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CENTRAL AND PERIPHERAL ACTIONS OF PRONETHALOL

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Pronethalol is a potent antiarrhythmic agent, more active than quinidine, and is a local anaesthetic with 1.8-times the activity of procaine (Vaughan Williams & Sekiya, 1963; Sekiya & Vaughan Williams, 1963a,b; Gill & Vaughan Williams, 1964). It seemed worth while, therefore, to investigate what protective action might be offered by pronethalol against arrhythmias induced by adrenaline and chloroform. In the event, even during light chloroform anaesthesia, pronethalol precipitated heart block and circulatory failure, and it was necessary to estimate the depth of anaesthesia with some precision, to which end withdrawal reflexes were recorded in response to trains of electric shocks. This led to the observation that pronethalol blocked the flexor reflex. In the course of these investigations it was found that guinea-pigs, like dogs but unlike cats, responded after pronethalol with a rise in blood pressure to " microgram doses " of isoprenaline.

METHODS

Guinea-pigs of either sex, 400 to 800 g in weight, were given atropine (2 mg/kg) intraperitoneally, and were anaesthetized with various anaesthetics (see Results) to a depth sufficient to permit cannulation of trachea, artery and vein. They were given artificial ventilation throughout the experiments with a Palmer " suck-and-thrust " pump. Blood pressure was recorded from a carotid artery by a mercury manometer. The skin over the right ankle was clipped and anointed with electrode jelly, and two chlorided silver plates were then tied in position. The skin was stimulated with brief trains of shocks (1 msec duration, at 40 to 150 shocks/sec), administered at intervals of about 10 sec. The stimuli were adequate to cause withdrawal of the limb, and the force of the pull (in g) was recorded by a lever on a smoked drum. In most experiments the electrocardiogram was also recorded with a Cossor 1314 pen-writing instrument. The pelvis was immobilized by a clamp applied to the left ileum through a skin incision.

The required concentrations of chloroform and ether were obtained by filling plastic bags from specially calibrated EMO vaporizers. The vaporizers could not be used directly because, to obtain accuracy of concentrations, the rate of airflow through the vaporizer had to be much greater (6 l./min) than that required for ventilation. For administration of anaesthetic the bags were attached to the inflow of the ventilation pump. Although chloroform was soluble in the plastic used, this would not have reduced significantly the concentrations of chloroform administered. A concentration of 0.5%, in a bag similar to those used by us, fell to 0.36% in 20 hr (H. Rang, personal communication). In our experiments the bags were filled immediately before use, and were used within 1 hr. The drugs used were: chloroform (B.D.H., Analar), ether (Duncan Flockhart, anaesthetic ether), pentobarbitone sodium (Abbott, Nembutal), urethane (B.D.H.), noradrenaline bitartrate (Bayer), isoprenaline sulphate (Burroughs Wellcome), phentolamine hydrochloride (Ciba, Rogitine), pituitary (posterior lobe) extract B.P.C. (B.D.H.), pronethalol hydrochloride (I.C.I., Alderlin) and amyl nitrite (Savory & Moore).

RESULTS

The effect of pronethalol on cardiac arrhythmias produced by chloroform and adrenaline

In an attempt to discover how much pronethalol would be required to abolish the production of cardiac arrhythmias by adrenaline in the presence of chloroform and other sensitizing agents (Moore & Swain, 1960), it was found that, although pronethalol reduced the incidence of arrhythmias induced by adrenaline, it also appeared to increase the toxicity of chloroform. Stable anaesthesia could be maintained for long control periods with chloroform, 0.7 to 1%, but the injection of pronethalol invariably resulted in circulatory failure with heart block and ventricular asystole if the chloroform concentration was above 0.65%. In order that the level of anaesthesia might be accurately controlled, therefore, further experiments were carried out with a simultaneous record of the withdrawal reflex.

The record of the withdrawal reflex provided an objective and reasonably quantitative estimate of the depth of anaesthesia. In the experiment shown in Fig. 1,*a*, the reflex was still lively with 0.8% chloroform, but when the concentration of chloroform was changed to 0.5% this was insufficient to maintain anaesthesia, and the reflex became very vigorous. The concentration of chloroform was then changed to 1.6% for a few minutes, and this alone was sufficient to abolish the reflex. The animal was respired with air only (Fig. 1,*c*)

