SOME ASPECTS OF THE PHARMACOLOGY OF ORPHENADRINE

BY G. ONUAGULUCHI* AND J. J. LEWIS

From the Department of Materia Medica and Therapeutics and Division of Experimental Pharmacology, Institute of Physiology, University of Glasgow

Received December 14, 1962

Orphenadrine possesses muscle-relaxant activity resembling that of tubocurarine in preparations of the hen, rat and frog. It antagonises suxamethonium-induced contracture in the hen but increases the duration of depression of the twitch height. The bearing of these findings upon the anti-Parkinson's activity and other uses of orphenadrine is discussed.

CLINICAL experience has shown that the skeletal musculature is involved to a considerable degree in the rigidity and weakness of Parkinsonism. Despite this, relatively little attention has been paid to the effects of anti-Parkinson drugs on skeletal muscle. The most comprehensive study of the pharmacology of orphenadrine is that of Bijlsma and others (1956), but the effect upon skeletal muscle was not studied. The present investigation therefore considers some of the effects of orphenadrine on skeletal muscle with some observations upon its anticonvulsant action and effects upon spinal reflexes.

METHODS AND MATERIALS

Hen Gastrocnemius Muscle-Sciatic Nerve Preparation

The method used was based on that of Pelikan and his associates (1954). Hens weighing from 1·5 to 2·0 kg. were anaesthetised by 40 to 50 mg./kg. of sodium pentobarbitone given intravenously. The sciatic nerve on one side was exposed, shielded platinum electrodes placed on it and supramaximal stimulation applied from a square wave generator at a frequency of 8/min., 25 to 50 V, pulse width 4 msec. In each experiment, voltage, pulse width and frequency were constant. The contractions were recorded using a Sherrington myograph lever. The sciatic nerve was crushed centrally to the electrodes.

Effect of orphenadrine on suxamethonium-induced contracture and neuromuscular block. Control responses were obtained with 12·5 to 25·0 μg./kg. of suxamethonium. When these became reproducible, the effect upon subsequent responses of 1, 3, 5 or 6 mg./kg. of orphenadrine was investigated.

Effect of orphenadrine on tubocurarine-induced neuromuscular block. Control responses were obtained using 200 to 300 μg./kg. of tubocurarine. It was usually necessary to give three similar doses before the degree of neuromuscular block was constant. After two similar control responses to the same dose of tubocurarine were obtained, 3 mg./kg. of orphenadrine were given and after 5 to 10 min., tubocurarine (200 to 300 μg./kg.) was repeated. The dose of tubocurarine was constant in each experiment.

* Present address: Department of Pharmacology, University College, Ibadan.

Effect of orphenadrine on the response to indirect tetanisation. The muscle was tetanised at 10 to 15 min. intervals by giving 30 sec. bursts of square impulses at a frequency of 1,400 to 1,500/min. After taking two or three control records, 3 mg./kg. orphenadrine was injected. The frequency of the tetanising current and the rest period between successive tetanisations were constant in each experiment.

Cat Gastrocnemius Muscle-Sciatic Nerve Preparation

The preparation was set up by conventional methods using 2 to 3·5 kg. cats, anaesthetised by 60 mg./kg. sodium pentobarbitone given intraperitoneally. Stimulation of the sciatic nerve was by supramaximal square impulses at 25 to 60 V, pulse width 3 to 4 msec. and frequency of 8/min. Tetanus was induced by increasing the frequency to 1,600/min. In each experiment voltage, frequency and pulse width were constant.

Effect of orphenadrine on suxamethonium-induced neuromuscular block. Suxamethonium 50–150 μg./kg. was used, but the amount was constant for each experiment. At least two similar consecutive control responses were obtained before orphenadrine 3–6 mg./kg. was injected intravenously. 1–2 min. later a further dose of suxamethonium was administered and this was repeated when the contractions had returned to normal.

Effect of orphenadrine on tubocurarine-induced neuromuscular block. Control responses were obtained using tubocurarine 100 to 150 μg./kg., repeating administration until the responses were constant. Orphenadrine 3 to 5 mg./kg. was then injected. After 2 min. tubocurarine was again given and administration repeated at intervals until control levels were attained.

