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THE EFFECT OF PROPRANOLOL ON THE CARDIOVASCULAR RESPONSES TO ISOPRENALINE, ADRENALINE AND NORADRENALINE IN THE ANAESTHETIZED DOG

BY

R. G. SHANKS

From Imperial Chemical Industries, Pharmaceuticals Division, Research Department, Alderley Park, Macclesfield, Cheshire

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In 1948 Ahlquist suggested that there were two types of catechol amine receptor, which he designated α and β. The first compound shown to block selectively the β-receptors was dichloroisoprenaline (Powell & Slater, 1958). Moran & Perkins (1958) showed that in anaesthetized dogs dichloroisoprenaline effectively antagonized the myocardial rate and tension changes produced by catechol amines. They also found that dichloroisoprenaline itself increased heart rate and cardiac contractile force and reduced arterial pressure. These effects were attributed to a sympathomimetic action, which has been demonstrated in isolated heart preparations, conscious and anaesthetized animals and in man (Furchgott, 1959; Black & Stevenson, 1962; Glover, Greenfield & Shanks, 1962). Black & Stevenson (1962) described a compound, pronethalol, which was a specific β-receptor antagonist devoid of sympathomimetic activity although it produced hypotension associated with a peripheral vasodilatation (Ahlquist, 1963). Recent studies suggest that pronethalol may possess intrinsic sympathomimetic activity, but to a much lesser extent than dichloroisoprenaline. Donald, Kvale & Shepherd (1964) found that in anaesthetized dogs pronethalol increased cardiac output and stroke volume, and in conscious dogs with cardiac denervation it increased heart rate. In all dogs there was a fall in arterial pressure. Similar results were obtained in anaesthetized dogs by Maxwell, Robertson & Elliott (1963).

A new compound, propranolol, which is a β-receptor antagonist about ten times as active as pronethalol, has been described by Black, Crowther, Shanks, Smith & Dornhorst (1964). The effects of propranolol on the cardiovascular system of anaesthetized dogs and on the responses to isoprenaline, adrenaline and noradrenaline are described in this paper.

METHODS

Dogs weighing 8 to 16 kg were anaesthetized by the intravenous injection of pentobarbitone (30 to 40 mg/kg), or by the intravenous injection of thialbarbitone (30 mg/kg) followed by chloralose (60 mg/kg). A cuffed endotracheal tube was inserted and the animals artificially ventilated with room air throughout the experiment: observations were made on three dogs that breathed

spontaneously. Following thoracotomy through an intercostal or midsternal incision a strain-gauge arch (made by Mr G. B. Horsfall in our laboratories) was sutured to the epicardial surface of the right or left ventricle: in some experiments arches were sutured to both ventricles. As the results from both were similar, the responses of the right and left ventricles will not be distinguished (Cotton, 1953). The strain gauges were not calibrated, so that absolute changes in contractile force could not be determined. For each experiment cardiac contractile force was expressed as a percentage of that during the control period at the beginning of the experiment. In some experiments a probe for an electromagnetic flowmeter (Medicon, K 2000) was placed around the root of the aorta for the measurement of aortic flow. This is a measurement of left ventricular output (cardiac output) minus coronary artery flow. Mean flow was recorded. Arterial pressure was recorded from a cannula in the left carotid artery or in a femoral artery with an inductive-type differential pressure transducer (New Electronic Products). Heart rate was measured by means of a cardiotachometer triggered by the electrical activity of the QRS complex of the electrocardiograph (Horsfall, 1965).

All responses were monitored on a four-channel oscilloscope (Airmec) and recorded either on an ink-writing Mingograph recorder or on a Precision Instruments tape recorder (P.I.6108). The tape recorder was run continuously throughout an experiment, at the end of which the tape was re-run, the recordings displayed on an oscilloscope and the relevant portions recorded on the Mingograph.

Drugs were administered through catheters in the femoral veins. The continuous intravenous infusions were given by connecting the venous catheters to motor-driven syringes.

