Antibiotics and Neuromuscular Function

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Introduction

In the years following the introduction of the sulfonamides and penicillin into clinical medicine, a large number of other antimicrobial agents have been developed and used clinically. The wide clinical use of these drugs was accompanied by a significant incidence of side effects. The manifestations of these interactions and their severity depend on the antibiotic and the organ system involved. One of the most important side effects of antibiotics of concern to the anesthesiologist is the action of these drugs on the neuromuscular system. This effect can be of serious clinical significance as first reported by Pridgen in 1956.1

Classification of Drugs

For the purpose of this review, it would be preferable to classify antibiotics according to their mode of action at the neuromuscular junction (fig. 1). However, the actions of these drugs are not fully understood, and the available information suggests that many antibiotics have multiple sites of action. We therefore have chosen to classify these drugs according to their main mode of antibacterial action rather than by the incompletely understood mechanisms by which they produce neuromuscular block.

Weinstein2 has classified antibiotics according to their mode of antimicrobial action into several categories: 1) Agents inhibiting synthesis of bacterial cell wall (the penicillins, bacitracin, vancomycin, and rifostocetin); 2) Agents affecting the permeability of cell membrane [the polymyxins, colistimethate (polymyxin E), amphotericin, and nystatin]; 3) Agents primarily inhibiting protein synthesis by their effects on ribosomes (the aminoglycosides, tetracycline, chloramphenicol, erythromycin, oleandomycin, lincomycin, and clindamycin); 4) Agents affecting nucleic acid metabolism (rifampin and nalidixic acid); and 5) The antimetabolites (the sulfonamides, trimethoprim, and the sulfones).

Possible Sites of Action

The physiology and pharmacology of normal neuromuscular transmission have been well described3–5 and are not within the scope of this review. The basic elements of normal neuromuscular transmission that can be affected by antibiotics are: 1) Action potential transmission in the motor nerve and motor nerve terminal; 2) The process of synthesis, mobilization, and release of acetylcholine (Ach) from the nerve terminal; 3) The integrity of the postsynaptic cholinergic receptor; 4) Action potential generation and propagation in the muscle membrane; and 5) Normal excitation-contraction coupling in the muscle.

Thus a neuromuscular block (NMB) characterized by: 1) decreased acetylcholine release, 2) normal postsynaptic receptor sensitivity, 3) normal muscle response to direct stimulation, and 4) reversibility by calcium and 4-aminopyridine (4-AP) implies a predominant presynaptic site of action. The mechanism of action of these drugs is listed in table 1.

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by which calcium reverses this kind of NMB involves its actions at the nerve terminal. Calcium is necessary for the formation of release sites for Ach quanta from within the nerve. Thus an elevated calcium concentration increases miniature end-plate potential (MEPP) frequency and end-plate potential (EPP) amplitude while a decreased calcium concentration has the opposite effect. There is no effect of calcium on MEPP amplitude. The action of 4-AP in reversing a presynaptic NMB in the rat appears to be an enhancement of calcium influx into the nerve terminal during depolarization resulting in an enhancement of EPP amplitudes with no effect on spontaneous release.6

A pure cholinergic receptor blocker would produce NMB characterized by: 1) normal Ach release, 2) decreased sensitivity of the postsynaptic cholinergic receptor, 3) normal response to direct muscle stimulation, and 4) reversibility by anticholinesterases and partial reversibility by 4-AP and calcium administration. The reversal of this type of block by anticholinesterase administration is a result of a decreased rate of destruction of acetylcholine by the inhibited enzyme. The effect on the cholinergic receptors is a prolongation of transmitter action on the receptor resulting in increased MEPP and EPP amplitudes. The partial reversal of this type of block by calcium or 4-AP most likely results from the augmented transmitter release which competes with the blocking drug for the receptor.

A drug affecting the extrajunctional muscle membrane or excitation-contraction coupling would demonstrate: 1) normal Ach release, 2) normal postsynaptic receptor sensitivity, 3) inhibition of directly induced muscle contraction, and 4) failure to respond to calcium, or cholinesterase inhibitors.

The pharmacological agents described above, Ca++, Ach, anticholinesterase, and 4-AP have multiple sites of action which cloud interpretation of the data obtained in evaluating the various types of NMB. As an example, increased calcium concentration not only facilitates transmitter release but can also augment force of contraction by increasing sarcoplasmic calcium stores. It also stabilizes cell membranes which would inhibit action potential generation and could cause an increased blockade by this mechanism. Another example is the utilization of intra-arterially injected Ach to evaluate postsynaptic drug effects. This is a standard pharmacologic test. The effects of relatively large doses of Ach as used in this technique on presynaptic elements has not been adequately investigated. The same complex pharmacologic activity applies to the other drugs cited. Therefore, in evaluating the site of action of a neuromuscular blocking agent by pharmacologic means, it is always desirable to utilize the data from a number of tests and/or drugs, rather than to rely on that of a single test or drug.

