Br. J. Pharmac. (1973), **47**, 117–123.

Some pharmacological effects of the nematocide, morantel

S. O. A. BAMGBOSE, V. O. MARQUIS AND L. A. SALAKO

Department of Pharmacology, University of Ibadan, Ibadan, Nigeria

Summary

1. In isolated nerve-muscle preparations as well as in nerve-muscle preparations in intact anaesthetized animals, morantel exhibited neuromuscular blocking properties similar to those of depolarizing blockers. The drug also caused spastic paralysis of 3 day-old chicks and contracture of the isolated toad rectus abdominis muscle.

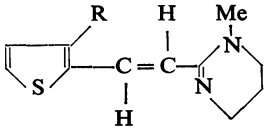
2. Morantel caused contraction of the guinea-pig and rabbit isolated small intestine. This effect was antagonized by atropine and hexamethonium.

3. Morantel caused an increase in the blood pressure of the anaesthetized rat and cat and contraction of the nictitating membrane of the anaesthetized cat. These effects were antagonized by hexamethonium.

4. It was concluded that morantel (like the related compound pyrantel) has acetylcholine-like action and that its structure is consistent with such action.

Introduction

Morantel (Fig. 1, R=methyl radical, Me) is an imidazoline derivative which was recently introduced as a veterinary nematocide (Cornwell, personal communication). It belongs to the same chemical group as the older nematocide, pyrantel (Fig. 1, R=H), and has been shown to be better tolerated (McFarland, Conover, Howes, Lynch, Chisholm, Austin, Cornwell, Danilewicz, Courtney & Morgan, 1969). The pharmacology of pyrantel was extensively investigated by Eyre (1970) and by Aubry, Cowell, Davey & Shevde (1970) who found that it possessed a neuromuscular blocking action of the depolarizing type. The neuromuscular blocking action of the drug is thus similar to that of bephenium (Broome, 1962) and tetramisole (Eyre, 1970) while it differs from that of piperazine which has been shown to block the action of acetylcholine at the neuromuscular junction (Norton & De Beer, 1957). The pharmacology of morantel has never been similarly investigated and a description of it is given here.



R=Me, MORANTEL
R=H, PYRANTEL

FIG. 1. Structure of morantel and pyrantel.

Methods

Isolated tissue experiments

Morantel was tested for its effects on the isolated rat diaphragm, chick biventer cervicis, toad rectus abdominis, rabbit jejunum and guinea-pig ileum.

The rat phrenic nerve-diaphragm preparation was set up as described by Bülbring (1946) in a 50 ml bath filled with aerated Tyrode solution containing double glucose at 26–28° C. Contractions of the diaphragm were elicited once every 10 s either by stimulating the phrenic nerve or by direct stimulation of the diaphragm. The nerve was stimulated maximally with square pulses (Palmer Square Wave Stimulator, Palmer, England) of 0·2 ms duration and 2–5 V. The muscle was stimulated directly by pulses of 20 ms duration and 20–50 V.

The effect of morantel on contraction of skeletal muscle *in vitro* was studied on the rectus abdominis muscle (Burn, 1952) of the local toad, *Bufo regularis*, in a 5 ml bath filled with aerated frog Ringer solution at room temperature (26–28° C).

The isolated biventer cervicis muscle of the chick was suspended in a 50 ml bath containing oxygenated Tyrode solution with double glucose following the method of Ginsburg & Warriner (1960). Contractions of the muscle were obtained by stimulating its motor nerve with square pulses of 0·2 ms duration and 2–5 V from a Palmer Square Wave Stimulator.

The effect of morantel on smooth muscle was tested on the rabbit jejunum and the guinea-pig ileum which were suspended in a 25 ml bath containing aerated Tyrode solution and maintained at 37° C and 32° C respectively. Isotonic contractions were recorded by means of a frontal lever writing on a smoked drum with a magnification of 7–10 fold.

Whole animal experiments

Blood pressure and nictitating membrane

The effect of morantel on blood pressure was investigated, in anaesthetized cats and rats, and its effect on the nictitating membrane was studied in anaesthetized cats.