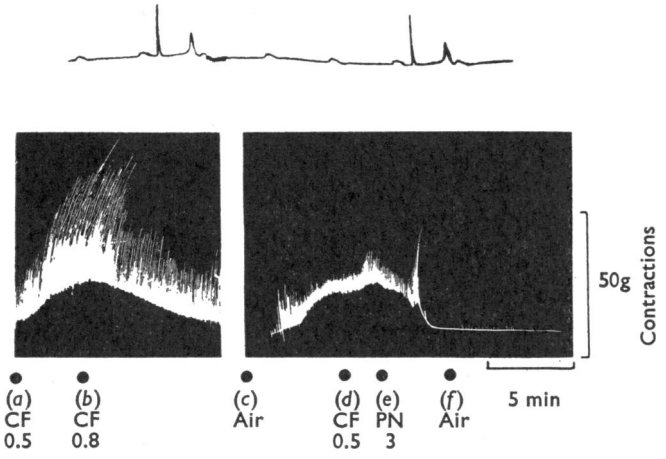

Fig. 1. Guinea-pig, anaesthetized with chloroform, to show effects of chloroform (CF, in %) and pronethalol (PN, in mg/kg) on the withdrawal reflex. Before (*a*) the animal breathed 0.8% chloroform. Between the two mountings, it breathed 1.6% chloroform. The electrocardiogram (above) was taken after (*f*).

and, when the reflex had returned, 0.5% chloroform was again administered (*d*). Pronethalol (3 mg/kg) was then injected. The unexpected result of this was that, in spite of the low chloroform concentration, the withdrawal reflex was abolished. The electrocardiogram was being recorded throughout this experiment, and it was observed that at the time the reflex was abolished atrio-ventricular block had developed.

It was evident from the first six experiments that the investigation of any antagonism by pronethalol to arrhythmias induced during chloroform anaesthesia was limited by the fact that both pronethalol and chloroform caused hypotension, and only small quantities

of both could be administered if the animal was to be kept alive. A further series of twelve experiments was undertaken in guinea-pigs anaesthetized with various amounts of anaesthetic, and the results have been presented in Table 1, in descending order of chloroform concentrations. Two conclusions can be drawn from the experiments. First, pronethalol did reduce the incidence of arrhythmias induced by adrenaline during light chloroform anaesthesia. Secondly, pronethalol increased the toxicity of chloroform. Indeed, unless the chloroform concentration was less than 0.65%, pronethalol invariably produced circulatory failure.

Effect of vasoconstriction

Since both chloroform and pronethalol had hypotensive actions, it seemed possible that the combination of the two drugs might be less dangerous if the blood pressure could be

TABLE 1

THE EFFECTS OF CONCENTRATION OF CHLOROFORM ON THE CARDIOVASCULAR ACTIONS OF ADRENALINE AND PRONETHALOL

In experiment 7 the blood pressure was 60 mm Hg before pronethalol, and in experiment 19 it was 70 mm Hg (after 1 hr of anaesthesia). In experiment 22 noradrenaline was injected at intervals to maintain blood pressure, for both chloroform concentrations

No. of expt.	Concentration of chloroform (%)	Adrenaline		Pronethalol		Adrenaline		Final effect
		Dose (μg)	Effect	Dose (mg/kg)	Immediate effect	Dose (μg)	Effect	
1	1	5	Extrasystole	5	Slowing	50	No arrhythmia	2:1 then
		10	Ventricular tachycardia			100	No arrhythmia	3:1 block
								Asystole
2	1	20	Ventricular tachycardia	4	Slowing	20	Extrasystole	Block
								Asystole
5	1	5	Ventricular tachycardia	5	Slowing			
					Block			
					Asystole			
25	0·8	None		5	Fall B.P.			
					Block			
7	0·8	None		1	Slowing	10	Rise B.P.	
				+4	Fall B.P.		No arrhythmia	
					Block			
					Asystole			
8	0·7	4	Extrasystole	3	Slowing	4	Rise B.P.	Block
					Fall B.P.		No arrhythmia	Asystole
19	0·7	None		5	Block			
					Asystole			
9	0·65	1	Sinus tachycardia	3	Slowing	2	Rise B.P.	
				+3	Block		No arrhythmia	
					Asystole			
15	0·65	None		5	Block			
					Asystole			
22	0·65	None		5+5	B.P. maintained			
	0·8			+5	Block			
					Asystole			
11	0·6	None		5	Fall B.P.			
					Block			
13	0·6	None		5	No block B.P. >50 mm Hg			
	0·8				Fall B.P.			
					Block			