There now exists a number of biophysiological tests to better evaluate the site of action of neuromuscular blocking agents. These tests have been little used on the antibiotic agents in question. These techniques include an evaluation of drug action on nerve terminals by recording spontaneous or drug-induced neural activity in the ventral root of the spinal nerve. A second group of techniques involve microelectrode recording of intracellular electrical activity. This would include recording both spontaneous and evoked transmitter release and its statistical analysis, as well as voltage clamping of these potentials. These tests, though more definitive, are technically difficult. However, data obtained from these tests are valuable in determining the exact site of action of any drug.

**Drugs Having Neuromuscular Effects (Table 1)**

**Drugs Inhibiting Synthesis of Bacterial Cell Wall**

**Penicillin.** In terms of producing NMB the penicillins are among the safest of the antibiotics available.
Table I. An Abbreviated Summary of the Current Concepts of the Sites of Neuromuscular Actions of some Antibiotics and the Effectiveness of Reversal Regimens

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Local Anesthetic</th>
<th>Site of Action</th>
<th>Cholinergic Receptor</th>
<th>Muscle Membrane</th>
<th>Ca**</th>
<th>Reversal</th>
<th>3A-Amino-pyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G and V</td>
<td>NA*</td>
<td>Dose-related, stimulation followed by depression</td>
<td>NA</td>
<td>NA</td>
<td>Adequate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Colistin</td>
<td>NA</td>
<td>Inhibition</td>
<td>? Depression</td>
<td>Depression</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Polymyxin</td>
<td>Yes</td>
<td>Dose-related, stimulation then depression</td>
<td>NA</td>
<td>Depression</td>
<td>No or slight</td>
<td>No</td>
<td>Good</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>NA</td>
<td>Depression</td>
<td>Depression</td>
<td>Adequate</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>Dose-related, stimulation then inhibition</td>
<td>Depression</td>
<td>NA</td>
<td>Adequate</td>
<td>Poor</td>
<td>NA</td>
</tr>
<tr>
<td>Neomycin</td>
<td>NA</td>
<td>Inhibition</td>
<td>Depression</td>
<td>NA</td>
<td>Adequate</td>
<td>Poor</td>
<td>NA</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>NA</td>
<td>Inhibition</td>
<td>Depression</td>
<td>NA</td>
<td>Adequate</td>
<td>Poor</td>
<td>Adequate</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>NA</td>
<td>Inhibition</td>
<td>NA</td>
<td>NA</td>
<td>Adequate</td>
<td>Adequate</td>
<td>NA</td>
</tr>
<tr>
<td>Amikacin</td>
<td>NA</td>
<td>Inhibition</td>
<td>NA</td>
<td>NA</td>
<td>Adequate</td>
<td>Poor</td>
<td>NA</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Adequate</td>
<td>Poor</td>
<td>NA</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Yes</td>
<td>Dose-related, stimulation followed by inhibition</td>
<td>Depression</td>
<td>Depression</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
</tr>
</tbody>
</table>

* NA = information not available.

With both Penicillin-V and Penicillin-G, the concentrations needed to produce any significant degree of NMB are well beyond those ordinarily used clinically. At low concentrations, 200 units/kg intra-arterially, or 10,000 units/kg intravenously in the cat soleus preparation, Penicillin-G produces repetitive firing in the nerve terminal which is transmitted antidromically to its parent axon. From this point the action potential spreads both antidromically and orthodromically. The antidromically conducted impulse can be recorded in the ventral root of the spinal nerve while the orthodromic spread produces both augmented twitch tension and posttetanic facilitation. This primarily presynaptic effect of Penicillin-G is supported by Futamachi and Prince who demonstrated excitatory junctional potentials after penicillin administration in the superficial flexor muscles of the crayfish preparation, and by Noebels and Prince who also demonstrated antidromic firing in the motor nerve terminal after the application of penicillin to the rat phrenic hemidiaphragm preparation. This penicillin-induced stimulation of the nerve terminal is thought to be akin to the epileptogenic effect of the drug when applied topically to the brain. Raines and Dretchen critically examined the possible mechanisms which might result in this type of repetitive firing. They concluded that penicillin resembles the anticholinesterases in its action on the nerve terminal, producing an augmented and prolonged negative after potential. This is believed to act as a constant current sink which induces the contiguous axon to fire repetitively. Noebels and Prince proposed the following as possible mechanisms of the excitatory phenomena: alteration of membrane sodium conductance, prolongation of the action potential, decreased membrane conductance for potassium and chloride, and increased specific membrane resistance. In their studies they observed that penicillin produced repetitive firing at concentrations which did not alter MEPP frequency or depolarize muscle membrane. This appears to rule out prolongation of the action potential as a major factor in the production of after discharges. This concept of altered membrane resistance does, however, agree with that of Raines and Dretchen. The studies involving nerve terminal stimulatory effects of drugs are able to give little evidence as to the potential of the drug to cause nerve terminal block.