Ten rats were anaesthetized with 0·7 ml/kg of 25% solution of urethane and the carotid blood pressure recorded on a smoked drum by means of a Condon mercury manometer. Drugs were administered through the femoral vein.

Seven cats were anaesthetized by intraperitoneal injection of 70 mg/kg chloralose with 5 mg/kg of pentobarbitone sodium. In three of the experiments the nictitating membrane of the cat was attached to a frontal writing lever with a 7-fold magnification and isotonic contractions recorded on a smoked drum. Drugs were administered into a femoral vein, and carotid artery pressure in mmHg (1 mmHg≡ 1·333 mbar) was recorded on smoked paper with a mercury manometer.

Nerve-muscle preparation in vivo

Eight cats weighing between 2 and 2·75 kg were anaesthetized with a mixture of 80 mg/kg chloralose and 5 mg/kg pentobarbitone sodium given i.p., and the sciatic nerve-tibialis anterior muscle preparation set up as described by Brown (1938). A shielded platinum electrode was placed on the sciatic nerve in the

thigh and the nerve ligated proximal to the electrode. Twitches (0·1 Hz) of the cat tibialis were elicited by stimulating the sciatic nerve with supramaximal pulses of 1–2 V and 0·2 ms duration. Tetani were obtained by increasing the stimulation rate to 50 Hz. Drugs were given either i.v. into a jugular vein, or close-arterially into a retrogradely cannulated branch of the femoral artery in the thigh.

Six 2·0–2·5 kg hens were anaesthetized with nembutal, 40 mg/kg, intravenously and the sciatic nerve-gastrocnemius muscle preparation set up as described by Brown & Harvey (1938). Drugs were administered i.v. through the jugular vein. Indirect maximal twitches of the gastrocnemius were elicited at the rate of 0·1 Hz with square pulses of 2–5 V and 0·4 ms.

Effect on chicks

Three day-old chicks weighing 25–30 g were given morantel intravenously and compared with similar chicks injected with suxamethonium i.v. according to the method of Buttle & Zaimis (1949).

Drugs

Drugs used were: acetylcholine chloride, atropine sulphate, phentolamine sulphate (B.D.H.); (+)-tubocurarine chloride, physostigmine sulphate, succinylcholine chloride (Burroughs Wellcome); morantel tartrate (Pfizer Ltd.); (−)-noradrenaline bitartrate (Winthrop Products); hexamethonium chloride (Koch-Light Laboratories).

All doses are expressed in terms of the salt. The results in the text are given as means ± standard error of the means.

Results

Effects of morantel on the neuromuscular junction

The results obtained on the effects of morantel on neuromuscular transmission are summarized in Figure 2.

In eight experiments, morantel 0·1–1·0 μg/ml (approximately 5×10^{-7}–5×10^{-6}M) increased the twitch response of the rat diaphragm to both direct and indirect electrical stimulation. A concentration of 0·25 μg/ml caused an approximately 50% increase in the twitch response to both nerve and muscle stimulation. The onset of the effect was immediate and the effect was sustained during an observation period lasting eight minutes. The effect was reversed by washing. In six experiments, 5–100 μg/ml morantel inhibited the contractions of the rat diaphragm elicited by stimulation of the phrenic nerve. The onset of the effect was immediate and the effect was dose-dependent. A concentration of 5 μg/ml caused 20 ± 4·5% reduction; 20 μg and 100 μg/ml gave 75% ± 7·3% and 100% reduction respectively. Direct stimulation of the muscle was unaffected by these concentrations of morantel (Fig. 2).

On the isolated chick biventer cervicis muscle preparation, morantel (2–10 μg/ml) produced a contracture which was similar to that obtained with suxamethonium, 1 μg/ml (Fig. 2).

