressures (mmHg, as change from control levels) in cats treated for 3-4 weeks with (a) lactose (placebo) or (b) oxyfedrine. Values are means ± s.e. The continuous line joining systolic and diastolic pressures at each point represents the pulse pressure. * Significantly different from the response in lactose treated cats at a level of $P < 0.001$.

animals. The haemodynamic effects are summarized in Table 1. Cardiac output was significantly lower than in the cats administered lactose (by a mean of 12%) and the systolic ejection time and PR interval were somewhat longer. It was of interest that the prolonged oral administration of propranolol did not reduce resting heart rate or systemic blood pressure although there was no doubt that treatment with this dose of propranolol (4 mg/kg daily) markedly reduced the vasodilator and positive chronotropic effects of isoprenaline (Figures 1 and 2). As with the oxyfedrine-treated cats, the vasodilator response of isoprenaline was more easily antagonized than the positive chronotropic response. About 80 times more isoprenaline was required to reduce diastolic blood pressure by 10-20 mmHg in the cats pretreated with propranolol than in the cats pretreated with lactose. In comparison, the ratio for increasing heart rate by 20-30 beats/min was only 10. The response of propranolol-treated cats to noradrenaline is shown in Table 3. Only at one dose level (200 ng/kg) was the pressor response to noradrenaline significantly potentiated.

Since the haemodynamic responses to the acute administration of oxyfedrine were largely unaltered in cats pretreated with that drug for 3-4 weeks, it was of interest to determine whether

Table 3 The effect of prolonged oral pretreatment with propranolol on the pressor response to noradrenaline

	Lactose treated		*Propranolol treated*	
Dose (ng/kg)	*Systolic pressure*	*Diastolic pressure*	*Systolic pressure*	*Diastolic pressure*
20	9 ± 3	6 ± 2	9 ± 3	8 ± 4
50	19 ± 4	10 ± 4	18 ± 5	15 ± 6
100	27 ± 6	13 ± 4	26 ± 6	22 ± 5
200	34 ± 1	17 ± 1	40 ± 7	29 ± 4*
500	49 ± 1	23 ± 5	56 ± 8	34 ± 6

Mean increase in blood pressure (mmHg) ± s.e.
* Significantly different from response in lactose treated cats ($P < 0.01$).

chronic propranolol treatment modified the response to acutely administered oxyfedrine. In these experiments the chest was not opened and only blood pressure, heart rate and cardiac output were measured. Oxyfedrine decreased systolic and diastolic blood pressures, and systolic ejection time, to the same extent in the cats pretreated with propranolol as in the cats administered lactose. Further, similar increases in heart rate (21 ± 5 beats/min with an oxyfedrine dose of 0.25 mg/kg, 22 ± 3 beats/min with 0.5 mg/kg and 25 ± 4 beats/min with 1.0 mg/kg) and in cardiac output (28 ml kg^{-1} min^{-1} with 0.25 mg/kg; 22 ml kg^{-1} min^{-1} with 0.5 mg/kg and 23 ml kg^{-1} min^{-1} with 1.0 mg/kg) were also obtained.

Discussion

Polster & Vaughan Williams (1973) have recently drawn attention to the importance of examining the chronic pharmacological effects of drugs which are given clinically over a long period for conditions such as angina pectoris. They point out that 'a drug may have quite different effects after chronic administration from those apparent when it is given acutely'. For example, they administered oxyfedrine to rabbits, in a daily dose of 15 or 40 mg/kg for four weeks, and observed, in atrial muscle taken from these animals, that the plateau phase of the cardiac action potential was significantly prolonged. This gave rise to an increased repolarization time, an effect not seen when the drug was administered acutely. Polster and Vaughan Williams suggested that the anti-anginal effect, which has been claimed for oxyfedrine, was in some way related to this prolongation of the cardiac action potential.

