Neuromuscular Block of the Polymyxin Group of Antibiotics

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Abstract □ The neuromuscular blocking effects of polymyxin and colistin were investigated in the unanesthetized rabbit, in the cat sciatic nerve–tibialis anterior muscle preparation *in vivo*, and in the frog rectus abdominis preparation *in vitro*. These antibiotics, along with certain others used for comparison, produced paralyses of different intensities in rabbits, depending on the dose, with no preceding fasciculation. In this regard, polymyxin was the most potent antibiotic studied. Polymyxin B sulfate (3–5 mg/kg) and colistimethate sodium (60–90 mg/kg) caused a blockade of neuromuscular transmission, partial paralysis of respiration, and hypotension in cats. The intraarterial injection of these antibiotics did not elicit muscle contraction; the response to the intraarterial injection of acetylcholine was reduced or abolished during the block; calcium and epinephrine antagonized the block; posttetanic potentiation occurred; edrophonium and decamethonium produced brief antagonism of the block; neostigmine, tetraethylammonium, and choline were without effect; and tubocurarine accentuated the block. During the block, muscle action potentials were reduced or abolished, and nerve action potentials were unaffected. (Response of the muscle to direct stimulation was reduced compared to the predrug response.) Both agents depressed muscle twitches elicited at the faster rate of stimulation (60/min) while the slow rate twitches (6/min) were hardly depressed. The serum ionic calcium level was not altered significantly by these antibiotics. Thus, the neuromuscular block displayed characteristics of a postsynaptic, nondepolarizing type that was noncompetitive in nature, with possible presynaptic elements and a depressant action on muscle fibers. Both polymyxin and colistin possess transient ganglionic blocking action.

Keyphrases □ Polymyxin—neuromuscular blocking effect in rabbits and cat and frog muscle preparations □ Colistin—neuromuscular blocking effect in rabbits and cat and frog muscle preparations □ Neuromuscular blocking effect—polymyxin and colistin in rabbits and cat and frog muscle preparations □ Antibacterials—polymyxin and colistin, neuromuscular blocking effect in rabbits and cat and frog muscle preparations

Several clinically important antibiotics produce somatic neuromuscular transmission blockade. This effect has been implicated in their paralyzing potentiality. Respiratory and motor paralysis have been observed clinically following the administration of streptomycin, polymyxin, and tetracycline groups of antibiotics to anesthetized and unanesthetized patients (1).

BACKGROUND

The neuromuscular blocking activity of streptomycin, polymyxin, and tetracycline groups of antibiotics has been demonstrated (2). Several studies (3, 4) led to the emergence of the "competitive hypothesis" concerning the mechanism of the neuromuscular blocking action of the streptomycin group of antibiotics. This hypothesis postulates that the antibiotics inhibit prejunctional release of acetylcholine primarily by competing with calcium ions for receptor sites on the motor nerve terminal while decreasing the sensitivity of the motor end-plate to the depolarizing action of acetylcholine.

The mechanism of the neuromuscular blockade produced by the polymyxin antibiotics has not been elucidated (2) and was investigated in this study.

Pittinger *et al.* (1) recently reviewed the clinical occurrences of antibiotic-induced paralysis and abstracted and analyzed the case histories of more than 100 incidences of hazardous antibiotic paralysis. The first clinical cases of respiratory arrest and muscular weakness associated with the administration of polymyxins were reported in 1962, and several such cases have been reported since then. This complication occurred in patients receiving large doses of polymyxin antibiotics, in myasthenic patients, and in some patients receiving routine therapeutic doses of these antibiotics.

Few studies have investigated the neuromuscular blocking effect of the polymyxin antibiotics. The neuromuscular blocking effect of polymyxins was demonstrated in the sciatic–gastrocnemius preparation of rabbits anesthetized with pentobarbital (5, 6). Supramaximal pulses were used at a frequency of 100 (5) and 250/sec (6) for 0.2 sec every 5 or 10 sec for stimulation of the sciatic nerve. Unfortunately, pentobarbital has a neuromuscular blocking effect of its own.

The effect of polymyxin was studied in the urethan-anesthetized rabbit sciatic–gastrocnemius preparation, employing supramaximal stimuli at 10-sec intervals with 0.2-sec bursts at a frequency of 100/sec (7). No correlation with respiratory effects was made because artificial respiration was applied throughout. The effect of the antibiotics was studied with the human intercostal nerve–muscle preparation and stimuli at the rate of 6/min (8).

The neuromuscular blocking action of colistin was studied in single muscle fibers of the rat hemidiaphragm preparation with the microelectrode technique (9). Even very high doses of colistin (1 g/liter) did not produce neuromuscular block. However, a combination of colistin and tubocurarine produced a block.

The response of the neuromuscular junction of the cat is much more similar to that of the human than is the response of the rabbit junction.

This paper reports an investigation of the neuromuscular block of polymyxin and colistin with a view to determining the mechanism of their neuromuscular blocking action and its relationship to the respiratory paralysis accompanying their use.

EXPERIMENTAL

The investigation was carried out on unanesthetized rabbits, the cat sciatic nerve–tibialis anterior muscle preparation *in vivo*, and the frog rectus abdominis preparation *in vitro*.