In seven experiments, 0·1–10 μg/ml morantel had no effect on the isolated toad rectus abdominis but potentiated the contracture produced by acetylcholine, 1 μg/

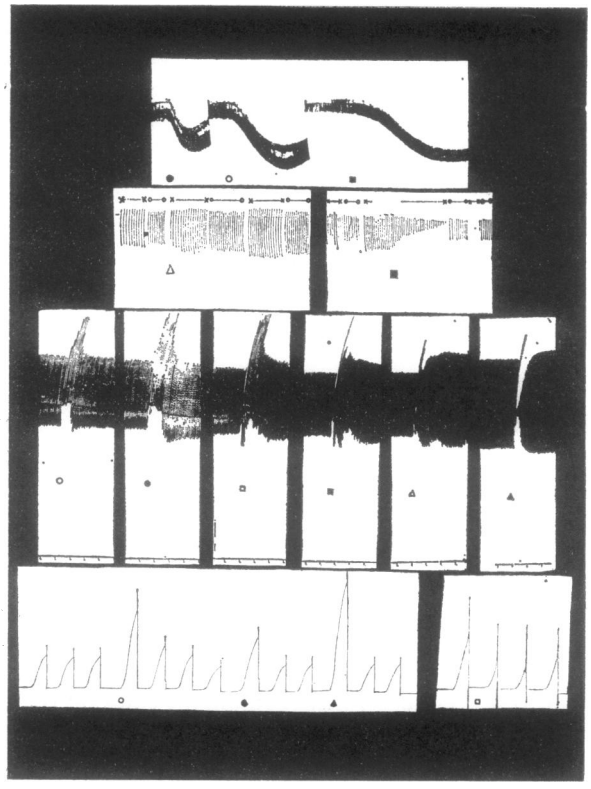


FIG. 2. Top-most panel: effect of morantel on the isolated chick biventer cervicis muscle stimulated through its motor nerve. At ●, 2 μg/ml morantel; ○, 10 μg/ml morantel and ■, 1 μg/ml suxamethonium, were added to the bathing medium. Second panel from top: effect of morantel on phrenic nerve–diaphragm. At ×——×, nerve stimulated at 2–5 V and 0·2 ms duration; ○——○, muscle stimulated at 20–50 V and 2 ms duration; △, 1 μg/ml morantel, and ■, 100 μg/ml morantel added to the bathing medium. Third panel from top: indirect maximal twitches of the left tibialis anterior muscle elicited by stimulating the sciatic nerve at the rate of 0·1 Hz. (Cat, 2·0 kg.) Effect of intravenous injection of different doses of morantel: ○, 0·25 mg/kg; ●, 0·5 mg/kg; □, 1 mg/kg; ■, 2 mg/kg; △, 3 mg/kg; ▲, 4 mg/kg. Time marker, 1 minute. Bottom panel: isolated toad rectus abdominis muscle preparation; 4 min cycles. Left hand panel: all contractions due to acetylcholine (2 μg/ml) acting for 60 s but those marked ○, ● and ▲ were preceded for 30 s by morantel 1 μg, 0·5 μg and 2 μg/ml respectively. Right hand panel: all contractions due to 100 μg/ml morantel acting for 60 s but that marked □ was preceded for 30 s by tubocurarine, 1 μg/ml. Recovery of the full effect of morantel after antagonizing it with tubocurarine took 8–10 cycles.

ml. The effect was dose-related (Fig. 2). Morantel at 100 μg/ml and higher concentrations produced a contracture of the isolated rectus abdominis which was partially antagonized by tubocurarine, 1 μg/ml (Fig. 2). Concentrations of morantel which potentiated acetylcholine-induced contracture of the isolated rectus abdominis also potentiated the contracture produced by carbachol, 1–10 μg/ml, although the potentiation was less with the larger concentration.

In eight experiments, intravenous injection of 5–150 μg/kg (approximately 2×10^{-2}–6×10^{-1} μmoles/kg) of morantel had no effect on the indirectly elicited maximal contractions of the cat tibialis anterior muscle. Doses of 0·2–2 mg/kg produced an increase in the contraction of the tibialis without a block while doses above 2 mg/kg gave an increased contraction followed by a short-lived block (Fig. 2). Similar results were obtained on injecting the drug close-arterially except that

much smaller doses were required to give the same effect, and the effects lasted longer. A sustained block could be produced by giving the drug as an i.v. infusion. The blocking effect was greater on single twitches than on tetanus. A tetanus elicited during a partial block was well maintained and did not antagonize the block which was increased by physostigmine.