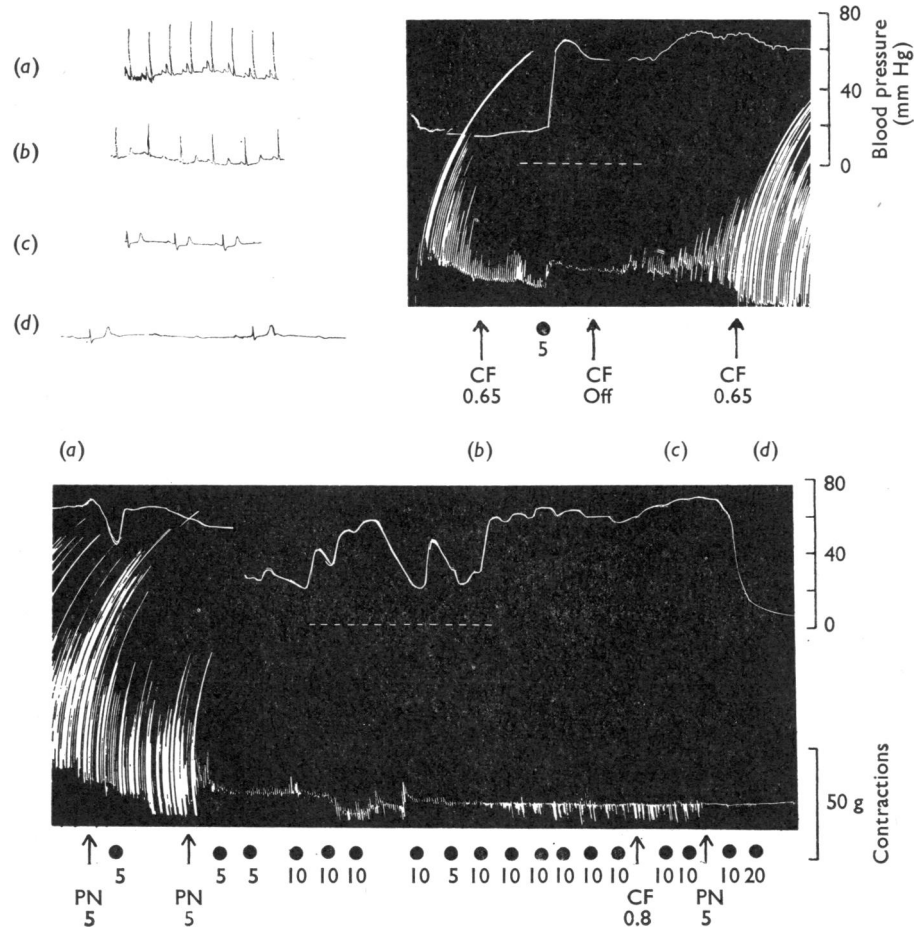

Fig. 2. Guinea-pig, anaesthetized with chloroform, to show the effect of vasoconstriction on toxicity of chloroform and pronethalol. The electrocardiographs were taken at the points indicated by the letters. The lower tracing continues the upper. Upper record, blood pressure; lower record, reflex contractions. The white interrupted lines give zero blood pressure. Chloroform (CF, 0.65%) and pronethalol (PN, 10 mg/kg) did not cause circulatory failure when vasoconstriction was produced by noradrenaline (at all dots, doses in μg). Noradrenaline did not prevent failure with 0.8% chloroform and a further 5 mg/kg of pronethalol.

maintained by vasoconstriction. Pronethalol has little action on sympathetic α-receptors, and the experiment shown in Fig. 2 illustrates the effects of chloroform and pronethalol in the presence of noradrenaline. At the beginning of the tracing the guinea-pig was breathing 1.3% chloroform, the blood pressure was low and the withdrawal reflex was rapidly diminishing. The chloroform concentration was reduced to 0.65%, and an intravenous injection of 5 μg of noradrenaline restored the blood pressure. The animal was temporarily allowed to breathe air until the withdrawal reflex had again become vigorous, and chloroform was then again administered at 0.65%. At this concentration, the reflex remained lively. Two injections of pronethalol produced hypotensive responses, but it

was found possible to maintain the blood pressure at above 60 mm Hg by a series of injections of noradrenaline, in contrast to the experiments 9 and 15 in Table 1. The chloroform concentration was then raised to 0.8%, and it was still possible to maintain the blood pressure with noradrenaline injections. A single injection of 5 mg of pronethalol, however, now caused circulatory failure and heart block, and it was apparent that the vasoconstriction had not ameliorated the fatal combination of pronethalol and a slightly higher concentration of chloroform.

