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THE ACTION OF PRONETHALOL ON SPINAL REFLEXES

BY

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Pronethalol was shown by Black & Stephenson (1962) to have many actions consistent with the view that its chief effect was blockade of sympathetic β-receptors. For example, in cats anaesthetized with chloralose, 2.5 mg/kg of pronethalol halved, and 5 mg/kg reduced by nine-tenths, submaximal accelerations of heart rate produced by injections of isoprenaline. However, in guinea-pigs anaesthetized with urethane (1.6 g/kg), it was found (Sekiya & Vaughan Williams, 1963a) that, although pronethalol (10 mg/kg) approximately halved the *spontaneous* heart rate, responses to isoprenaline were reduced to a lesser extent. Actions of pronethalol other than β-receptor blockade also came to light, and it was shown (Gill & Vaughan Williams, 1964) that pronethalol was a local anaesthetic with nearly twice the potency of procaine.

Further investigation (Sekiya & Vaughan Williams, 1963b, 1965) provided evidence that pronethalol had some central nervous action which merited further study, in particular the depression or abolition of the reflex withdrawal of a limb in response to electric shocks to the skin. The present paper represents an attempt to carry the analysis of this effect a stage further. It was possible that the depression of the reflex responses was related to the local anaesthetic action of pronethalol. On the other hand, an *a priori* case could be made for its being connected with blockade of β-receptors in the spinal cord, for Bülbring & Burn (1941) had reported that, in dogs in which the spinal cord and a limb were perfused with separate circulations, adrenaline greatly potentiated the flexor reflex (contractions of tibialis anterior in response to stimulation of the posterior tibial nerve). It was thus conceivable that the depression of the flexor reflex by pronethalol might have involved the removal of a facilitatory influence in the spinal cord mediated by β-receptors, but before any such hypothesis could be entertained a number of other possible explanations for the depression needed investigation.

METHODS

Contractions of the quadriceps were recorded in response to a train of stimuli (0.9 msec duration, 150 shocks/sec) to the skin or to the ipsilateral sciatic nerve, which was crushed and tied peripherally. The limb was immobilized by transfixation of the femur. Tendon jerks were elicited from the other limb by a solenoid-operated hammer, and when both reflexes were recorded simultaneously ball-bearing myographs were employed (Vaughan Williams, 1964). For tests on neuromuscular conduction, contractions of the gastrocnemius muscle were recorded in response to stimuli to the sciatic nerve, which was crushed

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and tied centrally. When it was desired to prevent hypotension, the animals were injected with heparin (3 mg/kg) and a carotid cannula was connected via a T-piece to a 30-ml. reservoir of heparinized blood obtained from another animal of the same species. A mixture of 95% oxygen and 5% carbon dioxide was admitted to the top of the reservoir from a 5-l. aspirator filled with the gas mixture to any desired pressure. The aspirator was attached to a separate manometer, and the pressure was adjusted to equal that shown on the blood pressure manometer before the blood-reservoir was put in communication with the circulation.

In all the experiments the preparations were given artificial ventilation, and the drugs used and other details were similar to those described in the previous paper (Sekiya & Vaughan Williams, 1965). The first experiments were done on guinea-pigs, since these animals were used for the previous investigation, but the blood pressure control was not always efficient because small cannulae were necessary and frequent checks had to be made that they had not become blocked. Rabbits were, therefore, used for the majority of the experiments.

RESULTS

Neuromuscular conduction

One possible explanation for failure of the flexor reflex could have been a block of neuromuscular conduction. This was not thought to be probable, however, because contractions of the interossei, presumably stimulated via motor nerves excited by the shocks to the skin over the ankle, had continued when the reflex had been blocked in

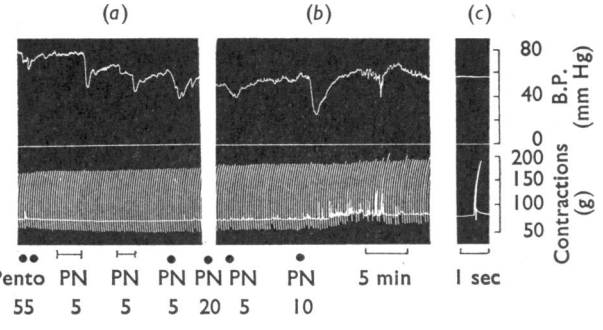


Fig. 1. Effect of pronethalol on neuromuscular conduction. Rabbit, 1.34 kg; pentobarbitone, 55 mg/kg. Contractions of soleus-gastrocnemius in response to single maximal shocks to sciatic nerve. (*a*) At Pento, further intravenous injections of 5 mg/kg of pentobarbitone. At each PN, 5 mg of pronethalol were injected intravenously slowly, during periods indicated. Between (*a*) and (*b*), four further injections of 5 mg of pronethalol were made during 32 min. (*b*) A further 15 mg of pronethalol caused movements of the whole animal on the pin fixing the femur. These movements were due to the pronethalol and not to lightening anaesthesia because the rabbit again became quiescent a few minutes later (compare Fig. 4). (*c*) Record of twitch on fast drum (compare the reflex contraction in Fig. 2,*d*).

previous experiments (Sekiya & Vaughan Williams, 1965). Sciatic-gastrocnemius preparations were set up in guinea-pigs and rabbits, and there was no evidence of any depression of neuromuscular conduction by pronethalol in either species (Fig. 1).