In five experiments, 100 μg/ml suxamethonium (approximately $3{\cdot}5 \times 10^{-4}$M) was infused at a rate of 0·5 ml/minute. At this rate of infusion suxamethonium had no effect on the indirectly elicited maximal contractions of the cat tibialis anterior muscle. Doses of 50 μg/kg and 100 μg/kg of morantel given intravenously, which under normal conditions had no effect on the preparation, produced a block when administered during the course of infusion of suxamethonium at this rate. With the higher dose of morantel there was a total block from which recovery occurred only after the infusion was stopped. A similar result was obtained when suxamethonium was infused in sufficient amount to produce an initial steady block of 50–75%. On the other hand, when 100 μg/kg of morantel was administered during the recovery phase of a tubocurarine-induced block, the rate of recovery was briefly increased.

On the hen sciatic nerve-gastrocnemius muscle preparation, morantel (400 μg/kg) produced a contracture of the gastrocnemius which was similar to that produced by depolarizing blockers.

Slow intravenous injection of 1 mg of morantel in three day-old chicks (25–30 g in weight) produced spastic paralysis similar to that obtained with 100 μg of suxamethonium; in both cases there was no recovery. Doses of 100 μg of morantel and 10 μg of suxamethonium had a transient effect lasting less than 1 min, while 250 μg and 25 μg respectively produced an effect which lasted 10–20 minutes.

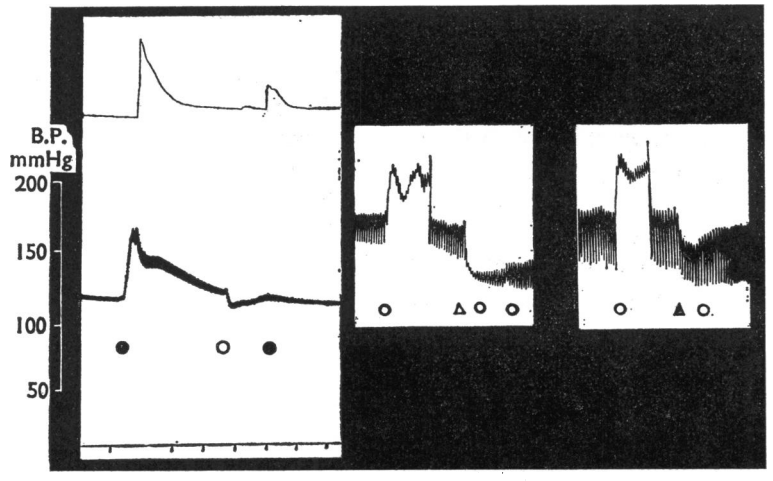


FIG. 3. Left hand panel: effect of morantel on the arterial blood pressure and nictitating membrane of the anaesthetized cat. At ●, morantel 25 μg/kg, and at ○, hexamethonium 1 mg/kg were given i.v. Time marker, 1 minute. Middle and right panels: effect of morantel on the isolated rabbit jejunum. At ○, 1 μg/ml morantel; △, hexamethonium 1 μg/ml and ▲, atropine 0·1 μg/ml, were added to the bathing medium. Morantel, 1 μg/ml produced a contraction of the jejunum that was abolished when hexamethonium or atropine was present in the bathing medium. In the middle panel the solution was not washed out between the last two additions of morantel.

Effect of morantel on smooth muscle and blood pressure (Fig. 3)

On the isolated rabbit jejunum (eight experiments) and guinea-pig ileum (seven experiments), morantel (1–10 μg/ml) produced contractions which were blocked by atropine (0·1 μg/ml) and hexamethonium (1 μg/ml) (Fig. 3). Contractions of the guinea-pig ileum produced by acetylcholine were potentiated by small doses of morantel (0·5 μg/ml and less) which had no spasmogenic effect of their own.

When administered to anaesthetized rats or cats, morantel 0·1–1 mg/kg produced a dose-dependent rise in arterial blood pressure. The hypertensive effect of morantel was blocked by phentolamine (1 mg/kg), phenoxybenzamine (1 mg/kg) and hexamethonium (1 mg/kg) in both the rat and the cat. Morantel (25 μg/kg) also caused contraction of the nictitating membrane of the chloralose-anaesthetized cat. The effect was antagonized by previous injection of 1 mg/kg hexamethonium (Fig. 3).