Two dogs were first treated with syrosingopine (0.5 mg/kg/day) given by intravenous injection for 2 days to deplete the peripheral stores of noradrenaline (Orlans, Finger & Brodie, 1960). The dogs were anaesthetized with pentobarbitone 16 hr after the second dose of syrosingopine. Depletion of the noradrenaline stores was demonstrated by the great reduction or absence of increases in heart rate and in arterial pressure to bilateral carotid arterial occlusion, stimulation of the central end of a cut vagus nerve and phenylethylamine (Stone, Ross, Wenger, Ludden, Blessing, Totaro & Porter, 1962).

The following drugs were used: (−)-adrenaline bitartrate (Burroughs Wellcome); (±)-isoprenaline sulphate (Burroughs Wellcome); (−)-noradrenaline bitartrate (Winthrop); (±)-phenylephrine hydrochloride (Boots); atropine sulphate (May & Baker); (±)-propranolol hydrochloride (Inderal, I.C.I.). These were dissolved in 0.9% saline at the required concentration expressed in terms of the salt.

RESULTS

Effects of propranolol

Observations were made on twenty-five dogs in which propranolol (0.1 to 1.0 mg/kg) was given by intravenous injection. Twenty-one were anaesthetized with pentobarbitone and the remainder with chloralose. Thoracotomy was performed in twenty dogs and in these heart rate, arterial pressure and cardiac contractile force were measured, and in twelve aortic flow. In the remaining five the chest was not opened and only heart rate and arterial pressure were recorded. The averaged results from all these experiments are given in Table 1. The results from the dogs anaesthetized with pentobarbitone have been divided into two groups according to the amount of propranolol administered—0.1 to 0.4 and 0.5 to 1.0 mg/kg. Observations were made on four dogs previously treated with atropine (2 mg/kg) and in two previously treated with syrosingopine.

The intravenous injection of propranolol produced a fall in resting heart rate in dogs anaesthetized with pentobarbitone or with chloralose (Table 1). The degree of bradycardia was not related to the initial heart rate or to the amount of propranolol given. In two experiments propranolol (0.25 mg/kg) produced falls in heart rate of 20 and 22

TABLE 1

THE EFFECTS OF PROPRANOLOL ON RESTING HEART RATE, MEAN ARTERIAL PRESSURE, ASCENDING AORTIC FLOW AND CARDIAC CONTRACTILE FORCE IN ANAESTHETIZED DOGS

These are averaged results and the standard errors are given when the number of animals in a group exceeded five. * Closed chest. Propranolol was given intravenously

			Propranolol		Heart rate (beats/min)		Mean blood pressure (mm Hg)		Aortic flow (ml./min)		Cardiac contractile force
Anaesthetic	Pretreatment	No of dogs	Administration	Total dose (mg/kg)	Before	After	Before	After	Before	After	(% change)
Pentobarbitone	Nil	13	Injection	0·1–0·4	151±7	124±6	106±5	94±5	793±105	610±110	−16±6
	Nil	3	Injection	0·5–1·0	112	94	94	84	950	900	−12
	Nil	3*	Injection	0·5–1·0	149	138	157	140	—	—	—
	Atropine	2*	Injection	0·5–1·0	136	113	100	90	—	—	—
		10	Infusion	0·1	149±5	128±4	103±6	98±6	834±100	780±120	−19±4
Chloralose	Nil	2	Injection	1·0	155	121	123	113	850	850	−14
	Atropine	2	Injection	1·0	152	124	125	120	—	—	−16
Pentobarbitone	Syrosingopine	2	Injection	0·5–1·0	94	94	89	88	—	—	0

beats/min ; the subsequent injection of 0.5 and 1.0 mg/kg of propranolol produced no further change in heart rate. The falls in heart rate after the administration of propranolol were as great in four dogs treated with atropine (2 mg/kg) by intravenous injection. In the two dogs previously treated for 2 days with syrosingopine resting heart rate was low (86 and 102 beats/min) ; the intravenous injection of propranolol (0.5 mg/kg) produced no change in rate in either dog. The fall in resting heart rate produced by propranolol was of rapid onset and was maximal within 2 min of completion of the injection. The heart rate remained at this level for a period that depended on the amount of propranolol administered but generally returned slowly towards the control level. In dogs anaesthetized with pentobarbitone or chloralose, the intravenous injection of propranolol reduced cardiac contractile force (Table 1). This occurred in the dogs previously treated with atropine but not in those treated with syrosingopine. Propranolol also slightly decreased mean arterial pressure in the artificially ventilated and in the spontaneously breathing dogs and in those previously treated with atropine. There was no correlation between the fall in pressure and the amount of propranolol injected. There was no change in arterial pressure when propranolol was given to two dogs previously treated with syrosingopine. The rate of blood flow through the ascending aorta was measured in twelve dogs. In all of these the intravenous injection of propranolol produced a fall in aortic flow (Table 1). This indicates that there was a decrease in cardiac output, as other results obtained by us have indicated that propranolol has no effect on coronary artery flow.