Penicillin-V possesses more potential for NMB than does Penicillin-G. Penicillin-G in iv doses of 50,000 units/kg depresses posttetanic potentiation and produces NMB and with 250,000 units/kg doses. Like the blockade from Penicillin-G, a blockade induced by Penicillin-V requires high drug concentrations and is preceded by a modest increase in twitch tension. The blockade is reversed by calcium but is unaffected by neostigmine. This suggests that the probable site of the neuromuscular blocking effect of penicillin
is at the nerve terminal. However, further investigations are needed to elucidate the exact site of action.

**Bacitracin.** Little information is available concerning the neuromuscular blocking effects of bacitracin. In the clinical reports suggesting neuromuscular blockade, the drug was always combined with others known to have blocking properties.¹¹

**Agents Affecting the Permeability of the Cell Membrane**

**Polymyxins A, B, and E (Colistin)**

Both the polymyxins and colistin are simple polypeptides with three amino groups which are usually charged at physiologic pH.¹² These charged groups are essential for the antibacterial effect but are also responsible for the drug's neuromuscular blocking properties. Both of these properties are inhibited by methane-sulfonation and as a result, colistimethate must be converted to colistin in the body to be effective.¹²

The neuromuscular blocking properties of polymyxin-B are apparently of complex origin. Wright and Collier¹³ observed local anesthetic effects on the desheathed frog sciatic nerve which were similar in quality and quantity to those of lidocaine. However, the drug concentration necessary to produce local anesthetic effects are higher than those needed to produce NMB of the indirectly stimulated rat phrenic diaphragm. This observation does not rule out the possibility of a local anesthetic effect on the small and unmyelinated nerve terminal which would respond to lower concentrations of drug than the heavily myelinated sciatic nerve.

These authors also found that polymyxin increased spontaneous Ach release and had either no effect or caused a slight enhancement of induced Ach release in the rat phrenic diaphragm preparation. These effects were similar to those of Dretchen et al.¹³ in the frog sciatic-gastrocnemius preparation. These two studies use similar techniques except for the analysis for Ach. They were unsupported by data utilizing other methods of evaluating nerve terminal function. The drug concentration required to block the directly stimulated rat diaphragm was higher than that needed to block the indirectly stimulated preparation.

Reversal of a polymyxin-induced block is difficult. Neostigmine has proved to be ineffective in the hands of most investigators. For example, Lee et al.¹⁴ found only a partial and transient reversal of polymyxin-induced block with small doses (0.02–0.04 mg/kg) of neostigmine while both he and Van Nyhuis et al.¹³ found augmentation of the block by larger doses (>0.08 mg/kg) of neostigmine. The administration of calcium has proved more effective but still incomplete in reversing a polymyxin-induced block. Viswanath and Jenkins¹⁵ obtained an effective reversal of the cumulative neuromuscular blocking effect of a second dose of polymyxin in cats. However, the modes of stimulation of the preparation (0.1–1.0 Hz) were slow compared to those used clinically.

In contradistinction, Singh et al.¹⁶ using the mouse diaphragm, and Lee et al.,¹⁴ using the cat, were unable to achieve complete reversal with calcium in doses as high as 50 μg/kg. Though neither calcium nor neostigmine appear to cause significant reversal of a polymyxin-induced block, Lee et al.¹⁷ and Singh et al.¹⁸ have described complete reversal by 4-AP of a neuromuscular block induced by polymyxin B. Our current knowledge of the pharmacology of 4-AP is inadequate to explain this observation. This is particularly so in that the primary effect of 4-AP appears to be to facilitate Ach release possibly through calcium-related mechanisms. Electrophysiologic studies of the actions of these drugs might shed more light on their modes of action and interaction.

From the available evidence, it appears that the primary site of action of polymyxins on the neuromuscular function is postsynaptic. These studies give only indirect evidence of the locus of the drugs action. More definitive studies of neuromuscular function are needed to elucidate the exact mode of action of polymyxin.