The present experiments were concerned with the haemodynamic effects of prolonged oxyfedrine treatment. They have demonstrated that, when administered chronically in a dose (14 mg/kg) rather higher than that so far used in man, oxyfedrine had no effect on resting cardiac output, left ventricular dP/dt *max* or heart rate, yet produced an appreciable degree of β-adrenoceptor blockade, as shown by a parallel shift in the isoprenaline dose-response curves. If the positive chronotropic effect of isoprenaline was taken as the criterion the shift was about five-fold; if peripheral vasodilatation was taken as the criterion, the shift was about 20-fold. If these results can be extrapolated to anginal patients receiving the drug, then it would appear that a significant degree of β-adrenoceptor blockade can be achieved without a reduction in cardiac output or myocardial contractility. There was certainly no evidence in the present experiments of the myocardial depression that has been observed when large doses of oxyfedrine are given acutely (Thalinger & Lefer, 1970).

It is clearly relevant to compare the effects of prolonged oxyfedrine administration with those obtained with a standard β-adrenoceptor blocking agent. Propranolol, when administered in a daily oral dose of 4 mg/kg, significantly reduced cardiac output (by a mean of 12%). There are a number of possible explanations for this difference between the chronic effects of oxyfedrine and of propranolol. Firstly, the degree of β-blockade with propranolol was more substantial. This is apparent from an examination of Figures 1 and 2. If the decrease in cardiac output were an effect of β-blockade *per se* then one might expect that the greater the degree of blockade, the more pronounced the effect on resting cardiac output. Another possible explanation for the difference between the two drugs is that the inherent (and pronounced) intrinsic sympathomimetic activity of oxyfedrine could counteract a reduced myocardial contractility resulting from β-blockade. This argument has been advanced in favour of other partial agonists at β-adrenoceptors such as alprenolol (Ablad, 1967) which, in man, achieves a similar degree of β-blockade to propranolol without reducing cardiac output (Forsberg & Johnsson, 1967). It has been suggested that drugs like alprenolol, whilst inhibiting the cardiac effects of excessive sympathetic drive, 'keep the adrenergic receptors in the heart moderately activated, thereby reducing the risk of cardiac failure' (Ablad, 1967). There are dangers in such a simplified approach to the clinical use of β-adrenoceptor blocking agents (Fitzgerald, 1969), but there was certainly evidence from the present experiments that oxyfedrine, when administered over several weeks, both maintained cardiac contractility and output and reduced the actions of at least one β-adrenoceptor stimulant. Although such effects could result from partial agonist activity at β-adrenoceptors, there is an alternative explanation that warrants consideration. There is some evidence that part of the acute effects of oxyfedrine are mediated through the release of neuronal noradrenaline. For example, Grobecker, Hellenbrecht, Lemmer, Palm & Schmid (1972) have demonstrated, by direct tissue analysis, that oxyfedrine releases noradrenaline from heart and brain whilst Westermann, Neuvonen, Onken & Vapaatalo (1972) have concluded that a significant part of the hyperglycemic action of the drug may be due to release of noradrenaline from sympathetic nerve endings by a tyramine-like action. This noradrenaline release may contribute to some, though by no means all, of the haemodynamic changes which result from the

acute administration of the drug. The evidence in favour of this is that oxyfedrine-induced increases in heart rate and left ventricular d*P*/d*t* *max* are largely prevented by the prior administration of the adrenergic neurone blocking drug bethanidine (Moore & Parratt, unpublished and discussion following the paper by Grobecker *et al.*, 1972). The present study does not enable a definite conclusion to be reached as to whether this tyramine-like release of noradrenaline, or the direct stimulation of β-adrenoceptors, is primarily responsible for the maintenance of myocardial contractility observed after the prolonged administration of oxyfedrine.

It is now possible to summarize the possible reasons for the claimed efficacy of oxyfedrine as an anti-anginal drug. Parker (1972) has recently summarized the haemodynamic effects of angina when induced either by exercise or by atrial pacing. There is usually a marked elevation of left ventricular end-diastolic pressure (LVEDP) and evidence of depression of left ventricular function. The change in end-diastolic pressure would be expected to decrease sub-endocardial blood flow. Oxyfedrine has been shown to substantially reduce LVEDP and end-diastolic volume, heart size and myocardial metabolic heart production (Moore & Parratt, 1972) with a subsequent reduction in intramyocardial wall tension, an important determinant of myocardial oxygen consumption. In addition to these acute effects, which in some ways are similar to those of nitroglycerin, the present study provides evidence for a degree of β-adrenoceptor blockade after prolonged administration. A combination of these haemodynamic effects would adequately explain the anti-anginal action of oxyfedrine.