The effects of the continuous intravenous infusion of propranolol at 5 μg/kg/min for 20 min were similar to those obtained when the drug was given by intravenous injection but were of slower onset (Table 1).

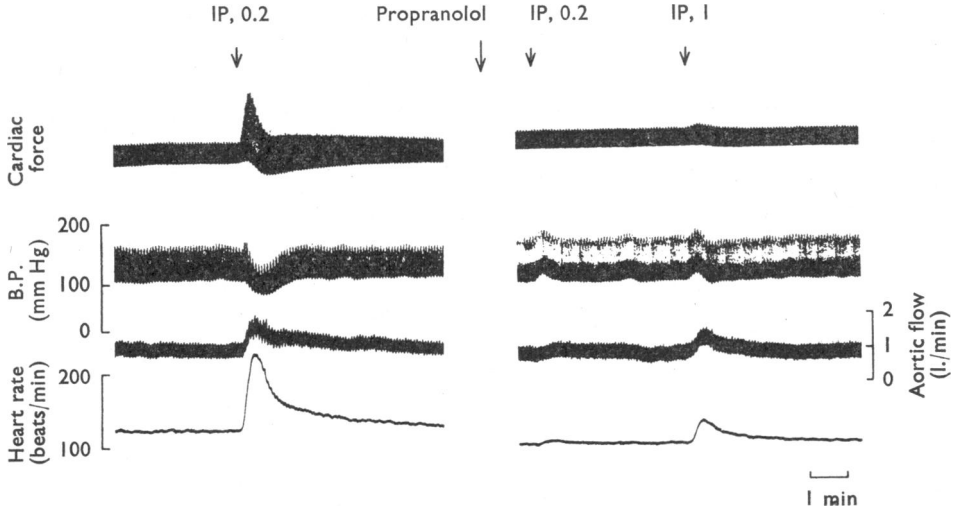

Fig. 1. Dog, 14.0 kg, pentobarbitone anaesthesia. Records of cardiac contractile force (right ventricle), femoral arterial pressure (B.P.), ascending aortic flow and heart rate. Responses to the intravenous injection of isoprenaline (IP, doses in μg/kg) before and after the intravenous injection of propranolol (0.5 mg/kg).

TABLE 2

AVERAGE CHANGES IN HEART RATE, MEAN ARTERIAL PRESSURE, CARDIAC CONTRACTILE FORCE AND ASCENDING AORTIC FLOW PRODUCED BY ISOPRENALINE, ADRENALINE, NORADRENALINE AND PHENYLEPHRINE BEFORE AND AFTER THE INTRAVENOUS ADMINISTRATION OF PROPRANOLOL

(*a*) Observations on dogs anaesthetized with pentobarbitone. (*b*) Observations on dogs anaesthetized with chloralose. (*c*) Observations after atropine (2 mg/kg intravenously).