The effect of pronethalol on the withdrawal reflex

In the experiments described above the withdrawal reflex had been measured in order to monitor the depth of anaesthesia. It was apparent from the experiment illustrated in Fig. 2, however, that after two injections of pronethalol (5 mg/kg) the reflex was virtually abolished although the chloroform concentration was only 0.65% and the blood pressure had been restored by injections of noradrenaline. This suggested that pronethalol itself had affected the reflex independently of the anaesthetic. It seemed advisable, therefore, to investigate this possibility by employing anaesthetics less toxic than chloroform.

Ether. In four experiments anaesthesia was induced with 10% ether, and subsequently maintained with various concentrations. In two of them, with 5% ether, although pronethalol caused severe hypotension, circulatory failure did not occur. The withdrawal reflex was greatly reduced. In a third experiment, anaesthesia was maintained for 1 hr on 6% ether, with a stable blood pressure. Pronethalol (5 mg/kg) reduced the reflex, the blood pressure slowly declined, and heart-block developed 30 min later. In the fourth, with 7% ether, pronethalol caused rapid failure of both circulation and reflex. It was concluded that ether was not a suitable anaesthetic for the investigation.

Urethane. In previous experiments (Vaughan Williams & Sekiya, 1963) up to 25 mg/kg of pronethalol had been given to guinea-pigs, anaesthetized with 1.6 g/kg of urethane, without killing them. In the present experiments it was found that 1.6 g/kg of urethane abolished the flexor reflex. Accordingly the animals were given 0.9 g/kg of urethane intraperitoneally, and were anaesthetized further, if necessary, with small increments of 0.2 g to 0.3 g/kg intravenously. In the experiment shown in Fig. 3, the animal had been prepared during open ether anaesthesia, which had been discontinued 2 hr before the beginning of the tracing; a total of 0.9 g/kg of urethane had been given intravenously meanwhile. Pronethalol abolished the flexor reflex, and the blood pressure fell to 18 mm Hg, but there was no atrio-ventricular block. On this occasion the blood pressure was restored with posterior pituitary extract, but the withdrawal reflex did not return.

In a further five experiments in guinea-pigs anaesthetized with urethane, injections of 5 to 15 mg/kg of pronethalol abolished or depressed the withdrawal reflex without causing circulatory failure, although the blood pressure was low. When the blood pressure was raised by injections of noradrenaline the reflex did not return. In the absence of pronethalol, the blood pressure was maintained as low as 18 mm Hg for 20 min by administration of amyl nitrite, but the withdrawal reflex was not diminished.

Pentobarbitone. The effects of pronethalol on the withdrawal reflex were studied in seven guinea-pigs anaesthetized with pentobarbitone. In the experiment shown in Fig. 4 the guinea-pig had been given pentobarbitone, 19 mg/kg intraperitoneally, and anaesthesia

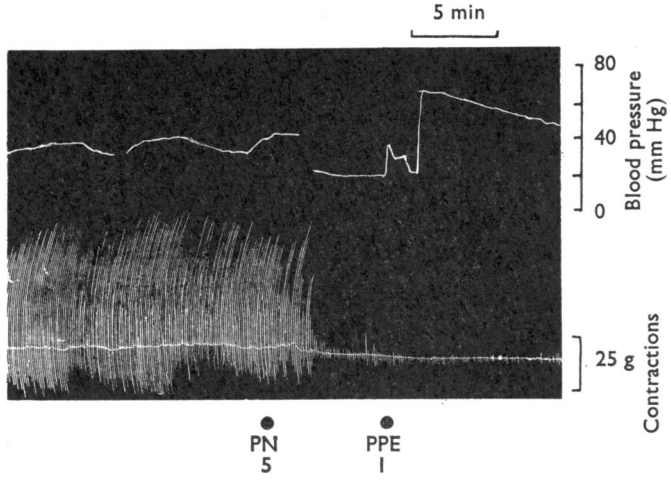

Fig. 3. Guinea-pig, anaesthetized with urethane (0.9 g/kg), to show depression of withdrawal reflex by pronethalol (PN, in mg/kg) in the absence of heart-block. Records as in Fig. 2. Pronethalol abolished the reflex, but did not produce atrio-ventricular block with urethane anaesthesia, so that the blood pressure could be restored by vasoconstriction with posterior pituitary extract (PPE, in U/min).

remained light throughout the experiment, so that further small intravenous increments of pentobarbitone had to be administered, at the times indicated, to suppress spontaneous movements. A rise of blood pressure (from 50 to 85 mm Hg) was produced by 8 μg of noradrenaline, and a prolonged fall (to 5 mm Hg) followed exposure to amyl nitrite, but neither of these wide variations in blood pressure affected the withdrawal reflex. An injection of 8 μg of isoprenaline caused a small fall in blood pressure, but after 8 mg/kg of pronethalol, which halved the reflex response, a second injection of 8 μg of isoprenaline now resulted in a rise of blood pressure. A further 8 mg/kg of pronethalol caused a large fall in blood pressure and the reflex was again depressed. There was no heart-block, however, in spite of prolonged hypotension, and a small dose of posterior pituitary extract partially restored the blood pressure. A further 8 μg/kg of isoprenaline now had a dramatic effect, raising the blood pressure above the original level to 60 mm Hg, but the reflex responses did not return.