The paralytic progression patterns of polymyxin, colistin, tetracycline, and oxytetracycline were studied by injecting different doses intravenously through a needle cannula inserted in the marginal ear vein of rabbits. Their effect on serum ionic calcium levels was determined in rabbits from blood samples obtained by intracardiac puncture before and after injection of paralyzing doses of antibiotics. The serum ionic calcium levels were measured with a calcium-selective electrode[1].

Cats of either sex, 2–4 kg, anesthetized with a mixture of chloralose (70 mg/kg ip) and pentobarbital (8 mg/kg ip), were used for the sciatic-tibialis preparation. A schematic representation of the experimental setup in the cat is presented in Fig. 1. The anesthetized cat was placed on the myograph stand, the trachea was cannulated, and artificial respiration was applied when necessary with a small animal respirator. Hindlimbs were immobilized by drills inserted through the lower end of the tibia and condyles of the femur. The lateral popliteal branch of the sciatic nerve was ligated and sectioned, and platinum electrodes were placed on the nerve for stimulation. The electrodes were then connected to the stimulator[2].

The tendon of the tibialis was connected to a force-displacement transducer precalibrated for recording the force of contraction in grams, and the contractions were recorded on a four-channel polygraph. A resting tension of 75 g was maintained on the muscle and tendon. Drugs were injected through a polyethylene cannula into the jugular vein. The carotid artery was cannulated, and the arterial blood pressure was recorded with a pressure transducer. Respiratory movements were recorded with a pneumograph. Muscle action potentials of the tibialis anterior muscle in response to nerve stimulation were recorded with a concentric needle electrode (positioned in the muscle) attached to the high gain preamplifier of the polygraph. Nerve action potentials were recorded similarly with a high gain preamplifier from the lateral popliteal nerve through a shielded platinum electrode placed on the nerve.

[1] Orion.
[2] American Electronics Laboratory (104A).

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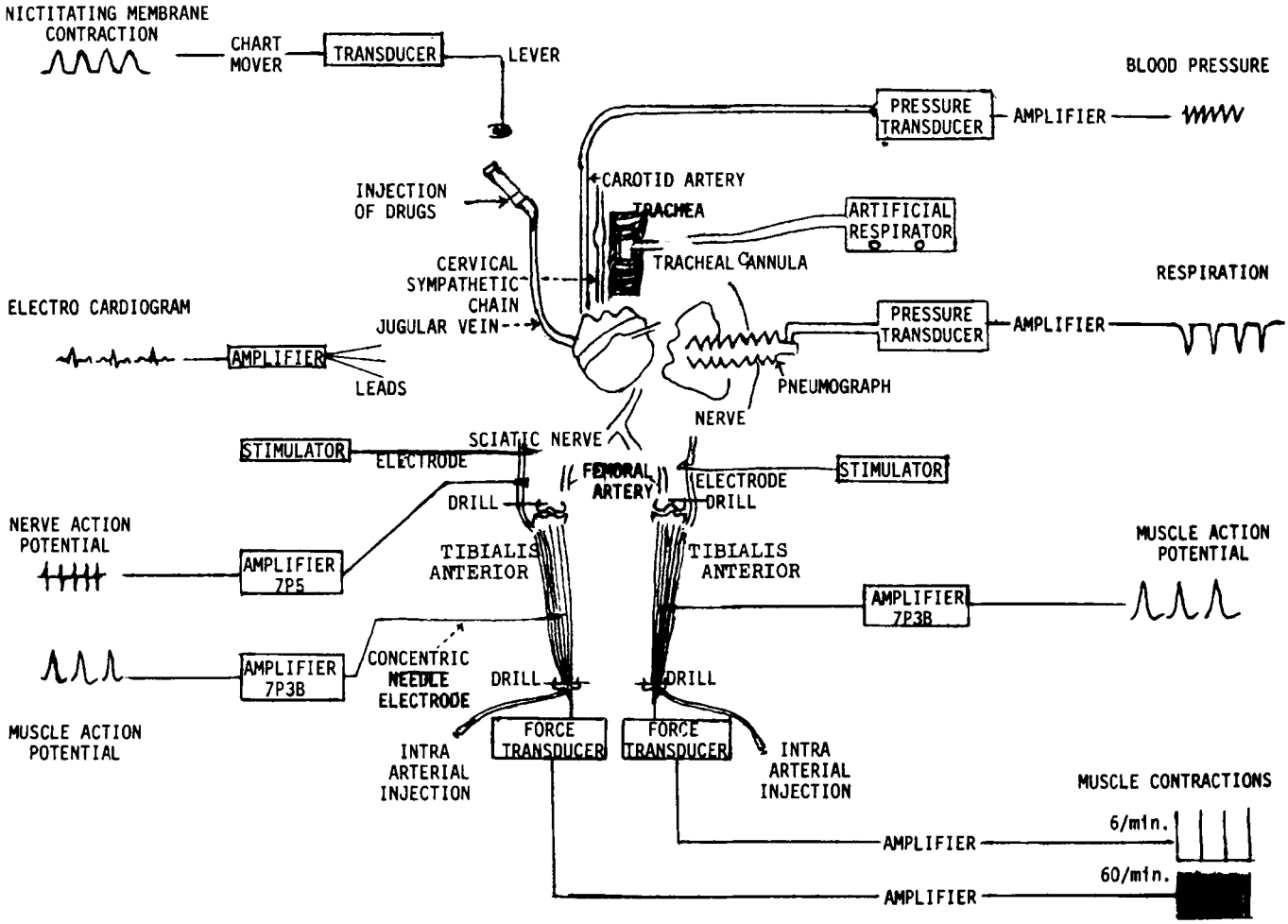