Drug	Condition	No. of dogs	Heart rate (beats/min)		Mean arterial pressure (mm Hg)		Cardiac contractile force (% change)		Aortic flow (ml./min)	
			Before	After	Before	After	Before	After	Before	After
Isoprenaline	(*a*)	10	+84±7	+13±6	−29±5	0±1	+143±17	+3±3	+405	+25
(injection, 0·2 μg/kg)	(*b*)	2	+57	0	−21	−5	+120	0	+200	0
Isoprenaline	(*a*)	5	+72±16	+8±4	−4±5	+9±3	+97±18	+4±2	+522 ±180	+14 ±60
(infusion, 0·2 μg/kg/min)										
Adrenaline	(*a*)	12	+27±7	+1±1	+45±8	+61±6	+109±23	0	+310±105	−110±65
(injection, 1 μg/kg)	(*b*)	2	−25	−13	+13	+32	+130	0		
Adrenaline	(*a*)	5	−1±5	−14±6	+52±12	+52±11	+58±11	+7±4	+340±156	−206±80
(infusion, 1 μg/kg/min)										
Noradrenaline	(*a*)	15	+46±4	+2±1	+64±6	+45±4	+143±20	+4±1	+195	−105
(injection, 1 μg kg)	(*b*)	2	−35	−4	+53	+28	+280	−10	+160	−150
	(*c*)	2	+30	+5	+62	+56	+230	+5	−	−
Phenylephrine	(*a*)	5	−4	−2	+48±2	+43±2	0	0	−110	−95
(injection, 10 μg/kg)	(*b*)	2	−39	−17	+28	+32	0	0	−100	−100

Effect of propranolol on the responses to isoprenaline

The results of a typical experiment on a dog anaesthetized with pentobarbitone showing the increases in heart rate, cardiac contractile force and aortic flow and the reduction in arterial pressure produced by the intravenous injection of isoprenaline (0.2 μg/kg) are shown in Fig. 1. After the intravenous injection of propranolol (0.5 mg/kg) the cardiac effects of isoprenaline were greatly reduced ; the depressor response was abolished and there was instead a slight increase in pressure. The effects of a larger dose of isoprenaline (1.0 μg/kg) on cardiac contractile force, heart rate and aortic flow were small ; there was an increase in arterial pressure. The averaged results from ten dogs anaesthetized with pentobarbitone and two with chloralose are given in Table 2 ; these are the effects of propranolol (0.5 or 1.0 mg/kg) on the responses to isoprenaline (0.2 μg/kg). The intravenous infusion of propranolol at 5 μg/kg/min abolished the responses to the intravenous infusion of isoprenaline at 0.2 μg/kg/min (Table 2).

Effect of propranolol on the responses to noradrenaline

In dogs anaesthetized with pentobarbitone, the intravenous injection of noradrenaline (1.0 μg/kg) increased cardiac contractile force, arterial pressure and aortic flow (Fig. 2). There was a transient increase in heart rate followed by a slight fall to below the resting level. After the intravenous injection of propranolol (0.5 mg/kg) the cardiac actions of noradrenaline were antagonized—there was no increase in cardiac contractile force, a