In the above experiment, although the withdrawal reflex was not greatly affected by large variations in blood pressure, the failure of the reflex after pronethalol was associated with hypotension, and it seemed possible that the hypotension was concerned, at least as one auxiliary factor, in the loss of the reflex response. In the experiment shown in Fig. 5 the guinea-pig had received only 18 mg/kg of pentobarbitone intraperitoneally, and the dissection had been carried out with some additional open ether. The reflex responses were extremely vigorous, and were reduced in distinct stages by two further intravenous injections of pentobarbitone (4 mg/kg), which illustrated well that the reflex record gave a reasonably quantitative estimate of the depth of anaesthesia. After 30 min, when anaesthesia had lightened and small spontaneous movements were occasionally occurring, an infusion of 0.1 U/min of posterior pituitary extract was started. This raised the blood pressure from 54 to 100 mm Hg. The rate of infusion was reduced to 0.05 U/min and was

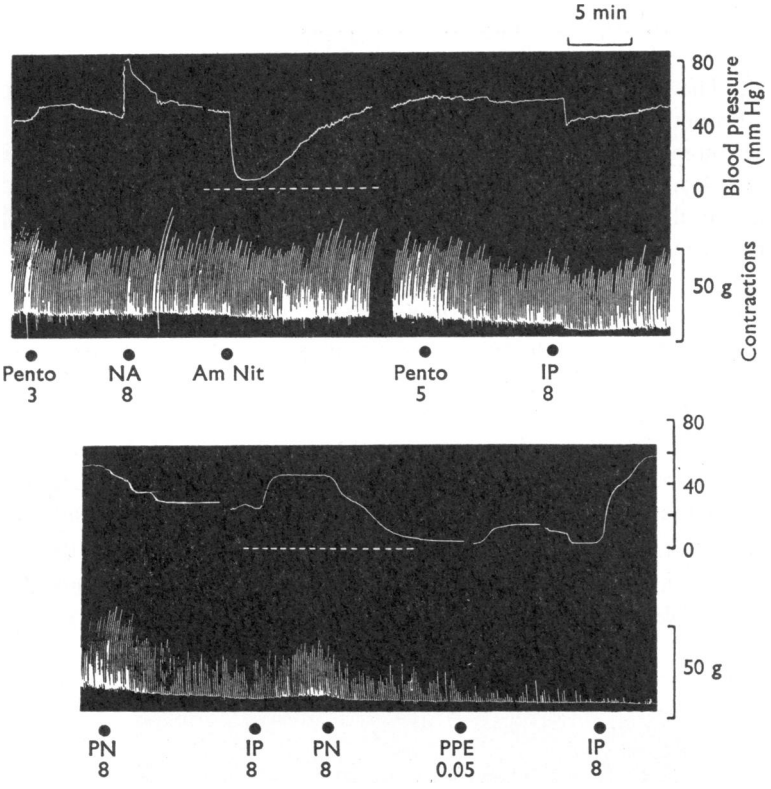

Fig. 4. Guinea-pig, anaesthetized with pentobarbitone (Pento, in mg/kg), to show the effect of blood pressure variations on the withdrawal reflex. Records as in Fig. 2. A rise in blood pressure produced by noradrenaline (NA, in μg/kg), and a fall produced by amyl nitrite (AmNit, for 5 sec), did not affect the reflex, nor did isoprenaline (IP, in μg/kg). Pronethalol (PN, in mg/kg) abolished the reflex, which did not recover when the blood pressure was restored with posterior pituitary extract (PPE, in U/min) and isoprenaline.