Figure 1—*Experimental setup in the cat.*

In the unilateral preparation, the tibialis twitches of one hindlimb were elicited by stimulating the corresponding (lateral popliteal) nerve with supramaximal pulses of 0.4-msec duration at a frequency of 6/min. In the bilateral preparation, tibialis twitches of both hindlimbs were elicited by stimulating one lateral popliteal nerve at a frequency of 6/min and the other at 60/min. Stimuli to one tibialis muscle were passed through a 1:1 isolation transformer. The tendons of the tibialis muscles were attached to different force–displacement transducers, and the contractions of the muscles were recorded isometrically on the polygraph.

Close-arterial injection of drugs to the tibialis was made according to the method described by Brown (10). Cooling of the tibialis anterior muscles was avoided by allowing warm saline, heated to 37° (by using a constant-temperature circulator[3] with condenser), to soak a thin layer of cotton spread over the muscle. As in similar studies, heat lamps assisted the cat in maintaining body temperature.

The dose of the antibiotic producing a 50% reduction in the amplitude of indirect maximal twitches (ED_{50}) was calculated from data obtained by administering at different times a dose of antibiotic reducing the amplitude of these twitches, slow (6/min) and fast (60/min), to an extent greater than, less than, and approximately 50% of their original value.

Responses to direct stimulation (70–90 v) of the muscle and tetanic stimulation at rates of 50 and 100/sec were determined before and during partial and complete neuromuscular block.

In some experiments, the antagonistic effects of neostigmine methylsulfate, calcium chloride, edrophonium chloride, choline chloride, guanidine hydrochloride, sodium bicarbonate, and potassium chloride on the antibiotic block were studied, as were the effects of tubocurarine chloride and decamethonium bromide.

For the *in vitro* rectus abdominis preparation, the rectus muscle strip was dissected out from the pithed frog and suspended in a tissue chamber filled with frog Ringer solution. The contraction responses of the muscle to acetylcholine were picked up by a transducer and recorded on a polygraph. The antagonism of the response to acetylcholine of increasing concentrations of each antibiotic was determined to establish whether the antagonism was competitive or noncompetitive.

The following drugs were used during the investigation: polymyxin B sulfate, colistimethate sodium, oxytetracycline, tetracycline hydrochloride, acetylcholine chloride, neostigmine methylsulfate (50–100 μg/kg), calcium chloride (10% solution in distilled water) (12–15 mg/kg), edrophonium chloride (100–200 μg/kg), choline chloride (1–5 mg/kg), sodium bicarbonate (2–5 mg/kg), potassium chloride (2–5 mg/kg), epinephrine (8–10 μg/kg), tubocurarine chloride (100–200 μg/kg), and decamethonium bromide (30 μg/kg).

RESULTS

The antibiotics—*viz.*, polymyxin, colistin, tetracycline, and oxytetracycline, produced paralyses of varying intensities in unanesthetized rabbits, according to the antibiotic and the doses used. Polymyxin was the most potent. The animals recovered from the paralysis when the intensity was mild or moderate. The doses of each antibiotic producing head drop and respiratory arrest, respectively, are presented in Table I. Polymyxin was about 70 times less potent than curare and eight times more potent than colistin in these respects.

The progressive paralytic patterns elicited by the antibiotics were determined. Slowing of respiration was observed initially in most animals, followed by the inability to walk, head drop, and loss of the righting reflex. A further decrease in respiratory activity leading to respiratory arrest resulted in death. No fasciculations such as those occurring with decamethonium were observed. Mild asphyxial convulsions occurred in some instances.

In the cat sciatic–tibialis preparation, intravenous injection of polymyxin B sulfate (3–5 mg/kg) and colistimethate sodium (60–90 mg/kg) produced partial to complete abolition of maximal twitches elicited at the rates of 6 and 60/min and partial to complete paralysis of respiration and hypotension (60–70% of predrug pressure level). The onset of the neuromuscular block was rapid and persisted for 30–40 min.

The doses of antibiotics responsible for a 50% block of indirect maximal twitches were determined graphically. The ED_{50} values of polymyxin B

[3] Haake.

Table I—Paralyzing Doses of the Antibiotics in Unanesthetized Rabbits

Dose	Polymyxin B Sulfate, mg/kg	Oxytetracycline, mg/kg	Colistimethate Sodium, mg/kg	Streptomycin, mg/kg	Tubocurarine Chloride, mg/kg
Head drop dose	11.1 ± 1	450 ± 5	90 ± 2	263 ± 3	0.16 ± 0.02
Loss of righting reflex dose	12.2 ± 1	460 ± 5	100 ± 2	273 ± 3	0.22 ± 0.02
Respiratory arrest dose	13.6 ± 1	476 ± 5	112 ± 2	282 ± 3	0.32 ± 0.02
Cardiac arrest dose	13.9 ± 1	477 ± 5	113 ± 2	291 ± 3	—

sulfate were 5.2 mg/kg for twitches elicited at the rate of 6/min and 2.7 mg/kg for twitches elicited at the rate of 60/min. The respective ED_{50} values for colistimethate sodium were 100 and 61 mg/kg. Polymyxin and colistin produced a far greater depression of fast twitches than slow twitches. For example, a dose of polymyxin B sulfate eliciting a 50% block of twitches at a frequency of 6/min produced a 100% block of twitches at 60/min.