Effects of orphenadrine on the response to indirect tetanisation. The muscle was tetanised at 15 min. intervals for 1 hr. using 30 sec. bursts of square impulses at 1,600/sec. After two control records had been obtained, orphenadrine 3 to 5 mg./kg. was given and tetanisation continued.

The Frog Rectus Abdominis Muscle Preparation

The muscle was set up in a 10 ml. bath containing frog Ringer's solution. Uniform, submaximal responses to acetylcholine were obtained using a 4 min. time cycle. Orphenadrine 15 to 25 μg./ml. was given 15 sec. before the subsequent dose of acetylcholine.

The Isolated Rat Phrenic Nerve-diaphragm Preparation

The method was essentially that of Bülbring (1946) using a 100 ml. organ bath containing double glucose Tyrode's fluid at 29 $\pm$ 0·5° and Bell's (1952) electrode so that the muscle could be stimulated both directly and indirectly. Nerve stimulation was by square impulses; frequency 6 to 8/min. at 10 to 15 V and pulse width 0·5 to 1·0 msec. Direct stimulation of the muscle was at the same frequency but 30 to 50 V and pulse width 1·5 to 2·0 msec. In any experiment frequency, voltage and pulse width were constant. Drugs in aqueous solution were added to the bath and allowed to act for 3 min.

Effects of Orphenadrine on the Patellar and Crossed Extensor Reflexes in the Cat

Cats weighing between 2·0 and 5·5 kg. were anaesthetised by 50 mg./kg. sodium pentobarbitone given intraperitoneally, the hind brain and upper cervical cord destroyed, and maintained upon artificial respiration. The patellar reflex was elicited by stimulating the patellar tendon electrically at a frequency of 6/sec., 25 to 60 V and pulse width of 1·5 to 3·5 msec. The reflex responses were elicited for periods of from 2 to 3 min. with rest periods of 3 min. In any given experiment the period of stimulation, frequency, voltage and pulse width were constant. The crossed extensor reflex was elicited by stimulating supramaximally the right sciatic nerve and recording the contractions of the left quadriceps muscle. Single shocks from a square wave generator were employed at a frequency of 6 to 10/min., 10 to 40 V, pulse width 1·5 to 3·5 msec.

In any experiment frequency, voltage and pulse width were constant.

Effect of Orphenadrine on Leptazol and Electroshock Convulsions in Mice

Leptazol seizures were induced in female albino mice weighing between 18 and 26 g. The mice were divided into groups of 10. Four control groups received leptazol alone, each group receiving either 20, 30, 40 or 60 mg./kg. Other groups were pretreated with 1, 3 or 15 mg./kg. of orphenadrine, and leptazol at the above dose levels given 25 to 35 min. later. All drugs were given by injection into the tail vein. Electroshock seizures were induced by the method used by Ahmad and Lewis (1960) using the ear-clip electrodes of Hoyt and Rosvold (1951). Four groups of 20 female albino mice weighing between 15 and 21 g. were used. The current intensity was 17 mA in the groups treated with 3 or 12 mg./kg. of orphenadrine. 20 mA was employed in the groups which received 6 or 15 mg./kg. of orphenadrine. The current was not allowed to act for more than 5 sec. and was interrupted earlier if it produced tonic extension of the hind limbs. This was taken as the end-point. Seizure threshold was determined in each of the four groups of mice. Twenty-four hr. later the mice were given the appropriate dose of orphenadrine by injection into the tail vein and the electrical current applied 25 to 35 min. later.

Results

In 3 out of 8 suxamethonium-treated hens, 3 mg./kg. of orphenadrine diminished the degree and duration of the contracture and increased the duration of the inhibition of the twitch height. In one hen this dose of orphenadrine itself produced a fall in the twitch height which lasted for about 20 min. In 6 hens, pretreatment with orphenadrine, 3 to 6 mg./kg., increased the degree and duration of the suxamethonium-induced block and in two preparations, 60 and 90 μg./kg. of neostigmine antagonised a suxamethonium block after initial treatment with orphenadrine (Fig. 1). Pretreatment with 3 mg./kg. of orphenadrine increased the degree of muscle relaxation caused by tubocurarine. As a rule, both the intensity and duration of effect were increased but in some instances duration only