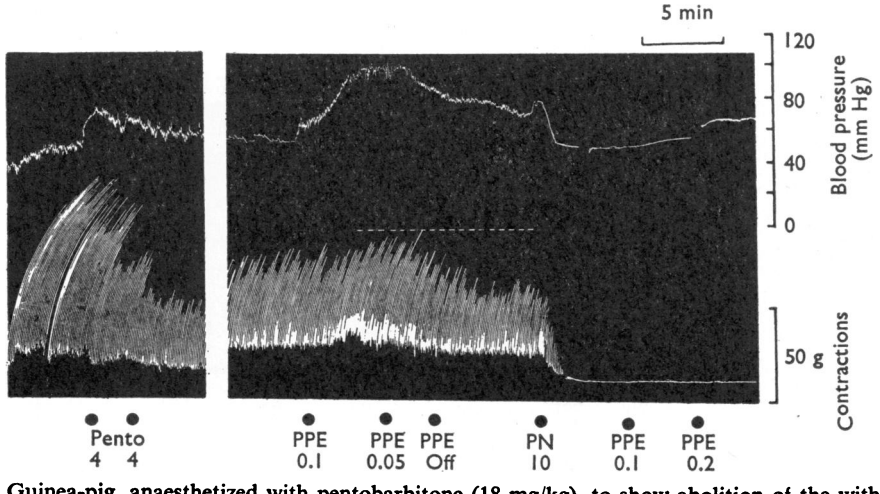

Fig. 5. Guinea-pig, anaesthetized with pentobarbitone (18 mg/kg), to show abolition of the withdrawal reflex by pronethalol without the production of hypotension. Records as in Fig. 2. Pentobarbitone (Pento) and pronethalol (PN) in mg/kg; posterior pituitary extract (PPE) in U/min.

then stopped. The blood pressure declined at a slow rate, dropping from 80 to 72 mm Hg in 12 min. Pronethalol (10 mg/kg) was now given and the reflex response was rapidly abolished, although the blood pressure fell only to 51 mm Hg. The pituitary infusion was restarted after 14 min at 0.1 U/min, and after a further 12.5 min it was raised to 0.2 U/min. This restored the blood pressure to nearly 70 mm Hg, well above the level at the beginning of the record, yet there was no sign of any return of the flexor reflex.

Pressor responses to isoprenaline after pronethalol

In a recent paper Butterworth (1963) reported that, in cats anaesthetized with chloralose, after large priming doses of isoprenaline or pronethalol, further injections of isoprenaline caused pressor responses only if " milligram doses " were given. He concluded that the responses were due to stimulation of sympathetic α-receptors. In view of the pressor responses to " microgram doses " of isoprenaline shown in Fig. 4, it was of interest to determine whether such responses would still be obtained after blockade of α-receptors.

In the experiment shown in Fig. 6, after 24 mg/kg of pentobarbitone the guinea-pig was only lightly anaesthetized, although there were no spontaneous movements, and a further 4 mg/kg of pentobarbitone intravenously reduced the withdrawal reflex response by

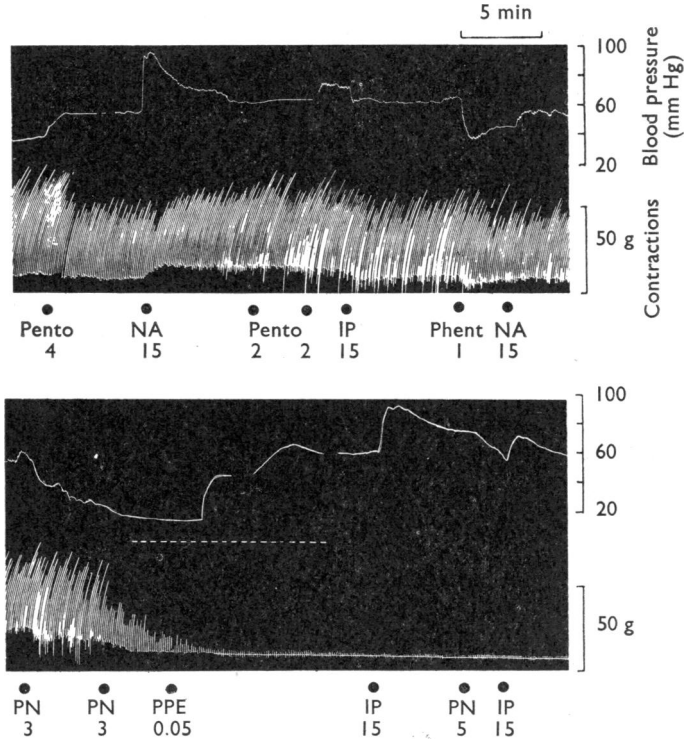

Fig. 6. Guinea-pig, anaesthetized with pentobarbitone, to show evidence that the pressor response after pronethalol to 15 μg/kg of isoprenaline was not due to stimulation of α-receptors. Records as in Fig. 2. Doses of pentobarbitone (Pento), phentolamine (Phent) and pronethalol (PN) in mg/kg; of noradrenaline (NA) and isoprenaline (IP) in μg/kg; of posterior pituitary extract (PPE) in U/min.