Some characteristics of the neuromuscular block of the antibiotics and their comparison with those of curare and decamethonium are summarized in Table II. With polymyxin and colistin, stimulant effects were absent. The response to a tetanic stimulation of 50 and 100/sec, respectively, was not maintained or only partially maintained during partial neuromuscular block; such response was absent or involved an initial twitch only during complete block. Maximal posttetanic potentiation occurred immediately after tetanus during partial neuromuscular block with these antibiotics. Also, during the block, the response to direct stimulation of the muscle was decreased as compared to the predrug response, and the response to intraarterially injected acetylcholine was reduced or abolished. During the abolition, increasing the dose of acetylcholine injected failed to restore the response. The administration of calcium chloride intravenously gave rise to a partial or complete antagonism of the block; neostigmine was without any effect on the block.

During the block, muscle action potentials were reduced or abolished, while nerve action potentials were unaffected.

Intraarterial injection of antibiotic in doses of 1–500 μg elicited no contractions. An intraarterial dose of 500 μg of polymyxin B sulfate (Fig. 2) and 10–20 mg of colistimethate sodium yielded about a 70–80% block of indirectly elicited maximal twitches, an effect that was not spontaneously reversible. However, intraarterial injection of calcium chloride and epinephrine, but not norepinephrine, partially antagonized the block (Fig. 2). Polymyxin produced depression of respiration concomitant with the block of twitches. A 3-mg/kg dose produced slowing and a decrease in depth of respiration of about 30–35% of the original value, while a 5-mg/kg dose produced cessation of respiration. The ED_{50} values of polymyxin B sulfate and colistimethate sodium with respect to respiratory interference were 3.6 and 41 mg/kg, respectively. Cessation of respiration occurred just after the twitches elicited at 60/min were abolished.

The effect of intravenous polymyxin on indirect maximal twitches and on intraarterial acetylcholine-elicited twitches recorded simultaneously appears in Fig. 3. During depression of indirect maximal twitches at 60 and 6/min, respectively, the twitch response to intraarterial acetylcholine was completely abolished. Acetylcholine contractions were depressed more than indirect twitches at various doses of polymyxin. Hence, polymyxins seem to possess a prominent postsynaptic blocking action.

The administration of the same doses of polymyxin produced more pronounced and prolonged neuromuscular block, eventuating often in complete depression of indirect twitches. This cumulative neuromuscular blocking effect of polymyxin was investigated.

A dose of polymyxin of 3 mg/kg, capable of producing a significant block, was used. Doses were repeated when recovery from each preceding dose became apparent. A second injection of the same dose of polymyxin produced a 50–60% greater neuromuscular block than the first, and a third injection produced about a 40–50% greater block than the second. The administration of calcium chloride effectively reversed the cumulative neuromuscular blocking effect of polymyxin. The first injection of polymyxin of 4 mg/kg produced a 43% block of slow twitches and a 100% block of fast twitches. After administration of calcium chloride, the second injection of polymyxin produced only a 5% block of slow twitches and a 55% block of fast twitches.

Polymyxins depressed blood pressure within seconds to minutes of administration. A 4-mg/kg dose of polymyxin B sulfate and 62.5 mg of colistimethate sodium/kg yielded an average decrease in mean arterial blood pressure of about 50% of the predrug level. The blood pressure rose after a few minutes but then fell again and remained 10–15% below the control level. During the reduced arterial pressure, administration of calcium chloride elevated blood pressure (Fig. 4). Sympathetic stimulation and injection of epinephrine also increased this pressure, while vagal stimulation accentuated the polymyxin fall in blood pressure. The contractions of the nictitating membrane obtained by preganglionic cervical sympathetic stimulation were partially abolished by these antibiotics as they exerted their effect to lower arterial blood pressure, while those obtained by intravenous epinephrine were unaffected. The ECG was unaffected during the production of hypotension by these antibiotics.

In the frog rectus abdominis preparation, both polymyxin B sulfate and colistimethate sodium, preadministered, antagonized acetylcholine-induced contractions. Polymyxin at a dose half that of acetylcholine was responsible for a depression of acetylcholine-induced rectus contractions of approximately 35%. At a dose equivalent to the dose of acetylcholine, a depression of approximately 87% occurred; and at a dose twice that of acetylcholine, a depression of approximately 96% occurred. Polymyxins produced no contracture and had no curative effect on acetylcholine contractions. The contraction responses to various doses of acetylcholine were obtained in the presence of increasing concentrations

Table II—Characteristics of the Neuromuscular Block of Polymyxin and Colistin in the Cat Sciatic-Tibialis Preparation

Antibiotic or Other Agent	Stimulant Effects	Response to Tetanic Stimulation		Posttetanic Facilitation of Response	Response to Intra-arterial Acetylcholine	Direct Stimulation of Muscle	Effect of	
		During Partial Paralysis[a]	During Complete Paralysis[a]				Calcium Chloride	Neostigmine
Polymyxin B sulfate and colistimethate sodium	Absent	Partially maintained/ not maintained	Initial twitch/ absent	Present: maximum immediately after tetanus	Reduced or abolished	Decreased response	Partial to complete antagonism	No significant effect
Curare	Absent	Not maintained	Initial twitch/ present	Present: maximum immediately after tetanus	Reduced or abolished	Normal response	No or partial antagonism	Complete antagonism
Decamethonium	Present (facilitation of twitches)	Maintained	Initial twitch/ absent	Absent	Reduced or abolished	Decreased response	No effect	Accentuation
Magnesium	Absent	Maintained	Maintained	Present: maximum immediately after tetanus	Reduced or abolished	Decreased response	Complete or almost complete antagonism	

[a] Indirect maximal twitches.