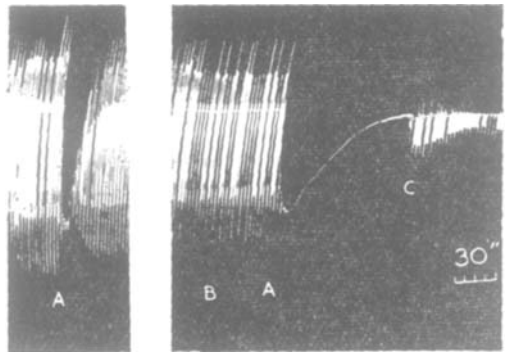

FIG. 1. Hen gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation by the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, Suxamethonium, 12·5 μg./kg. B, Orphenadrine, 3·0 mg./kg. C, Neostigmine, 90 μg./kg.

was increased. Orphenadrine, 3 mg./kg., given alone did not alter the response to an indirect tetanisation.

In the cat, orphenadrine, 3 to 6 mg./kg., produced no muscular relaxation but antagonised the neuromuscular block induced by suxamethonium (Fig. 2). It increased the duration and amplitude of a tubocurarine block (Fig. 3) but did not alter the response to indirect tetanisation.

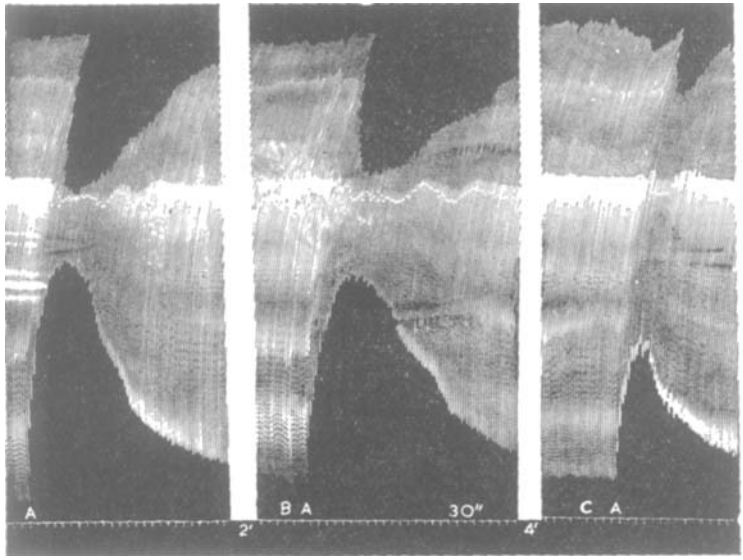

FIG. 2. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation by the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, Suxamethonium, 150 μg./kg. B, Orphenadrine, 3 mg./kg. C, Orphenadrine, 6 mg./kg.

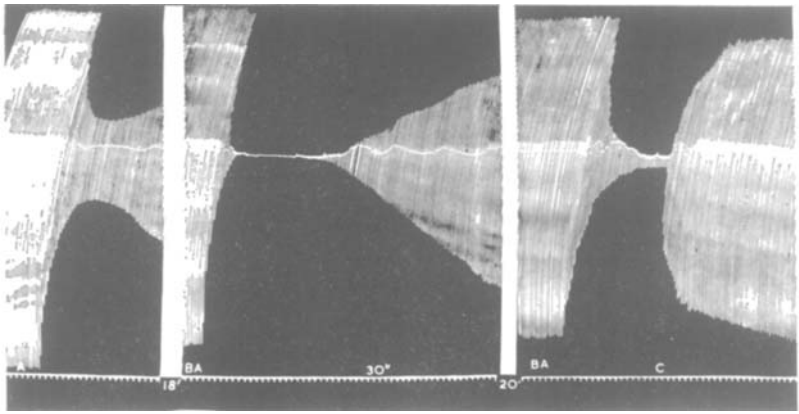

FIG. 3. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation by the sciatic nerve. Contractions downwards. Drugs administered intravenously.
At A, Tubocurarine, 125 μg./kg. B, Orphenadrine, 3·0 mg./kg. C, Neostigmine, 100 μg./kg.