Local anaesthesia

Pronethalol is a potent antiarrhythmic drug (Vaughan Williams & Sekiya, 1963; Payne & Senfield, 1964) with an activity greater than quinidine in conventional tests (Sekiya & Vaughan Williams, 1963b). Most antiarrhythmic agents have local anaesthetic properties, and it was found that pronethalol possessed 1.8-times the activity of procaine as a local

anaesthetic (Gill & Vaughan Williams, 1964). One might have looked no further for an explanation of the effects of pronethalol on spinal reflexes, but for the recollection that the discovery of the properties of xylocholine (TM10) was postponed for several years by the coincidence that it was also a local anaesthetic (Bain, 1960). The evidence presented in Fig. 1 proved that there was no block of conduction in nerve trunks by amounts of pronethalol larger than those required to depress the reflex withdrawal of a limb. The concentration of pronethalol in a guinea-pig skin wheal required to halve the number of positive responses to pinpricks was 3 mg/ml. Since depression or block of reflexes was seen with 5 to 15 mg/kg in guinea-pigs it was unlikely that conduction in peripheral nerves could have been blocked by such doses.

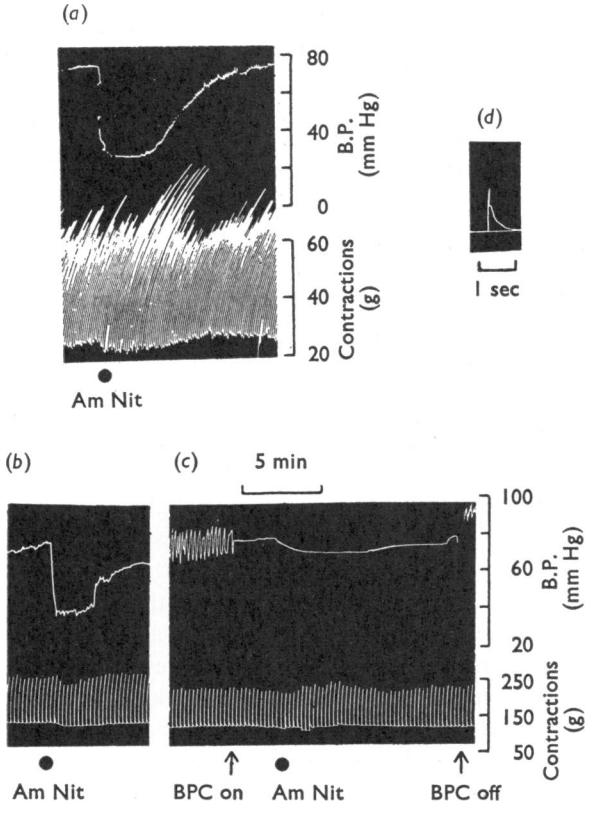


Fig. 2. Blood pressure control. (*a*) Guinea-pig, 550 g, anaesthetized with pentobarbitone, 20 mg/kg. Upper tracing, blood pressure (B.P.); lower tracing, withdrawals of right leg in response to shocks to skin. At Am Nit, amyl nitrite was added to inspired air for three strokes of the pump. (*b*) Rabbit, 1.3 kg, given pentobarbitone (60 mg/kg), atropine (1 mg) and heparin (3 mg). Upper tracing, blood pressure; lower tracing, contractions of quadriceps in response to stimuli to ipsilateral sciatic nerve. At Am Nit, amyl nitrite as above. Between (*b*) and (*c*) 30 min elapsed, during which a further 4 mg/kg of pentobarbitone was injected intravenously. At BPC on, the blood reservoir at controlled pressure was put in communication with the circulation, and it was disconnected at BPC off. Same time scale for (*a*), (*b*) and (*c*). (*d*) Reflex contraction of quadriceps with a faster drum (continuation of *c*).