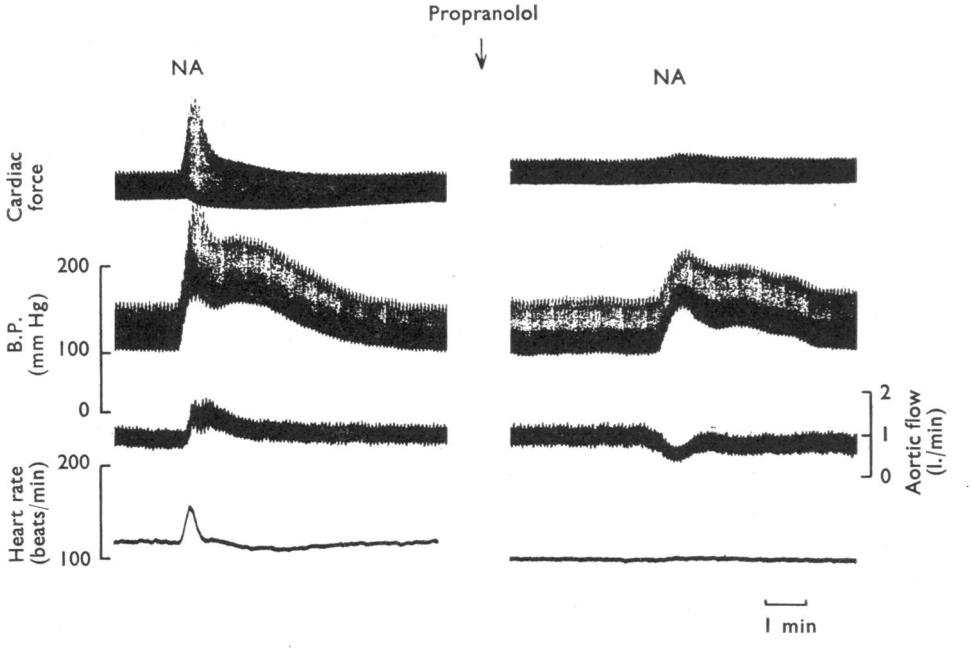

Fig. 2. Dog, 14.0 kg, pentobarbitone anaesthesia. Records of cardiac contractile force (right ventricle), femoral arterial pressure (B.P.), ascending aortic flow and heart rate. Responses to the intravenous injection of noradrenaline (NA, 1 μg/kg) before and after the intravenous injection of propranolol (0.5 mg/kg).

transient decrease in aortic flow and no change in heart rate, both the initial increase and the secondary fall being abolished. The pressor response to noradrenaline was reduced. Similar results were obtained in fourteen other experiments and the averaged results are given in Table 2. In Table 2 only the initial increase in heart rate has been recorded. Observations were also made in four dogs anaesthetized with chloralose ; the averaged results are given in Table 2. In two of these experiments atropine (2 mg/kg) was given intravenously after the control responses to noradrenaline but before the administration of propranolol. The responses of cardiac contractile force, arterial pressure and aortic flow to noradrenaline before and after propranolol were similar to those in the dogs anaesthetized with pentobarbitone but the heart rate responses were different (Fig. 3). Noradrenaline produced a fall in heart rate ; after atropine there

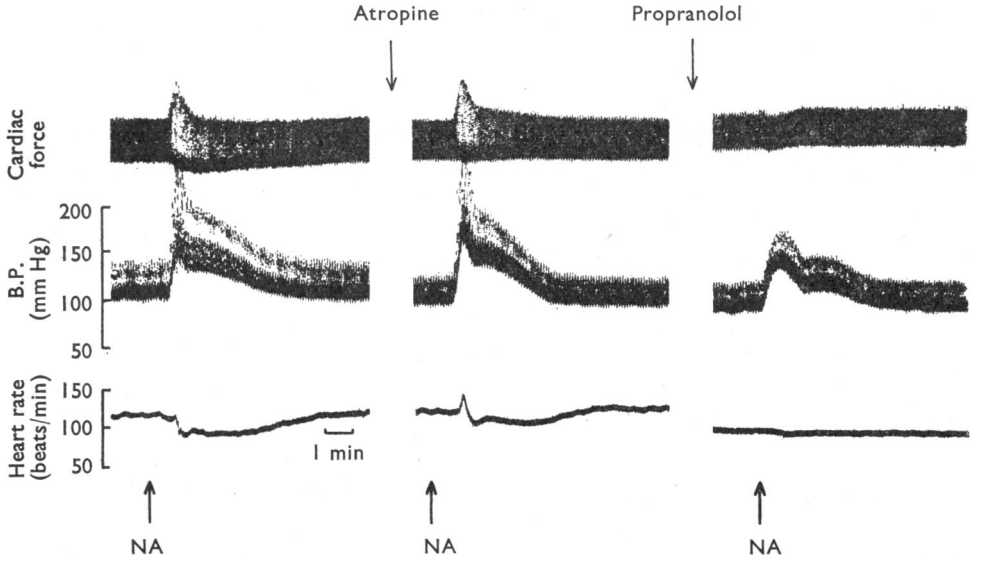

Fig. 3. Dog, 7.0 kg, chloralose anaesthesia. Records of cardiac contractile force (right ventricle), femoral arterial pressure (B.P.) and heart rate. Responses to the intravenous injection of noradrenaline (NA, 1 μg/kg) during the control period, after the intravenous injection of atropine (2 mg/kg) and after the intravenous injection of propranolol (0.5 mg/kg).

was a biphasic response—an initial increase followed by a fall in rate, both of which were abolished by the subsequent administration of propranolol.