Discussion

Our results show that morantel is a depolarizing neuromuscular blocking agent which also stimulates ganglia and has acetylcholine-like actions on smooth muscle. In these actions it resembles pyrantel and appears to have about the same activity, though we have not made a direct comparison. Thus the doses of pyrantel used by Eyre (1970) are similar to those used for morantel on smooth and skeletal muscles. The doses of antagonists (atropine and hexamethonium) used are of the same order. Both drugs also cause an increase in blood pressure and contraction of the nictitating membrane at about the same dose range comparing our results with those of Eyre (1970) and Aubry *et al.* (1970). Both morantel and pyrantel contain a sulphur atom in a thiophene ring which may be compared with the ether atom present in muscarine, methylfurmethide and F2268. The *N*-methyl group in the tetrahydropyrimidine ring of morantel is strongly basic (pKa>12, Cornwell, personal communication) and so is largely protonated at body pH and can be compared with the onium group in acetylcholine. The acetylcholine-like properties of these compounds, however, are not normally a therapeutic complication because when given orally there is practically no absorption of the drug into the circulation. In one instance, however, in which the drug was accidentally administered into the trachea instead of the oesophagus of a sheep, the animal suffered respiratory embarrassment, muscle tremors, and an immediate rise in blood pressure, suggesting that some of the material may have been absorbed from the alveolar capillary bed (Cornwell, personal communication).

We are indebted to Dr. R. L. Cornwell, Head of Parasitology Research, Pfizer Group of Companies, Sandwich, for his kindness in supplying morantel and to Mr. E. M. Ebenzor, for technical assistance.

REFERENCES

AUBRY, M. L., COWELL, P., DAVEY, M. J. & SHEVDE, S. (1970). Aspects of the pharmacology of a new anthelmintic: pyrantel. *Br. J. Pharmac.*, **38**, 332–344.

BROOME, A. W. J. (1962). Mechanisms of anthelmintic action with particular reference to drugs affecting neuromuscular activity. In: *Drugs, Parasites and Host*, ed. Goodwin, L. G. & Nimmo-Smith, R. H., pp. 43–61. London: Churchill.

BROWN, G. L. (1938). The preparation of the tibialis anterior (cat) for close arterial injection. *J. Physiol., Lond.*, **82**, 22P.

BROWN, G. L. & HARVEY, A. M. (1938). Reactions of avian muscle to acetylcholine and eserine. *J. Physiol., Lond.*, **94**, 101–117.

BÜLBRING, E. (1946). Observations on the isolated phrenic nerve diaphragm preparation of the rat. *Br. J. Pharmac. Chemother.*, **1**, 38–61.

BURN, J. H. (1952). *Practical Pharmacology*, pp. 1–6. Oxford: Blackwell.

BUTTLE, G. A. H. & ZAIMIS, E. J. (1949). Action of decamethonium iodide in birds. *J. Pharm. Pharmac.*, **1**, 991–992.

EYRE, P. (1970). Some pharmacodynamic effects of the nematocides: methyridine, tetramisole and pyrantel. *J. Pharm. Pharmac.*, **22**, 26–36.

GINSBURG, B. L. & WARRINER, J. (1960). The isolated chick biventer cervicis nerve-muscle preparation. *Br. J. Pharmac. Chemother.*, **15**, 410–411.

MCFARLAND, J. W., CONOVER, L. H., HOWES, JR. H. L., LYNCH, J. E., CHISHOLM, D. R., AUSTIN, W. C., CORNWELL, R. L., DANILEWICZ, J. C., COURTNEY, W. & MORGAN, D. H. (1969). Novel anthelmintic agents, II. Pyrantel and other cyclic amidines. *J. med. Chem.*, **12**, 1066–1079.

NORTON, S. & DE BEER, E. J. (1957). Investigations on the actions of piperazine on *Ascaris lumbricoides*. *Am. J. trop. Med. Hyg.*, **6**, 898–905.

(*Received July* 12, 1972)