Hypotension

Block of the flexor reflex by pronethalol had often been accompanied by hypotension and, although this had been corrected by vasoconstrictor drugs without a return of the reflex (Sekiya & Vaughan Williams, 1965), it was thought desirable to study the effect of pronethalol without the complication of additional drugs. In the experiment shown in Fig. 2,*a*, a guinea-pig was anaesthetized with pentobarbitone and the withdrawal of a limb was recorded in response to shocks to the skin, as described previously. A large fall in blood pressure was produced by admitting amyl nitrite to the input of the ventilation pump for three strokes. The force with which the limb was withdrawn did not diminish during the hypotension, and actually increased during the phase of recovery. In Fig. 2,*b* a record was made of contractions of the right quadriceps in response to stimuli to the ipsilateral sciatic nerve, in a rabbit anaesthetized with pentobarbitone. Exposure to amyl nitrite caused a fall in blood pressure, but had little effect on the reflex response. A period of 30 min elapsed between Fig. 2,*b* and *c*, and a further 4 mg/kg of pentobarbitone had been administered 10 min before the start of Fig. 2,*c* and had caused a small reduction in the contractions. The normal spontaneous fluctuations in blood pressure had meanwhile become exceptionally large, but were " smoothed out " as soon as the circulation was put in communication with the blood pressure control system. A second exposure to amyl nitrite again had little effect on the reflex, which was once more slightly increased during the phase of recovery. There was no large fall of blood pressure, however, since at the peak of the effect approximately 20 ml. of blood entered the circulation, most of which was returned to the reservoir during the subsequent 10 min. Some was still retained, however, so that, when the blood pressure control was clamped off from the circulation, the animal's mean blood pressure was about 16 mm Hg higher than at the beginning of the tracing.

Influence of anaesthesia

Although pronethalol blocked flexor reflexes in very lightly anaesthetized animals (Sekiya & Vaughan Williams, 1965), it was possible that the anaesthetic was having some synergistic depressant effect, and it was thought desirable to study the effect of pronethalol on reflexes in the absence of anaesthetic. In Fig. 3 contractions of the right quadriceps were recorded in response to stimuli to the ipsilateral sciatic nerve, in a rabbit decerebrated during open ether anaesthesia 1 hr before the record. The blood pressure was maintained throughout the experiment at over 60 mm Hg. Pronethalol (5 mg/kg followed by 7 mg/kg) caused a depression of the reflex. The blood pressure fell little because blood ran into the animal from the reservoir, and, although most of it was subsequently returned, the dose of pronethalol must have been diluted to some extent, which may have accounted in part for the short duration of the depression of the reflex. A further two doses of 5 mg/kg of pronethalol depressed the reflex further, but after a third 5 mg/kg the reflex was not blocked altogether as in previous experiments, but the responses to the stimuli became larger and more prolonged, until eventually the animal convulsed. The stimuli now either caused no response at all, or were followed by convulsions. The animal was not convulsing spontaneously because, when the stimulator was turned off, there were no movements at all, but violent convulsions were precipitated when the stimuli were restarted. It seemed probable that convulsions had not been seen previously because the activity of that part of the central nervous system which was responsible for their occurrence had been depressed

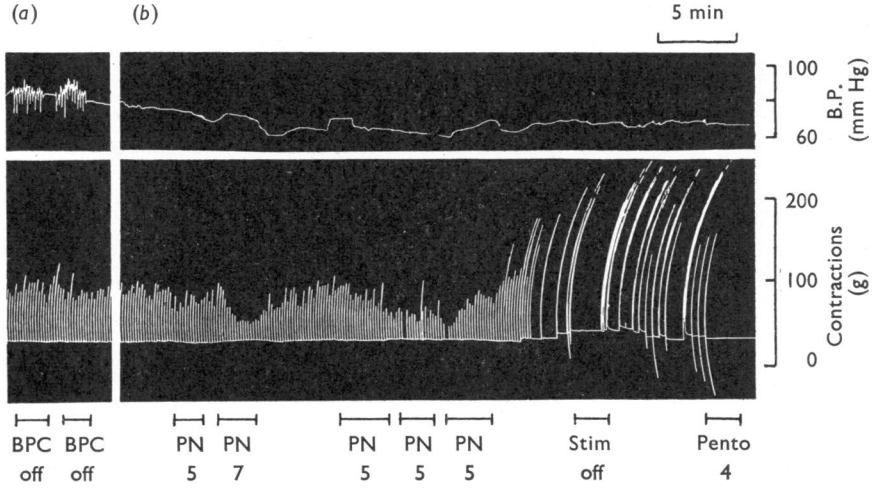


Fig. 3. Effect of pronethalol in decerebrate rabbit, 1.64 kg. Records as in Fig. 1. BPC=blood pressure control. (*a*) Spontaneous fluctuations in blood pressure (B.P.) were smoothed out by the controlling reservoir. (*b*) At PN, pronethalol (doses in mg/kg) was administered by slow intravenous infusion during the periods indicated by the bars. After the second dose the reflex response had fallen to 40% of the control, but quickly recovered. The response was again reduced by two further injections of 5 mg/kg, but after a third the responses increased and the animal went into convulsions. Thereafter the stimuli were followed by convulsive movements, but the animal was quiescent when the stimulator was turned off (Stim off). When the stimuli were restarted there was either no response at all, or a convulsion: 4 mg/kg of pentobarbitone (Pento) abolished all responses.

by the anaesthetic. A small dose of pentobarbitone was therefore given, and all responses to the stimuli were immediately abolished.