The one marked haemodynamic effect of the chronic administration of oxyfedrine was the elevated systemic arterial pressure. There are two possible explanations for this effect. Firstly, oxyfedrine is metabolized predominantly to norephedrine (phenylpropanolamine; Sakai, Sugano, Watanabe, Fukushima, Takanashi & Nishii, 1972). This has quite different pharmacological actions from oxyfedrine both *in vitro* (Beckett & Foster, 1972) and *in vivo*. The most pronounced cardiovascular effects are increased arterial pressure and heart rate (Sakai *et al.*, 1973). Since these effects are not observed in reserpine-treated dogs it has been concluded that the effects of norephedrine, like those of tyramine, are indirect and are due to noradrenaline release. A second possible explanation for oxyfedrine-induced elevations in resting arterial pressure, is that oxyfedrine itself releases noradrenaline (see above) and also inhibits neuronal uptake. Inhibition of noradrenaline uptake by oxyfedrine, rather than a β-blocking action of the drug, is also the most likely explanation for the potentiated pressor responses to intravenously administered noradrenaline (Figure 3). Potentiation of the noradrenaline pressor response was not observed in cats chronically pretreated with propranolol although marked noradrenaline potentiation has been observed after the acute administration of pronethalol in the dog (Parratt, 1965), probably mainly because of inhibition of noradrenaline uptake (Iversen, 1967). The pressor effect of noradrenaline is usually slightly reduced after the acute administration of propranolol (Shanks, 1966 in the dog; Parratt, 1969 in the monkey).

A finding common to both oxyfedrine and propranolol treatment was that the vasodepressor response to isoprenaline was more easily antagonized than the positive chronotropic response (Figures 1 and 2). This suggests that both drugs have more affinity for vascular (β_2) adrenoceptors than for cardiac (β_1) adrenoceptors. This differential blockade has also been described by Shanks (1966) for propranolol and by Parratt & Wadsworth (1970) for alprenolol. However, although blockade of vascular β-adrenoceptors was more complete than blockade of cardiac β-adrenoceptors after the chronic administration of oxyfedrine, there was some evidence that the cardiac receptors were preferentially stimulated by the drug. Thus, marked increases in left ventricular d*P*/d*t* *max*, heart rate and cardiac output occur with very little peripheral vasodilatation (Moore & Parratt, 1972 and Table 2). We should nevertheless hesitate to call oxyfedrine a 'specific' β_1-stimulant (Osswald & Guimães, 1971) since, at least in isolated tissues, there is ample evidence that the drug causes a long-lasting stimulation of both β_1- and β_2-adrenoceptors in similar concentrations (Beckett & Foster, 1972; Mackenzie & Parratt, 1973). In view of the degree of β-adrenoceptor blockade achieved with both oxyfedrine and propranolol it was perhaps surprising that the acute stimulant effects of oxyfedrine were unaffected by long-term treatment with oxyfedrine (Table 2) or with propranolol. This is reminiscent of the observation by Beckett & Foster (1972) that propranolol is less effective in reducing the depressor effect of oxyfedrine than of isoprenaline. For some reason, the β-stimulant effects of isoprenaline are more easily antagonized than the stimulant effects of oxyfedrine. This might best be explained on the basis of the 'indirect' cardiac stimulant effect of oxyfedrine discussed above. Neuronal noradrenaline, released by the drug, might well be more resistant to block than exogenous isoprenaline.

These studies have re-emphasized the impor-

tance of examining the long-term pharmacological effects of drugs given regularly over long periods of time for the treatment of conditions such as angina pectoris. It is clear, as Polster & Vaughan-Williams (1973) have pointed out, that oxyfedrine has 'different effects after chronic administration from those apparent when it is given acutely'. The most obvious differences were a moderate systemic hypertension and a substantial degree of β-blockade without a reduction in cardiac output. The studies also underline the difficulties of interpreting results obtained with drugs which have a number of possible mechanisms of action and whose metabolites have effects different again from those of the primary drug. Interpretation may well be helped by studies on the tissue distribution of oxyfedrine and its major metabolites. This has yet to be attempted after prolonged administration of the drug.

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