In all experiments propranolol reduced the increase in arterial pressure produced by noradrenaline. This appeared to result from blockade of the inotropic action of noradrenaline and not as a result of blockade of its peripheral vasoconstrictor action as the increase in total peripheral resistance (obtained by dividing mean arterial pressure by aortic flow) produced by noradrenaline was greater after propranolol. This conclusion was confirmed by observations in seven dogs in which phenylephrine (10 μg/kg) was given before and after propranolol. The results of a typical experiment in a dog anaesthetized with pentobarbitone are given in Fig. 4. The intravenous injection of phenyl-

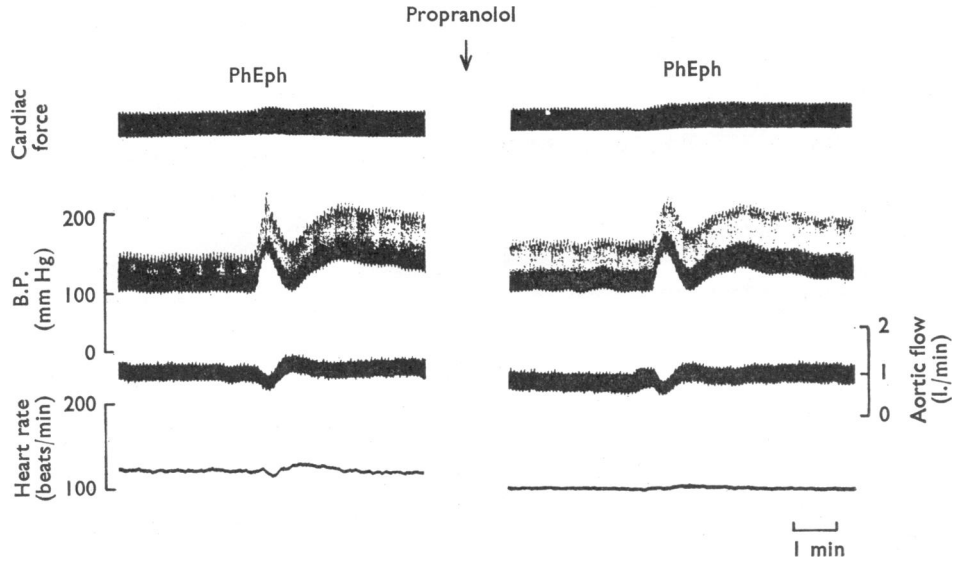

Fig. 4. Dog, 14.0 kg, pentobarbitone anaesthesia. Records of cardiac contractile force (right ventricle), femoral arterial pressure (B.P.), ascending aortic flow and heart rate. Responses to the intravenous injection of phenylephrine (PhEph, 10 μg/kg) before and after the intravenous injection of propranolol (0.5 mg/kg).

ephrine produced a considerable increase in arterial pressure but little change in cardiac contractile force, aortic flow or heart rate. The pressor response was unaffected by the intravenous injection of propranolol (0.5 mg/kg). Similar results were obtained in six other experiments and the averaged results are given in Table 2. In the two dogs anaesthetized with chloralose, phenylephrine produced a fall in heart rate which was reduced but not abolished by propranolol (Table 2).

The effects of propranolol on the responses to adrenaline

Observations were made on twelve dogs anaesthetized with pentobarbitone; the results of a typical experiment are shown in Fig. 5. The intravenous injection of adrenaline (1.0 μg/kg) produced considerable increases in cardiac contractile force, mean arterial pressure and heart rate; smaller increases occurred in aortic flow and in pulse pressure. After the intravenous injection of propranolol (0.5 mg/kg), the inotropic and chronotropic actions of adrenaline were completely blocked, and no increase in pulse pressure occurred although the increase in mean arterial pressure was potentiated; there was a fall in aortic flow. The averaged results are given in Table 2. In dogs anaesthetized with chloralose the effects of adrenaline on cardiac contractile force, arterial pressure and aortic flow before and after propranolol were similar to those in the dogs anaesthetized with pentobarbitone but the heart rate responses were different. The intravenous injection of adrenaline produced a fall in heart rate. After the intravenous injection of atropine (2 mg/kg) adrenaline produced a biphasic change in heart rate, an initial transient tachycardia followed by a more prolonged bradycardia. The intravenous