In previous experiments with anaesthetized animals, smaller amounts of pronethalol had been sufficient to block the flexor reflex than were required in decerebrate rabbits, and once block of the reflex had been achieved further amounts of pronethalol had not been given. In the experiment shown in Fig. 4,*a* a rabbit was anaesthetized with pentobarbitone, and reflex contractions of the quadriceps were recorded in response to ipsilateral sciatic stimulation. The blood pressure was maintained throughout at 90 mm Hg. Pronethalol (5 mg/kg) greatly reduced the reflex and, at the point at which it appeared to be fading out two further injections of 1 mg/kg of pronethalol were given. The result was a series of convulsive responses followed by complete abolition of the reflex. In another similar experiment (Fig. 4,*b*) the blocking concentration of pronethalol was approached very slowly, 2 mg/kg being injected every few minutes until the reflex was blocked, but there were again convulsive responses before the responses were abolished. When further injections of 2 mg/kg of pronethalol (Fig. 4,*c*) were made during the block, occasional convulsive responses were observed. It was noted that the responses were multiple. An immediate contraction was followed after a pause by a series of further contractions. Multiple responses of this kind were still being obtained 45 min later, and one of them is shown on a fast drum in Fig. 4,*d*. In these experiments strong stimuli were being given directly to the sciatic nerve, so that the whole spectrum of afferent fibres was being stimulated. It was noted that, even in the control period before the administration of pronethalol, reflex

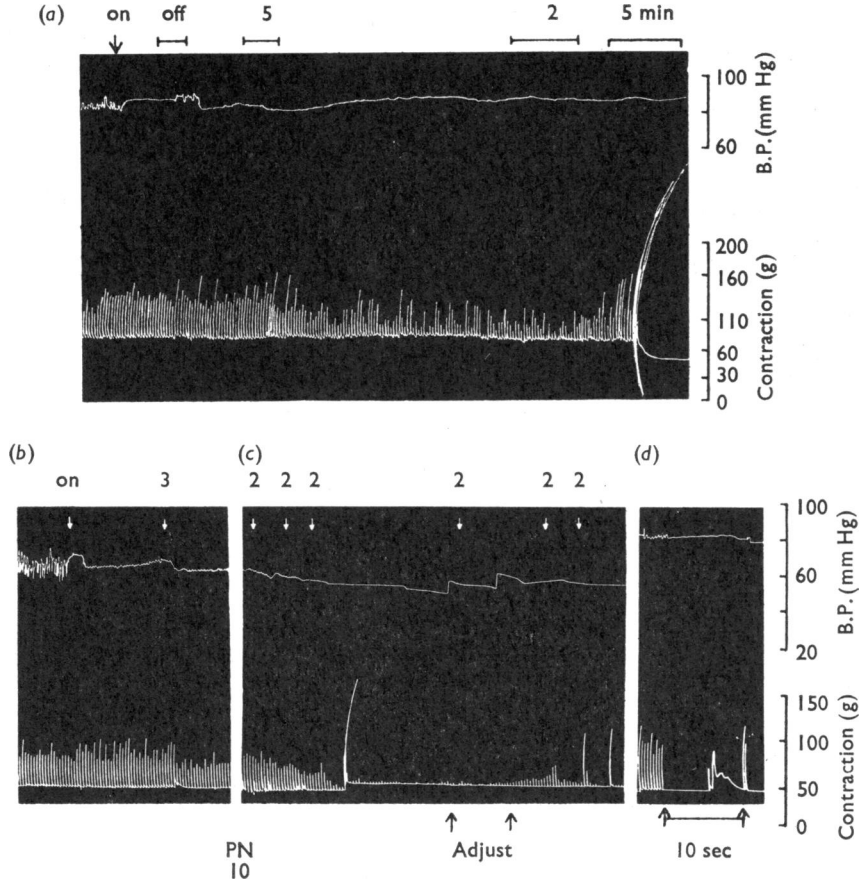


Fig. 4. Convulsive responses to sciatic nerve stimulation after pronethalol. (*a*) Rabbit, 1.24 kg, given 56 mg/kg of pentobarbitone and 1 mg of atropine. Blood pressure controlled at "on." The control reservoir was disconnected briefly during the period marked "off" and then reconnected. Pronethalol (PN), 5 mg/kg, greatly depressed contractions of the quadriceps in response to stimuli to the ipsilateral sciatic nerve. A further 2 mg/kg caused convulsions followed by complete block of the reflex. (*b*) and (*c*) Rabbit, 1.28 kg, anaesthetized with 55 mg/kg of pentobarbitone. Records as for (*a*). Pronethalol (18 mg/kg) administered during 30 min caused depression of the reflex, convulsions and block of the reflex. Further pronethalol during the block provoked intermittent multiple responses to the stimuli. (*d*) Multiple responses to stimuli still occurred 45 min later. Interval between (*b*) and (*c*), 48 min; between (*c*) and (*d*), 47 min. (*d*) was recorded with a faster drum speed.

responses to stimulation of the sciatic nerve exhibited a prolonged phase of relaxation (Fig. 2,*d*). Nevertheless, stimulation of the whole sciatic nerve was not a condition for the provocation of convulsive responses, as these were also seen when the skin was stimulated (Fig. 5,*b*).