Orphenadrine, 25 μg./ml., antagonised acetylcholine-induced contractions of the isolated frog rectus abdominis muscle. Recovery was slow despite frequent washing (Fig. 4). The effect of tubocurarine appeared to be additive with that of orphenadrine.

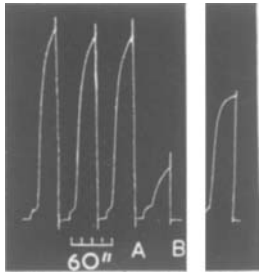

FIG. 4. Isolated frog rectus abdominis muscle. All unlabelled contractions due to 1 μg./ml. of acetylcholine acting for 90 sec. Contraction A was preceded 1 min. earlier by orphenadrine, 2·5 μg./ml.
B, Time interval of 52 min. during which tissue was stimulated by acetylcholine 1 μg./ml. at intervals of 4 min.

In the rat diaphragm, orphenadrine, 10 to 60 μg./ml., reduced the twitch height following indirect stimulation. Orphenadrine was from one-eighth to one-fifteenth as potent as tubocurarine on this preparation. Following complete paralysis with orphenadrine the muscle still responded to direct stimulation. Recovery was prolonged and usually incomplete except at very low dose levels.

In spinal cats the effects of orphenadrine on the patellar tendon and crossed extensor reflexes were variable. In some instances the magnitude of the response was slightly reduced; in others it was slightly increased;

in some there was no change. In some animals, muscular spasms which appeared within 1 min. of the injection were noted. These were usually short-lived but were sometimes associated with an increase in the magnitude of the reflex response (Fig. 5).

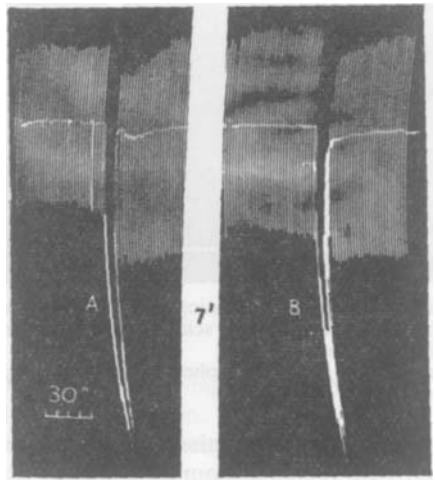

FIG. 5. Spinal Cat. Effect of orphenadrine on the crossed extensor reflex. At A, Orphenadrine, 3 mg./kg. B, Orphenadrine, 5 mg./kg.

At dose levels of 1, 3 and 15 mg./kg., orphenadrine did not alter the number of animals convulsing after dosage with leptazol although the intensity of the tonic phase was reduced. At the highest dose level there was a reduction in mortality. 3 and 6 mg./kg. of orphenadrine had no effect on the incidence of electroshock seizures in mice but reduced this at 12 and 15 mg./kg.

DISCUSSION

The experiments on the frog rectus abdominis muscle and the rat diaphragm indicate that orphenadrine has some muscle relaxant activity.

The antagonism to suxamethonium-induced block and potentiation of tubocurarine block in the cat also demonstrated that despite its very low potency some changes may take place at the neuromuscular synapse when this drug is given. It is possible that orphenadrine acts at the synapse by competing with acetylcholine and other depolarising drugs used. It is also possible that these effects are due in some part to a direct action on the muscle or, but more unlikely, to interneuronal block. As judged from these experiments the effects of orphenadrine last for about an hour.

In the hen, the actions of orphenadrine are difficult to assess. Orphenadrine-prolongation of suxamethonium block is an action not unlike that reported for tubocurarine by Crema, Scognamiglio and Bovet (1959). In the hen, orphenadrine appears therefore to mimic the actions of a non-depolarising neuromuscular blocking agent, although there is no direct evidence that it has in fact a tubocurarine-like action. In the rat

diaphragm and frog rectus abdominis muscle preparations, the actions of orphenadrine are more prolonged than those of tubocurarine but on these preparations it is much less potent.