about 20%. The blood pressure was stable at 53 mm Hg. Noradrenaline (15 μg/kg) raised it to 96 mm Hg at the peak of the effect. Spontaneous movements necessitated two further injections of 2 mg/kg of pentobarbitone. Isoprenaline (15 μg/kg) caused a fall in blood pressure from 72 to 63 mm Hg. Phentolamine (1 mg/kg) reduced the blood pressure to 47 mm Hg, and a further 15 μg/kg of noradrenaline now raised it to only 55 mm Hg, indicating a substantial block of α-receptors. Pronethalol (5 mg/kg) caused a fall in blood pressure and a further 3 mg/kg lowered the blood pressure to 18 mm Hg. An intravenous infusion of posterior pituitary extract was started from a motor-driven syringe at 0.05 U/min and rapidly restored the blood pressure to over 60 mm Hg, that is to a level higher than at the start of the record. A repetition of the small dose of isoprenaline (15 μg/kg) now caused a prolonged rise in blood pressure to more than 114 mm Hg. A further 5 mg/kg of pronethalol was administered, but another 15 μg/kg of isoprenaline still raised the blood pressure from 58 to 74 mm Hg. The withdrawal reflex was completely blocked.

It is clear that guinea-pigs differed from cats in that pressor responses could be obtained to " microgram doses " of isoprenaline in the presence of a β-receptor blocking agent. It was probable that this pressor response was not due to stimulation of α-receptors because the response to noradrenaline had been reduced by phentolamine by 80%, and the peripheral vessels were already constricted by posterior pituitary extract. Sekiya & Vaughan Williams (1963a, see Fig. 1) had found that, although pronethalol greatly reduced the spontaneous heart rate, isoprenaline still caused an increase in rate in the presence of large amounts of pronethalol. Although the electrocardiogram was not being recorded in the experiment shown in Fig. 6, it was noted that injections of isoprenaline did increase the heart rate.

DISCUSSION

In guinea-pigs with artificial ventilation and given concentrations of chloroform greater than 0.65%, pronethalol caused a profound fall in blood pressure, complete heart-block, and circulatory failure with ventricular asystole. Thus, although in those animals surviving long enough for the investigations to be carried out, pronethalol did reduce or prevent arrhythmias after intravenous adrenaline, it was evident that a serious circulatory hazard attended a combination of chloroform and pronethalol in doses sufficient substantially to reduce increases in heart rate produced by isoprenaline. Payne & Senfield (1964), however, found that in man very small doses of pronethalol (0.25 to 10 mg total dose) could safely be administered during anaesthesia with chloroform, halothane or cyclopropane, and were sufficient to abolish ventricular arrhythmias.

It was possible that the hypotension could have been due mainly to cardiac failure. Sympathetic activity facilitates atrio-ventricular conduction, and increases the rate and force of the heart beat (actions due to the stimulation of β-receptors), and the toxicity of chloroform to the heart might have been greater when pronethalol had deprived the organ of sympathetic drive. For three reasons, however, it has been concluded that the action of pronethalol was not due to a toxic effect on cardiac muscle alone. First, the amounts of chloroform and pronethalol necessary to produce block were larger in the presence of vasoconstrictor drugs. Secondly, with urethane or pentobarbitone anaesthesia no atrio-ventricular block developed, but pronethalol still produced severe hypotension. Thirdly, in recent experiments (Morales-Aguiléra & Vaughan Williams, 1965) it was found that the heart continued to beat after as much as 70 mg/kg of pronethalol when the blood pressure

was prevented from falling by an infusion of blood from a reservoir, and that a normal circulation was maintained when the reservoir was subsequently disconnected.

Pronethalol also depressed or abolished the withdrawal reflex, and in this respect would appear to have greater activity than several other drugs reputed to cause depression of polysynaptic reflexes. Roszkowski (1960) reported that chlorzoxazone, the most potent compound studied by him, produced a 14% depression of the flexor reflex in cats when 4 mg/kg were given, and a 58% depression after 10 mg/kg. Meprobamate (40 mg/kg) caused 11% depression, and mephenesin carbamate (40 mg/kg) produced 32% depression. In the present experiments, as little as 5 to 10 mg/kg of pronethalol abolished the reflex during light urethane or pentobarbitone anaesthesia. The depression of the reflex was often associated with the hypotensive effect of pronethalol, but it was concluded that the reflex was depressed independently of the hypotension for three reasons. First, the reflex was not reduced by large falls in blood pressure produced by amyl nitrite. Secondly, when the blood pressure was restored by vasoconstrictor drugs, the reflex was not. Thirdly, if high blood pressure was produced by vasoconstriction before the administration of pronethalol, the latter still abolished the reflex in the absence of hypotension.