In anaesthetized animals convulsions were only produced when the dose of pronethalol exceeded that required greatly to depress or to abolish the flexor reflex. In the absence of an anaesthetic, as in the decerebrate preparations, convulsive responses to stimuli were obtained before block of reflexes occurred.

Pronethalol on the knee-jerk

Pronethalol had much less effect on the knee-jerk. In the experiment shown in Fig. 5,*a*, contractions of the quadriceps were measured in response to taps on the patellar tendon. The blood pressure was controlled at 55 mm Hg. The rabbit had been given 67 mg/kg of pentobarbitone. Pronethalol (5 mg/kg and then 10 mg/kg) was injected every few minutes, but the knee-jerk was unaffected even when a total of 55 mg/kg of pronethalol had been administered. Pentobarbitone (25 mg/kg in divided doses) then abolished the reflex.

In the experiments described above, in which convulsive responses to nerve stimulation after pronethalol were described, the sciatic nerve had been stimulated. In the experiment

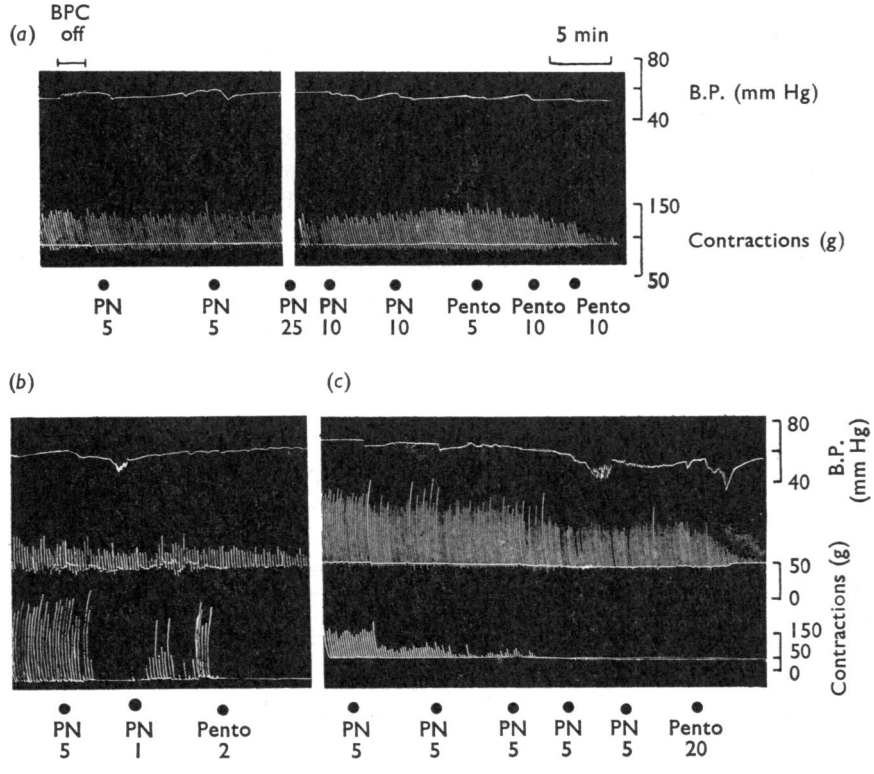


Fig. 5. Effects of pronethalol on the knee jerk. (*a*) Rabbit, 1.53 kg, given atropine (1 mg) and pentobarbitone (67 mg/kg). Blood pressure (B.P.) was controlled at the same pressure as was spontaneously maintained after anaesthesia. Record of knee-jerk in response to taps on the patellar tendon. A total of 55 mg/kg of pronethalol (PN) did not reduce the jerk, which failed rapidly after a further 25 mg/kg of pentobarbitone (Pento). Interval of 68 min between the two parts of (*a*). (*b*) Rabbit, 1.23 kg, given atropine (1 mg) and pentobarbitone (62 mg/kg). Blood pressure controlled. Middle record, left knee-jerk; lower record, responses of right quadriceps to stimulation of the skin over right ankle. Pronethalol (5 mg/kg) abolished the flexor reflex. A further 1 mg/kg provoked a few convulsive responses, followed by block. The knee-jerk was hardly affected, and persisted after 2 mg/kg of pentobarbitone. (*c*) Rabbit, 1.75 kg, given atropine (1 mg) and pentobarbitone (50 mg/kg). Blood pressure controlled. At start, the flexor reflex (lower record) had already been depressed by 5 mg/kg of pronethalol. Further injections of pronethalol abolished the flexor reflex, but not the knee-jerk.