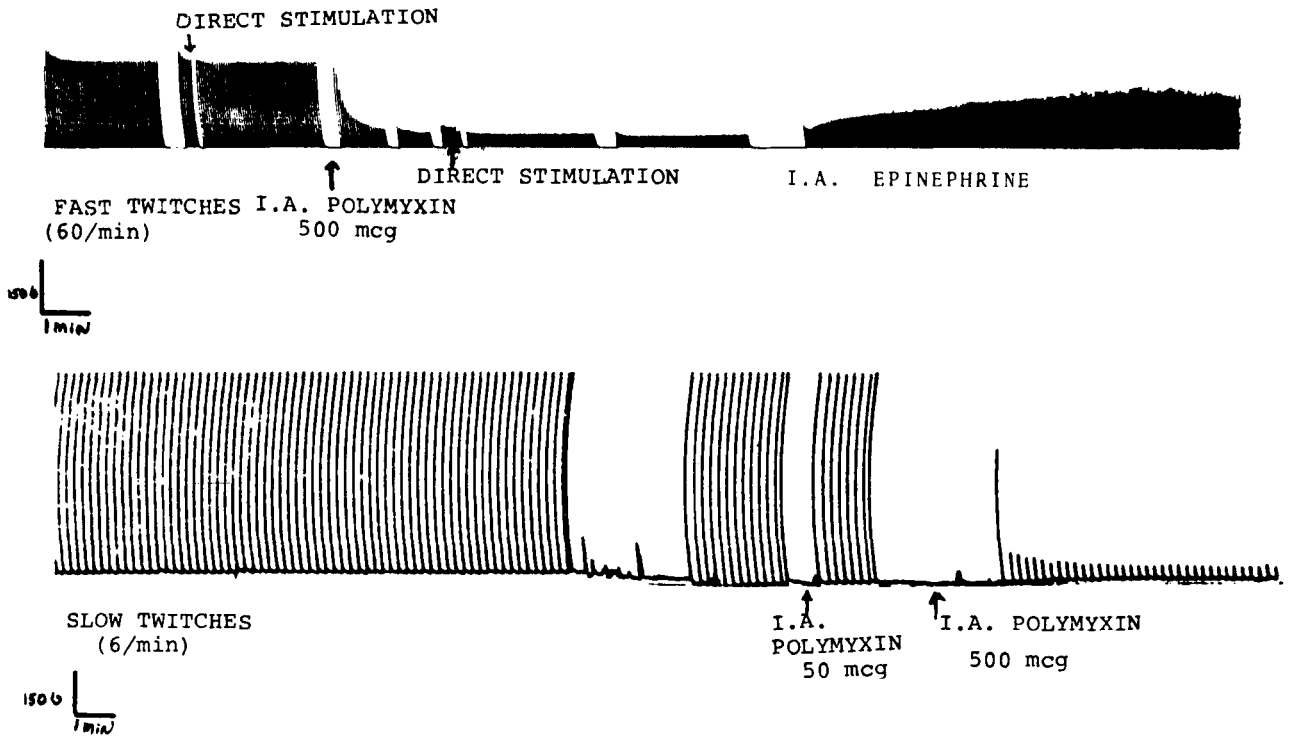

Figure 2—*Effect of intraarterial (I.A.) polymyxin and its antagonism by intraarterial epinephrine.*

of polymyxin and colistin. Each dose–response curve represented a given polymyxin concentration. The decrease in the maximal amplitude of acetylcholine contraction and the flattening of the curves with an increase in polymyxin concentration indicated a noncompetitive antagonism by these antibiotics (Fig. 5).

The effects of polymyxin B sulfate and colistimethate sodium on serum ionic calcium levels in rabbits are given in Table III. These antibiotics in paralyzing doses did not alter the calcium-ion level significantly.

DISCUSSION

The results confirm that polymyxins exert a potent neuromuscular block leading eventually to respiratory arrest. The possible actions at the postsynaptic site, the presynaptic site, and the nerve and muscle investigated show that polymyxin-induced neuromuscular block results from a prominent postsynaptic, nondepolarizing action. This conclusion is based on the following observations.