In mice, even rather large doses of orphenadrine (15 mg./kg.) had no apparent effect upon the convulsant activity of leptazol. This is in contrast to the results of Cronheim (1958) who found that orphenadrine lowered the threshold for leptazol-induced convulsions. On the other hand, it was noted that in the first minute after 15 mg./kg. of orphenadrine, the mice were more restless, and in two instances orphenadrine-treated mice died from convulsions within 2 min. At this dose level orphenadrine may therefore have an initial excitatory or facilitatory action which soon changes into one of depression. This high dose of orphenadrine did however reduce the mortality to leptazol and the intensity of the tonic phase of the seizure and the effect of electroshock. At this level orphenadrine may inhibit seizure spread in the cerebrospinal axis but peripheral muscle-relaxant activity may also contribute to the anticonvulsant activity.

In Parkinson's disease the facilitatory system of the reticular formation is over-active and this is associated with a great increase in the gamma efferent discharge to the muscle spindles. This, through the servo-mechanism of Kuffler, Hunt and Quilliam (1951) leads to hypertonia of the skeletal muscles. The reticular formation can influence the spinal cord and, through the spinal internuncial cells, the skeletal muscles. Rigidity or hypertonia can thus be modified or abolished by depression of the activity of the reticular formation, basal ganglia, diencephalon or cerebellum, of the spinal interneurones or, by breaking the reflex arc of the servo-mechanism responsible for the hypertonia.

Orphenadrine reduces rigidity and hypertonia in patients suffering from Parkinson's disease. Suxamethonium in subparalytic doses increases the efferent discharge from the muscle spindles (Granit, Skoglund and Thesleff, 1953). Smith and Eldred (1961) have suggested that this effect is due to depolarisation of the end-plate region of the intrafusal fibres. It is possible, therefore, that the beneficial action of orphenadrine in Parkinson's disease is in part due to a depressant effect on muscle spindle discharge. Local anaesthetic activity (Bijlsma and others, 1956) may also play a part in the anti-Parkinson's activity of orphenadrine. The euphoriant action (Onuaguluchi, 1961), vasodilation of skeletal muscle (Bijlsma and others, 1956) and an effect upon phosphate metabolism (Van Petten and Lewis, 1962) may also be involved. The experiments reported in this paper have led to trial of orphenadrine to prevent muscular pain following suxamethonium.

Acknowledgments. One of us (G.O.) is much indebted to Professor S. Alstead, Regius Professor of Materia Medica and Therapeutics in the University of Glasgow, for giving him the opportunity to take part in this study. We are grateful to Miss Gladys Marren for technical assistance and to Dr. G. Schmeidler of the Camden Chemical Company for a supply of orphenadrine. Our thanks are due to Dr. T. C. Muir for helpful discussions.

REFERENCES

Ahmad, K. and Lewis, J. J. (1960). *J. Pharm. Pharmacol.*, **12**, 163–174.
Bell, G. H. (1952). *Experimental Physiology*, 5th Edition, pp. 36–44. John Smith & Son (Glasgow) Ltd.
Bijlsma, U. G., Harms, A. F., Funcke, A. B. H., Tersteege, H. M. and Nauta, W. Th. (1956). *Arch. int. Pharmacodyn.*, **106**, 332–369.
Bülbring, E. (1946). *Brit. J. Pharmacol.*, **1**, 38–61.
Crema, A., Scognamiglio, W. and Bovet, D. (1959). *Arch. int. Pharmacodyn.*, **122**, 152–167.
Cronheim, G. (1958). *J. Pharmacol.*, **122**, 16A.
Granit, R., Skoglund, S. and Thesleff, S. (1953). *Acta physiol. scand.*, **28**, 134–151.
Hoyt, R. and Rosvold, H. E. (1951). *Proc. Soc. exp. Biol.*, N.Y., **78**, 582–583.
Kuffler, S. W., Hunt, C. G. and Quilliam, J. P. (1951). *J. Neurophysiol.*, **14**, 29–54.
Onuaguluchi, G. (1961). Ph.D. Thesis, Glasgow University.
Pelikan, E. W., Smith, C. M. and Unna, K. R. (1954). *J. Pharmacol.*, **111**, 30–42.
Smith, G. M. and Eldred, E. (1961). *Ibid.*, **131**, 237–242.
Van Petten, G. R. and Lewis, J. J. (1962). *Ibid.*, **136**, 372–377.