shown in Fig. 5,*b*, contractions of the right quadriceps were recorded (lower record) in response to stimuli applied to the skin over the ankle with surface electrodes. The blood pressure was controlled at 55 mm Hg, and the left knee-jerk was also recorded. Pronethalol (5 mg/kg) caused a temporary abolition of the flexor reflex, but not of the knee-jerk. A further 1 mg/kg of pronethalol provoked a few convulsive responses to the skin stimuli, after which the reflex failed altogether. The knee-jerk continued, and was not abolished by 2 mg/kg of pentobarbitone. In a similar experiment (Fig. 5,*c*) the whole sciatic nerve was again stimulated, and at the beginning of the record the flexor-reflex responses (lower record) had already been depressed by 5 mg/kg of pronethalol. A further 25 mg/kg of pronethalol were administered but, although the flexor reflex rapidly failed, the knee-jerk remained vigorous. This proved that pronethalol had not blocked conduction in peripheral nerves. The jerk also failed rapidly after 20 mg/kg of pentobarbitone.

Summing of effects of pronethalol and anaesthetic

Since the anaesthetic administered was itself capable of abolishing reflexes, some addition of the effects of pronethalol and the anaesthetic was to be expected. A quantitative estimate of the summing of the two actions was not easy, because both effects were diminishing as each experiment continued. Nevertheless it was felt worth while to collect the results from one species and one anaesthetic, and to compare the doses of pronethalol necessary to block the flexor reflex under anaesthesia with those required in a decerebrate preparation. In Fig. 6 the total amount of pronethalol required to block the flexor reflex in rabbits has been plotted as ordinate, and the total dose of pentobarbitone administered as abscissa.

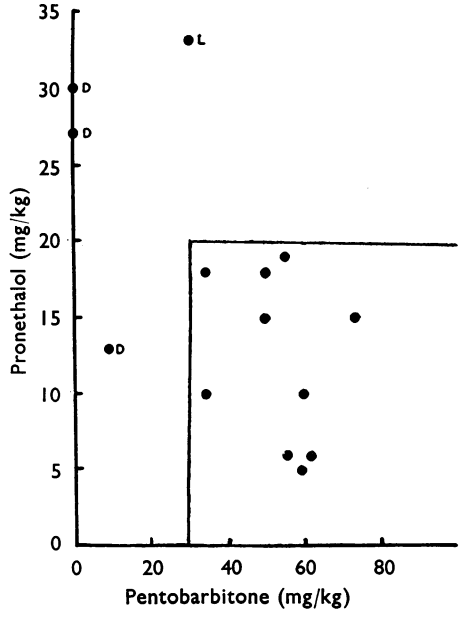


Fig. 6. Influence of pentobarbitone on the amount of pronethalol required to block the flexor reflex. Ordinate: total pronethalol injected in mg/kg. Abscissa: total pentobarbitone in mg/kg. D. Decerebrate preparations. L. Experiment in which the pronethalol was injected 2.5 hr after 30 mg/kg of pentobarbitone.

The graph makes no pretence of representing a quantitative estimate of the summation of the effects of the two drugs, since the doses of both were administered over extended periods. Nevertheless it does indicate that, with one exception, block of the flexor reflex was produced by less than 20 mg/kg of pronethalol in animals which had received more than 30 mg/kg of pentobarbitone, whereas in decerebrate rabbits nearly 30 mg/kg of pronethalol were required. The exception, marked L, was a rabbit in which anaesthesia was extremely light, because only 30 mg/kg of pentobarbitone had been given, and the pronethalol was not injected until 2 hr later. The injection of a small amount of pentobarbitone (10 mg/kg) to a decerebrate animal reduced the dose of pronethalol required for block of the reflex to 13 mg/kg (compare, also, Fig. 3).

Effects of lignocaine and orphenadrine

Although it was evident that pronethalol blocked the flexor reflex without any interference with conduction in *peripheral* nerves, it was possible that its action was related to its " local anaesthetic " properties acting centrally rather than to its action as a competitor for sympathetic β-receptor sites, the existence of which in the cord is unproven. The block of the polysynaptic flexor reflex, without interference with the monosynaptic knee-jerk, has been employed as a test for centrally acting muscle relaxants (Roszkowski, 1960). It was apparent that pronethalol was as active in this test as some compounds used clinically as muscle relaxants. Orphenadrine, however, which is much used in spastic conditions, has been reported not to affect polysynaptic reflexes (Cronheim, 1962). We have confirmed this finding, in rabbits anaesthetized with pentobarbitone. A total of 52 mg/kg of orphenadrine, administered in divided doses over 30 min, although producing some hypotension, which was corrected by the blood pressure control, had no depressant effect either on the knee-jerk or on the reflex response of the quadriceps to ipsilateral sciatic nerve stimulation.