Polymyxin B sulfate and colistimethate sodium injected intraarterially did not cause contraction of the tibialis muscle in the cat, and these antibiotics elicited neuromuscular block when injected intravenously without any preceding fasciculation or facilitation of twitches, suggesting a nondepolarizing action. A simultaneous study of the effects of the antibiotic on the contraction response of the muscle to close-arterial injection of acetylcholine and on the indirect maximal twitch response elicited by nerve stimulation provides a sensitive means for determining whether the site of the blocking action is presynaptic or postsynaptic (11). During the neuromuscular block of the tibialis preparation in the cat, the contraction response to intraarterial injection of acetylcholine was reduced or abolished and was much more prominently affected than the simultaneously recorded indirect maximal twitches, indicating a significant postsynaptic action. The neuromuscular block was accentuated by curare and was briefly antagonized by edrophonium and decamethonium. Epinephrine and calcium chloride antagonized the neuromuscular block.

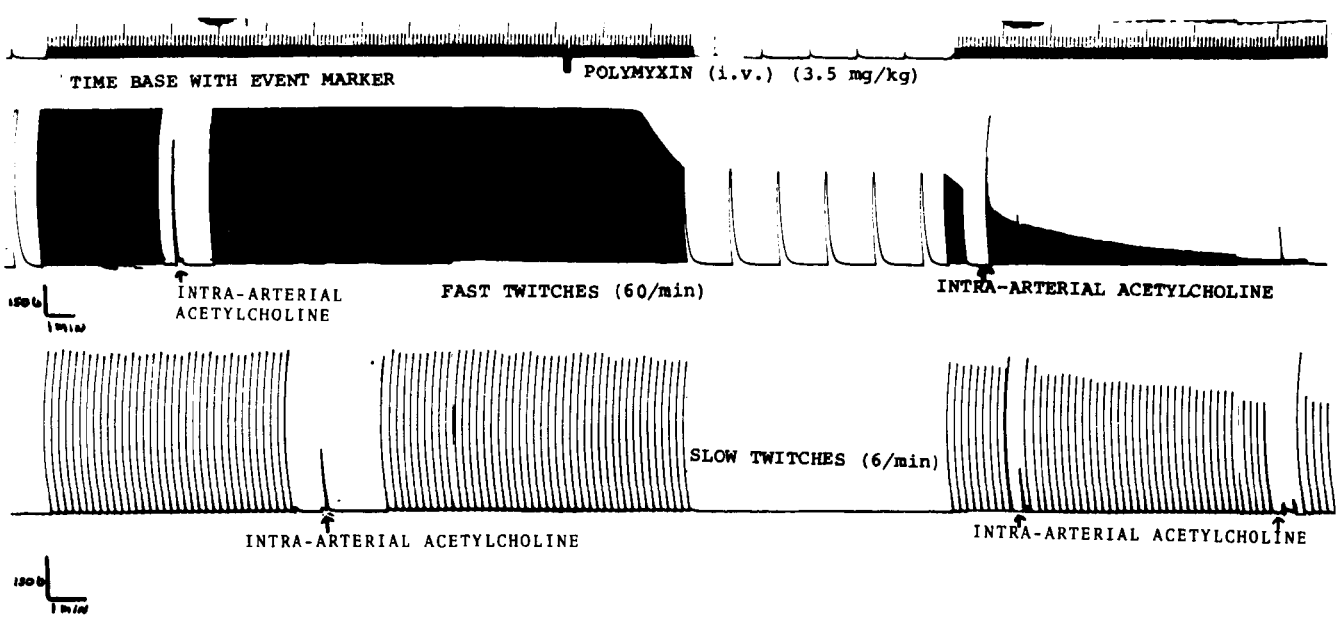

Figure 3—*Effect of intravenous polymyxin on indirect maximal twitches and the response to intraarterial acetylcholine.*