It would seem reasonable to conclude, therefore, that pronethalol has an action on the central nervous system which merits further analysis.

In the present experiments the guinea-pigs were anaesthetized, albeit not deeply, and it was possible that pronethalol might have had less central action in unanaesthetized animals. Secondly, the blood pressure was restored by drugs, which could themselves have had some central actions, such as vasoconstriction within the spinal cord, and it would be desirable to investigate the possibility that some of the apparent actions of pronethalol might be secondary to an associated hypotension, by using some physical method of controlling the blood pressure. Nevertheless, reduction of blood flow to the cord by vasoconstrictor agents was not a likely cause of the failure of the reflex, because noradrenaline and posterior pituitary extract did not reduce the reflex when given before pronethalol.

In the course of the investigation it was found that isoprenaline, in doses of a few micrograms, produced a pressor response after pronethalol. Woodbury, Braver & Ferguson (1950) reported pressor responses to isoprenaline in dogs given ephedrine and vasopressin. Walz & Maengwyn-Davies (1960) analysed the pressor responses to isoprenaline after priming doses of phenylephrine. They concluded that an action on the heart was not involved to a major extent on the grounds (1) that the pressor response persisted in the presence of dichloroisoprenaline; (2) that some pressor response was obtained in animals with an artificial circulation replacing the heart and lungs (Walz, Koppanyi & Maengwyn-Davies, 1960); and (3) vasoconstriction was observed in the perfused hind-limb. They suggested that phenylephrine in some way sensitized structures involved in the pressor response to the action of isoprenaline. They also found that, in cats given 1.0 mg/kg of phenylephrine, contractions of the nictitating membrane occurred in response to 1.0 μg/kg of isoprenaline. Butterworth (1963) found that in cats pressor responses to isoprenaline, after priming doses of isoprenaline itself or of pronethalol, were not obtained with doses of the order of micrograms. He concluded that the pressor responses to larger doses were due to stimulation of α-receptors, and that in this respect isoprenaline had about one-thousandth of the activity of adrenaline and noradrenaline. Our own experiments with guinea-pigs indicated that after pronethalol pressor effects were produced by doses of a

few micrograms of isoprenaline, and that these were especially large in the presence of a vasoconstrictor drug. It was unlikely that the pressor response was due to excitation of α-receptors for three reasons. First, the effect was obtained when the response to noradrenaline had been reduced to one-fifth by phentolamine. Secondly, the pressor response to isoprenaline was larger when vasoconstriction had already been produced by posterior pituitary extract. Thirdly, the response was associated with an increase in heart rate.

Pronethalol reduces the heart rate, but does not prevent isoprenaline from causing some increase from the new lower level unless very large amounts are given. The classification of responses to drugs as due to excitation of α- or β-receptors is convenient, but may not provide an accurate description at all sites, since receptors are abstractions which cannot be subjected to direct tests for uniformity. Clark (1933) long ago emphasized the unwisdom of assuming that receptors represent a homogeneous surface of the type studied by Langmuir, even though in some cases such an assumption may permit a closer fit for a dose/response relation than a simple logarithmic plot (Feigen, Vaughan Williams, Peterson & Nielsen, 1960). If variation in the structure of receptors is wide, care in selecting constants can never obscure the fact that any equation can only represent an approximation to a mean. Thus, structures whose excitation is responsible for increasing the heart rate may be classified broadly as "β-receptors," but may represent the extreme of a wide distribution, and have less affinity for pronethalol than structures responsible for vasodilatation.

SUMMARY

1. Reflex withdrawals of a limb in response to electric shocks to the skin, the blood pressure and the electrocardiogram have been measured in anaesthetized, artificially ventilated guinea-pigs.

2. Evidence was obtained for four effects of pronethalol. (*a*) Pronethalol reduced the incidence of cardiac arrhythmias induced by adrenaline during anaesthesia with chloroform. (*b*) Pronethalol increased the toxicity of chloroform. (*c*) Pronethalol reduced the withdrawal reflex. (*d*) After administration of pronethalol, doses of a few micrograms of isoprenaline caused a rise in blood pressure.

3. The pressor response to isoprenaline was still obtained when α-receptors had been blocked by phentolamine.

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