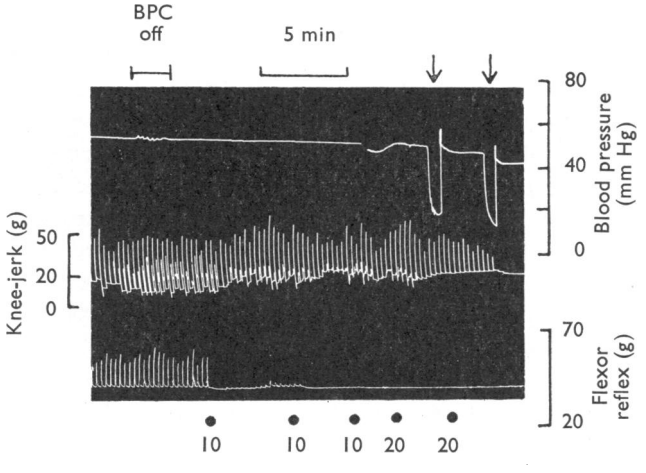


Fig. 7. Effect of lignocaine on spinal reflexes. Rabbit, 0.73 kg, given atropine (1 mg) and pentobarbitone (68 mm/kg). Blood pressure controlled. Lignocaine was given at the dots (doses in mg/kg) and abolished the flexor reflex, but not the knee-jerk. Further large doses produced hypotension of such severity that the blood reservoir (30 ml. capacity) emptied into the animal and had to be refilled (at the arrows) to maintain the blood pressure.

Pronethalol has approximately the same local anaesthetic activity as lignocaine. In the experiment shown in Fig. 7, both knee-jerk and flexor reflex were recorded simultaneously in a rabbit with controlled blood pressure. Lignocaine (10 mg/kg) abolished the flexor reflex, but did not affect the knee-jerk. Two further injections of 10 mg/kg caused some hypotension, but this was corrected by the blood pressure control. An injection of 20 mg/kg of lignocaine caused such severe hypotension, however, that the reservoir of 30 ml. of blood emptied into the rabbit, but the blood pressure was maintained at the control level after the reservoir had been refilled. The knee-jerk was depressed but not abolished. Another 20 mg/kg of lignocaine caused complete circulatory failure.

DISCUSSION

It had been found previously that pronethalol, administered in amounts causing only partial block of the action of isoprenaline on the heart rate, depressed or abolished the flexor reflex. The potency of pronethalol in this respect was as great or greater than that of some therapeutically useful centrally acting skeletal muscle relaxants, when effective doses of pronethalol were compared with those employed by Roszkowski (1960) in his comparative study of the activity of relaxants on spinal reflexes. For example, mephenesin carbamate (40 mg/kg) reduced the flexor reflex by 32%, and meprobamate (30 mg/kg) reduced it by 20%. With chlorzoxazone, the most active compound studied, 10 mg/kg produced a 58% reduction in the flexor reflex response. Thus the action of pronethalol seemed to merit further analysis.

Bülbring & Burn (1941) had found that the addition of adrenaline to the circulation in a perfused dog spinal cord greatly facilitated flexor reflexes, and the possibility had to be considered that β-receptors might be involved, excitation causing facilitation and blockade by pronethalol causing depression of the reflex. There were, however, a number of other possible explanations for the action of pronethalol on the flexor reflex, and the object of the present work was to investigate them.

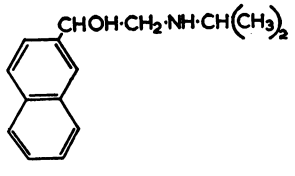
Large doses of pronethalol cause severe hypotension. In the present experiments, hypotension was prevented by connecting the carotid artery to a blood reservoir maintained at constant pressure. The animals were also artificially ventilated. It was found that even very large doses of pronethalol had no effect on neuromuscular conduction. Although pronethalol is a local anaesthetic with twice the potency of procaine, the amounts required to abolish the flexor reflex did not affect conduction in nerve trunks, and the reflex was still blocked when a possible effect on skin afferents was by-passed by stimulation of the sciatic nerve directly. The knee-jerk, although depressed to some extent by large amounts of pronethalol, was unaffected by doses which blocked the flexor reflex. These experiments proved that the action of pronethalol could not be attributed to interference with conduction in peripheral nerves.