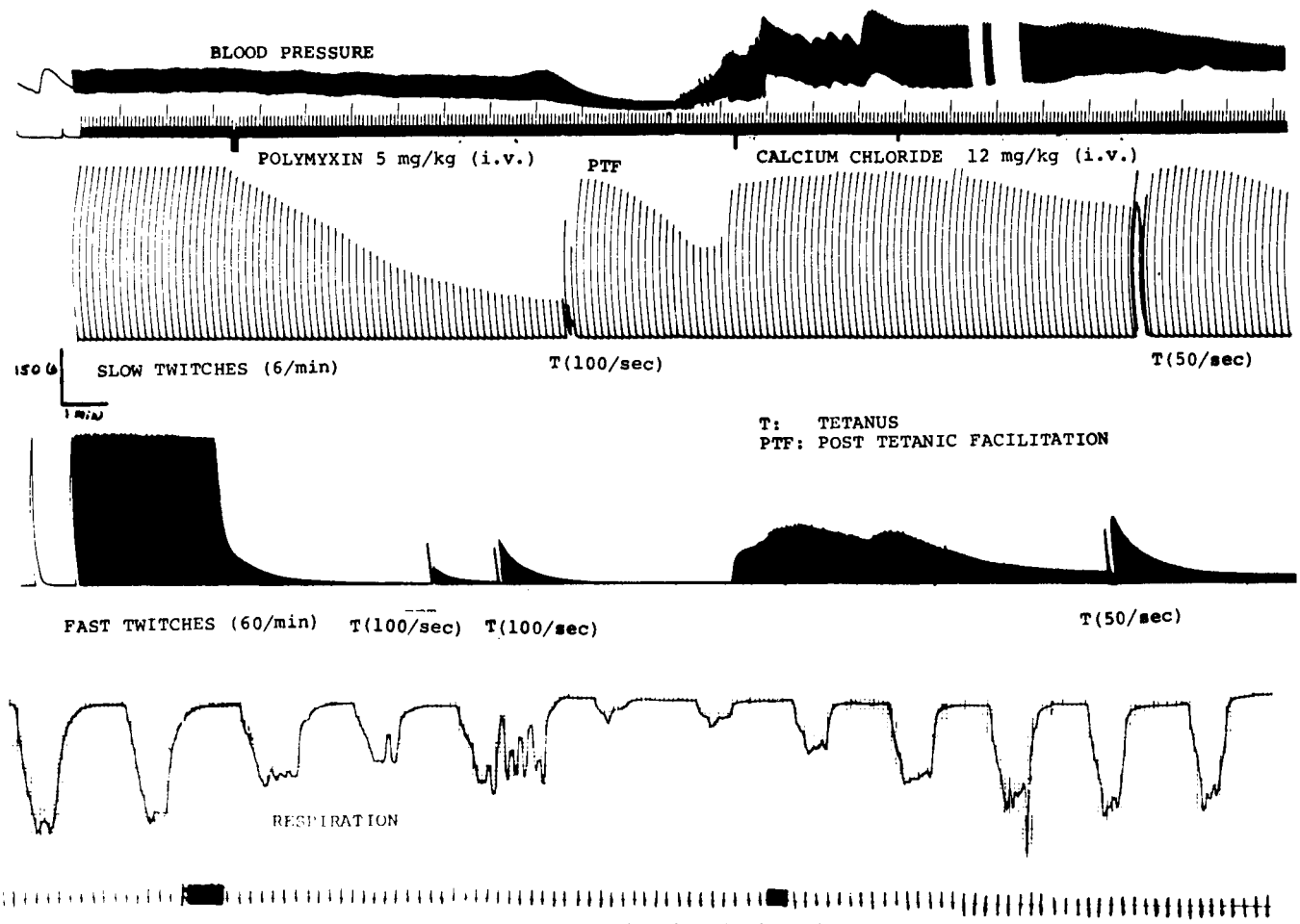

Figure 4—*Effect of calcium chloride on polymyxin-induced depression of maximal twitches, respiration, and blood pressure.*

Polymyxin B sulfate and colistimethate sodium antagonized the acetylcholine response in the frog rectus preparation, *i.e.*, depressed the response of the end-plate to the depolarizing action of applied acetylcholine and did not cause contraction of the rectus muscle by themselves,

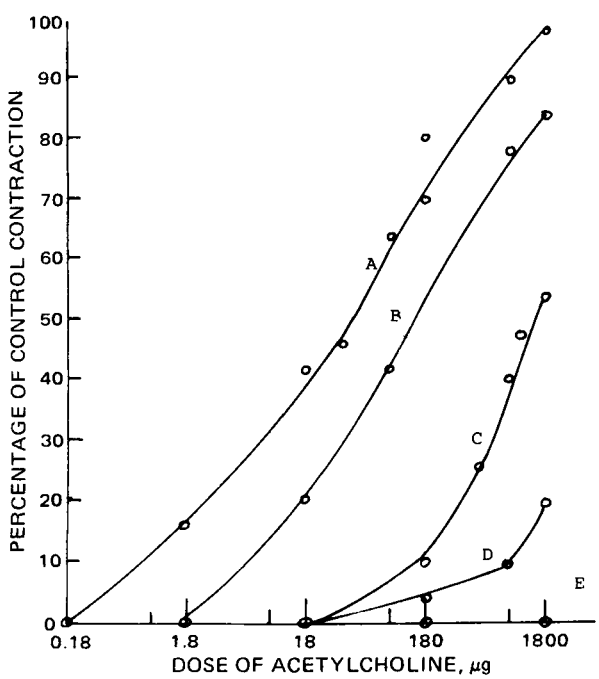

Figure 5—*Antagonism by polymyxin of the acetylcholine-induced contractions of the frog rectus abdominis muscle. Key (dose of polymyxin): A, 0 (control acetylcholine contraction); B, 100 μg; C, 200 μg; D, 300 μg; and E, 500 μg.*

suggesting a postsynaptic, nondepolarizing action. This nondepolarizing, postsynaptic blocking action was determined to be of noncompetitive nature, since:

1. The response to intraarterial acetylcholine in cats, which was abolished during the block, could not be obtained again by increasing the concentration of acetylcholine injected (in contrast to the response to acetylcholine during the curare block).
2. The cumulative log dose–response curve involving the effect of the antibiotics on the acetylcholine-induced frog rectus contraction response showed a decrease of the maximal amplitude and a flattening of the curves, demonstrating a noncompetitive antagonism.
3. Neostigmine did not produce antagonism of the neuromuscular block in cats.

During the block, the muscle action potentials were reduced or abolished while the nerve action potentials were unaffected, thus excluding any action of the antibiotic on the nerve trunk.