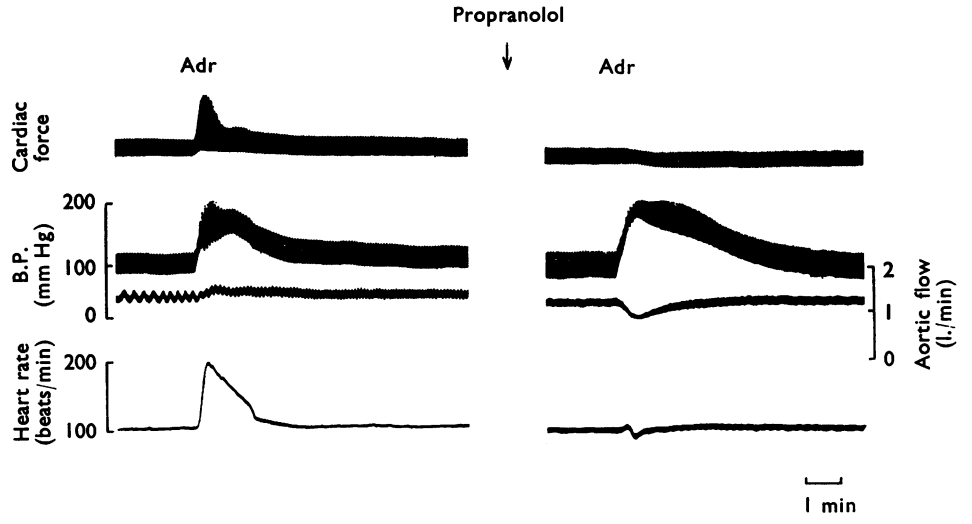

Fig. 5. Dog, 13.0 kg, pentobarbitone anaesthesia. Records of cardiac contractile force (right ventricle), femoral arterial pressure (B.P.), ascending aortic flow and heart rate. Responses to the intravenous injection of adrenaline (Adr, 1 μg/kg) before and after the intravenous injection of propranolol (0.5 mg/kg).

injection of propranolol abolished completely these changes in heart rate. The intravenous infusion of propranolol abolished the changes in contractile force, aortic flow and pulse pressure produced by the intravenous infusion of adrenaline at 5 μg/kg/min for 4 min ; the increase in mean arterial pressure was potentiated (Table 2).

DISCUSSION

In the present experiments the intravenous administration of propranolol reduced heart rate, cardiac contractile force and aortic flow in dogs anaesthetized with pentobarbitone or with chloralose. These changes resulted from blockade of resting sympathetic tone to the heart as they still occurred after the administration of atropine but not in dogs whose hearts had been depleted of catechol amines by syrosingopine. In dogs propranolol is devoid of the intrinsic sympathomimetic properties which dichloroisoprenaline clearly possesses (Moran & Perkins, 1958) and which pronethalol probably possesses although to a much lesser extent (Ahlquist, 1963 ; Donald *et al.*, 1964 ; Maxwell *et al.*, 1963 ; Black, Duncan & Shanks, 1965). Propranolol produced little change in arterial pressure. Propranolol is also devoid of sympathomimetic activity in cats (Black *et al.*, 1965).

Propranolol blocked the increases in cardiac contractile force, heart rate and aortic flow produced by isoprenaline and converted its depressor response to a pressor one. This latter action is unlikely to result from an action of isoprenaline on the α-receptors producing a peripheral vasoconstriction, as described in the cat by Butterworth (1963) using "milligram doses" of isoprenaline, as the pressor response is abolished by larger doses of propranolol but not by phenoxybenzamine (Shanks, unpublished). This isoprenaline-reversal probably results from complete blockade of the β-receptors, which

are responsible for the peripheral vasodilatation occurring before blockade of the cardiac receptors is complete. Consequently isoprenaline still increases cardiac output (Fig. 1), but as there is no associated peripheral vasodilatation arterial pressure is increased. This differential blockade of β-receptors has been described by Van Deripe & Moran (1965), who showed that α-methyl dichloroisoprenaline or 4-methyl-*N*-isopropylphenyl-ethanolamine (H 29/50) produced complete blockade of the vasodilator sympathetic receptors but only partial antagonism of the cardiac receptors.