In decerebrate preparations, the flexor reflex was still depressed by pronethalol, though larger doses had to be given, and these first provoked convulsive responses to stimulation of the sciatic nerve or the skin, followed by complete abolition of the flexor reflex. Convulsions had not been seen in anaesthetized preparations, because smaller amounts of pronethalol had been required to abolish the reflex. It was found, however, that convulsive responses were often observed even in anaesthetized preparations, when further amounts of pronethalol were injected when the reflex was on the point of fading out. Black & Stephenson (1962)

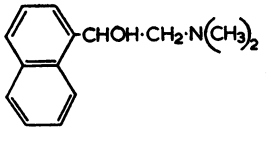
had observed convulsions in mice after lethal doses of pronethalol. In our experiments, with ventilation and blood pressure artificially maintained, the animals recovered from convulsive doses, and the flexor reflexes returned.

Injections of isoprenaline, adrenaline and noradrenaline during the period of block of the flexor reflex by pronethalol did not cause the reflex to return. Lignocaine had an effect similar to that of pronethalol, abolishing the flexor reflex after doses of 10 mg/kg or less, but not influencing the knee-jerk unless very large amounts were given, sufficient to cause circulatory failure.

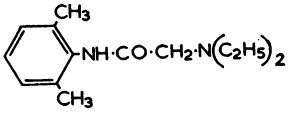
The local anaesthetic properties of pronethalol are not difficult to explain, since it closely resembles compound 1 of the series of local anaesthetics studied by MacIntosh & Work (1941) (Fig. 8,*b*). Also the isopropyl side-chain, and the absence of phenolic hydroxy groups, are presumably important for its blocking action on β-receptors, although studies of the sympathomimetic amines have shown that it is unwise to draw analogies between phenolic and nonphenolic amines. Comparison of the structure of pronethalol with other compounds possessing muscle relaxant properties which do (Fig. 8,*e* and *f*) and do not (Fig. 8,*d*) depress the flexor reflex, offers a structure-action problem of considerable dimensions. Depression of polysynaptic reflexes could be produced by drug action at more than one point, and it is still possible that block of β-receptors, if they exist in the spinal cord, might have contributed to the action of pronethalol. Spinal reflexes, however, are subject to so many facilitatory and inhibitory influences from other parts of the central nervous system that no conclusion can at present be reached about the action of pronethalol more precise than that it does have some central action. Although the amounts of pronethalol which depressed or abolished the flexor reflex in anaesthetized animals certainly did not



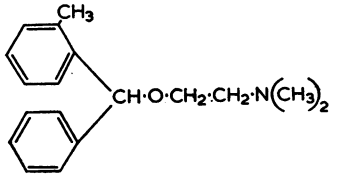
(*a*) Pronethalol



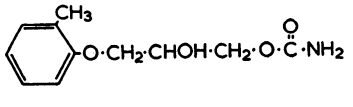
(*b*) MacIntosh & Work (1941); compound I



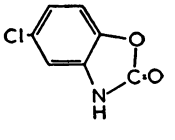
(*c*) Lignocaine



(*d*) Orphenadrine



(e) Mephenesin carbamate



(*f*) Chlorzoxazone

Fig. 8. Structures of compounds mentioned in the text.

cause block of peripheral nerves or interfere with neuromuscular conduction, nevertheless, some " local anaesthetic " action in the cord itself could not be excluded, especially in view of the depression of reflexes under the same experimental conditions by comparable amounts of lignocaine.

It is unlikely that the depression of the flexor reflex was solely a secondary consequence of the hypotension normally accompanying the action of pronethalol, because large variations of blood pressure in the absence of pronethalol had little effect on the reflex, and because the reflex was still depressed by pronethalol when the blood pressure was maintained by artificial control. Finally, the appearance of convulsions after the injection of large amounts of pronethalol in the decerebrate preparations came as a surprise in view of the depression of reflexes seen in anaesthetized animals. Presumably pronethalol itself activated, or released from inhibition, some facilitatory influence kept in abeyance by an anaesthetic.

SUMMARY

1. An attempt has been made to carry a stage further the analysis of the block of flexor reflexes by pronethalol previously described.

2. Evidence was obtained that the depression of the reflex was not due to block of conduction in peripheral nerves, nor to interference with neuromuscular conduction, since larger amounts of pronethalol than were needed to block the flexor reflex had no effect on the contralateral knee-jerk or on the responses of the gastrocnemius to sciatic nerve stimulation.

3. The flexor reflex was little affected by large variations in blood pressure produced by various means, and pronethalol still depressed the reflex when hypotension was prevented by artificial control of the blood pressure.

4. In decerebrate animals, and in lightly anaesthetized animals given large amounts of pronethalol, the flexor reflex was still blocked, but the block was preceded by convulsions.

5. It has been concluded that pronethalol has an action on the central nervous system, in addition to its peripheral effects. In unanaesthetized animals, it appeared that at first some facilitatory process was either directly excited or released from inhibition, but polysynaptic reflexes were subsequently depressed. In anaesthetized preparations, in which facilitatory mechanisms were already in abeyance, the depressant action of pronethalol predominated.

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