During the block of indirect maximal twitches, the response to direct stimulation was decreased as compared with the predrug response. So polymyxin probably acts on muscle fibers by decreasing their direct excitability. Polymyxin probably exerts a presynaptic action, since:

1. The tibialis twitches elicited at 60/min were depressed while twitches elicited at 6/min were unaffected in the bilateral preparation in cats. [The bilateral preparation (in which one sciatic nerve was stim-

Table III—Effect of Polymyxin in Paralyzing Doses on Serum Ionic Calcium Levels in Rabbits [a]

Animal	Calcium-Ion Level, m*M*/liter: Before Drug (pH of Sample)	After Drug (pH of Sample)
1	1.46 (7.33)	1.37 (7.13)
2	1.31 (7.24)	1.40 (7.08)
3	1.34 (7.30)	1.43 (7.14)
4	1.41 (7.37)	1.49 (7.06)
5	0.96 (7.34)	1.26 (7.19)
Mean	1.296 ± 0.176	1.39 ± 0.076

[a] Determined with calcium-selective electrode (Orion model).

ulated at 6/min and the other at 60/min) provides a means for distinguishing pre- and postsynaptic activities. Contractions elicited at the lower rate are blocked preferentially by compounds that act postsynaptically, while contractions elicited at the higher rate are blocked preferentially by compounds that act presynaptically.]

2. The neuromuscular block was antagonized partially or completely by calcium chloride administration.

3. The cumulative neuromuscular blocking effect of polymyxin also was antagonized by calcium chloride administration.

This presynaptic action may involve diminution of the calcium-ion function in the nerve terminal, occasioning a decrease in the mobilization and release of acetylcholine, or it may involve occupation of the superficial neuronal membrane sites by the antibiotics resulting in decreased transmitter release, and these actions could be antagonized by calcium administration.

The characteristics of the neuromuscular block of polymyxin and colistin resembled those of magnesium in its direct effect on muscle fibers, posttetanic response potentiation, and less strikingly, calcium antagonism of the block.

It is concluded that the neuromuscular block of polymyxin B sulfate and colistin results predominantly from their postsynaptic, nondepolarizing action, which is noncompetitive, but also from their action to depress the direct excitability of the muscle fibers and from a presynaptic action resulting in reduced transmitter release. The neuromuscular blocking action does not involve the chelation of calcium ions, since polymyxin in paralyzing doses did not alter significantly the serum calcium-ion level.

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Influence of High-Viscosity Vehicles on Miotic Effect of Pilocarpine

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Received October 31, 1977, from the *Biopharmaceutics Group and Pharmacology Group, Department of Ophthalmology, Alcon Laboratories, Fort Worth, TX 76101.* Accepted for publication January 12, 1978.

Abstract □ Gel formulations containing 2% pilocarpine hydrochloride were prepared from ethylene maleic anhydride, carbomer, hydroxyethylcellulose, polyacrylamide, ethylhydroxyethylcellulose, hydroxypropylcellulose, and poly(methylvinyl ether–maleic anhydride). The viscosity characteristics of each formulation were evaluated from rheograms developed at 37° using a cone and plate viscometer. Single-point viscosities were determined at room temperature using a single-point rotational viscometer. Plastic viscosity parameters correlated to miosis durations in the rabbit following ophthalmic dosing of 50 μl. Carbomer formulations varying in concentration between 0.9 and 5.0% (w/w) showed a discontinuous relationship when either yield value or plastic viscosity was plotted against miosis durations. At carbomer concentrations above 3%, miosis durations increased 1.5-fold. Above and below this range, plastic parameters did not correlate to miosis duration. It was reasoned that the increased duration was a consequence of the gel's increased yield value such that appreciable *in vivo* thinning of the gel does not take place with eyelid and/or eyeball movements. As a result, the residence time of the drug in the eye would be expected to increase, thus promoting an increased duration.

Keyphrases □ Pilocarpine—miotic effect, influence of various high-viscosity vehicles in rabbits □ Vehicles, high viscosity—influence on miotic effect of pilocarpine in rabbits □ Viscosity, high—in various vehicles, influence on miotic effect of pilocarpine in rabbits □ Miotic effect—of pilocarpine, influence of various high-viscosity vehicles in rabbits □ Ophthalmic cholinergics—pilocarpine, miotic effect, influence of various high-viscosity vehicles in rabbits

Polymers have been added to aqueous solutions of ophthalmic drugs to lengthen the contact time of the drug with the eye. This method is based on the assumption that drug absorption and, hence, duration can be improved.

The use of viscous solutions to prolong the effect of pilocarpine has shown that, in rabbits, large decreases in the drainage rate can be obtained when the viscosity is increased from 1 to 12–15 cps (1). Above this level, however, further increases in viscosity do not appreciably decrease drainage rates. When compared to an aqueous solution of pilocarpine nitrate, the testing of viscous solutions (100 cps) indicated that there is a twofold increase in drug aqueous humor concentration with a 100-fold increase in viscosity at 30 min following dosing to rabbits (2). It was hypothesized that the shear created by blinking resulted in thinning such that a large increase in instilled solution viscosity would not appreciably improve contact time and, therefore, bioavailability (2). For solutions, the approach to increasing bioavailability by increasing the vehicle viscosity is limited.

This study was conducted to determine if high-viscosity polymer systems could overcome the suspected thinning that occurs because of eye movements and/or blinking of the eyelids and prolong pilocarpine effects in the rabbits. Carbomer gel systems were primarily chosen for study because of the possibility of formulating a wide variation of high viscosities.

EXPERIMENTAL

Carbomer Gel Preparation—A series of carbomer[1] gels was pre-

[1] Carbopol 940, B.F. Goodrich.

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