In these experiments the changes in heart rate produced by adrenaline and noradrenaline were greatly influenced by the anaesthetic agent. In the dogs anaesthetized with pentobarbitone, resting heart rate was largely controlled by the sympathetic nervous system as the administration of atropine produced very little change in rate, whereas propranolol always produced a significant fall in rate. This control condition influenced the responses to the different amines. The intravenous injection of isoprenaline, adrenaline and noradrenaline produced increases in heart rate which were abolished by propranolol. In some dogs the tachycardia to noradrenaline was followed by a slight secondary fall in rate to below the control level. Even the intravenous injection of phenylephrine, which produced a large increase in arterial pressure and has been shown to be devoid of cardiac stimulant properties, produced little change in heart rate (Fig. 3); in three of the five other dogs phenylephrine produced a slight fall in heart rate which was abolished by propranolol. The heart rate responses to adrenaline, noradrenaline and phenylephrine were considerably different in the dogs anaesthetized with chloralose; all three amines produced a bradycardia. After the administration of atropine to abolish parasympathetic activity there was an initial transient increase in rate with adrenaline and noradrenaline. A secondary fall in rate to below the control level still occurred although the absolute fall was less than before the atropine, as was the bradycardia in response to phenylephrine. This remaining reflex bradycardia was abolished by propranolol. These results suggest that under the conditions of these experiments the reflex fall in heart rate in response to an acute elevation of arterial pressure results from a reflex increase in parasympathetic tone, which can be abolished by atropine. At the same time there is an inhibition of sympathetic activity which does not occur after propranolol, as this blocks all sympathetic activity to the heart. These mechanisms are only clearly demonstrated in the dogs anaesthetized with chloralose. In those anaesthetized with pentobarbitone no parasympathetic activity was present and the slight fall in rate to below the control level produced by noradrenaline and phenylephrine resulted from an inhibition of sympathetic activity as it did not occur after propranolol. These conclusions agree with those of Aviado & Wnuck (1957) but are at variance with the observations of Glick & Braunwald (1965), who showed that the slowing of heart rate in response to the elevation of arterial pressure by phenylephrine was completely abolished by atropine but not affected by pronethalol; they concluded that the slowing resulted entirely from increased parasympathetic activity.

The increase in arterial pressure produced by phenylephrine results entirely from a peripheral vasoconstriction. The drug is devoid of cardiac actions and does not increase cardiac output (Aviado, 1959). Its pressor response was unaffected by propranolol. In the present experiments noradrenaline increased arterial pressure by means of a peripheral vasoconstriction (Green & Kepchar, 1959) and by an increase in cardiac output. As

propranolol blocked the inotropic action of noradrenaline the latter's pressor action was reduced. Adrenaline has a double action on the blood vessels, as it constricts the vessels of the kidneys and skin but dilates those of the coronary and skeletal muscle vascular beds (Green & Kepchar, 1959). As a consequence mean arterial pressure and pulse pressure are both increased by adrenaline. Propranolol blocks the peripheral vasodilator action of adrenaline without affecting its vasoconstrictor action (Shanks unpublished). Consequently the pressor response is potentiated; the blockade of the vasodilatation more than compensates for the blockade of the increase in cardiac output produced by adrenaline before propranolol.

SUMMARY

1. In dogs anaesthetized with pentobarbitone or with chloralose the intravenous injection or infusion of propranolol (0.1 to 1.0 mg/kg) reduced heart rate, cardiac contractile force, arterial pressure and the rate of blood flow through the ascending aorta. These changes did not occur in dogs previously treated with syrosingopine, indicating that they result from blockade of resting sympathetic tone by propranolol.

2. Propranolol antagonized the cardiac actions of isoprenaline and converted its depressor action to the weak pressor one.

3. In the dogs anaesthetized with pentobarbitone the intravenous injection of adrenaline and noradrenaline produced an increase in heart rate which was abolished by propranolol.

4. In the dogs anaesthetized with chloralose adrenaline and noradrenaline produced a fall in heart rate; after atropine this response was converted to a biphasic one—an initial transient increase in rate followed by a fall to below the control level. After propranolol adrenaline and noradrenaline had no effect on heart rate.

5. In all dogs propranolol abolished the increases in cardiac contractile force and aortic flow produced by adrenaline and noradrenaline.

6. Propranolol reduced the pressor response to noradrenaline, potentiated that to adrenaline but it did not affect the response to phenylephrine.

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