The mechanism of colistin (polymyxin E)-induced NMB has been investigated by McQuillin and Engbaek¹⁸ who studied the effect of the drug on MEPP frequency and amplitude, and on the mechanism of Ach release during tetanic trains of end-plate potentials in the rat phrenic diaphragm preparation. No change in MEPP frequency was seen. They observed a decrease in quantum content of the end-plate potential and attributed it to a decrease in the size of the readily available store without a change in the probability of release. A slight decrease in MEPP amplitude was noted which most likely indicates a postsynaptic receptor block rather than alteration in quantum size. As with polymyxin A and B, reversal of a colistin-induced neuromuscular blockade is difficult. Singh et al.¹⁰ found that the blockade could not be successfully reversed by either calcium or neostigmine in the mouse hemidiaphragm, while Viswanath and Jenkins¹⁵ achieved partial reversal with calcium.

The polymyxin group of antibiotics produce a NMB of complex and as yet, not completely understood origin. Available data suggests a predominant post-
synaptic site of action. The complexity of blockade is demonstrated by the difficulty and unreliability of its reversal by neostigmine or calcium. The successful reversal of the blockade by 4-AP is difficult to explain and needs further study.

**Agents Inhibiting Protein Synthesis**

**Tetracycline and Oxytetracycline**

Both drugs possess weak and clinically insignificant neuromuscular blocking properties. The blockade is usually reversible by calcium, but not by neostigmine. The mode of action of tetracycline in producing neuromuscular block has not been completely elucidated. Calcium chelation, with a resultant inhibition of acetylcholine release, has been postulated as the underlying process. However, Wright and Collier found that rottetetracycline did not affect Ach release at a concentration that produced 50 per cent block of the indirectly stimulated rat phrenic nerve diaphragm preparation.

Minocycline, a compound structurally related to tetracycline, was found to produce a dose-related decrease in twitch tension of the rabbit's tibialis anterior preparation. This effect was augmented by a partial pancuronium-induced blockade and, in both instances, was reversed by calcium and neostigmine.

**The Aminoglycoside Antibiotics**

Albiero et al. compared the neuromuscular effects and acute toxicity of a group of aminoglycoside antibiotics. They found, in the rat sciatic-gastrocnemius preparation, a direct relationship between the neuromuscular blocking property and the LD₅₀ of the respective antibiotics studied.

Streptomycin. The effects of streptomycin on neuromuscular transmission have been studied by many investigators. The effect of streptomycin on frog sciatic nerve conduction was investigated by Sokoll and Diecke, who observed a local anesthetic-like action. In their studies, 400 mg/l of streptomycin was found to resemble the effect of 0.002 per cent lidocaine or 0.003 per cent procaine in decreasing the rate of rise of the action potential. This cell membrane stabilizing effect was also noted in the drugs ability to produce repolarization of a potassium chloride depolarized nerve.

The motor nerve terminal effects of streptomycin have been studied by several investigators. In the frog sciatic-sartorius preparation, Drenchen et al. observed an increase in MEPP frequency over a wide range of drug concentrations. This was associated with an increase in twitch tension which appeared immediately after the application of the drug and was later followed by NMB. Low drug concentrations were also noted to induce postdrug repetitive firing while higher concentrations were found to inhibit posttetanic repetitive activity. Both the increased twitch tension and postdrug repetitive firing are indications of drug actions on the nerve terminal. Wright and Collier demonstrated differing dose-response curves to nerve stimulation and close intravenous injection of Ach in the presence of streptomycin. Under those circumstances the observation that the muscle response was more depressed with indirect stimulation than by close intravenous injection suggests a presynaptic depressant activity. Drenchen et al. saw no change in induced Ach release, while Wright and Collier described a decrease in the induced Ach release. The former studies were performed on the frog using a bioassay for Ach, while the latter used the rat diaphragm and a radioenzymatic assay technique.

Drenchen et al. found that in higher concentrations, at which MEPP frequency was still elevated, streptomycin blocked contraction of the indirectly stimulated preparation with an associated decrease in MEPP amplitude and decrease in sensitivity of the postsynaptic receptor to iontophoretically applied Ach suggesting receptor blockade. Wright and Collier observed a decreased response to close intravenous injection of Ach which supports this postsynaptic site of action.

Brazil and Corrada investigated the neuromuscular blocking properties of streptomycin in both dogs and pigeons. In pigeons, the drug produced a flaccid paralysis, suggesting that it is devoid of depolarizing action on the cholinergic receptor. The drug caused profound NMB in the dog at adequate dosage. During partial block, tetanic stimulation caused an abrupt rise which either plateaued or continued to rise slightly with continuation of the tetanic stimulus. This type of response is characteristic of a NMB produced by magnesium. Posttetanic facilitation occurs with streptomycin as well as with magnesium and d-tubocurarine-induced neuromuscular blockades.

Dunkley et al. studied the effect of streptomycin in the cat in vivo and observed block of the indirectly elicited twitch while directly elicited contraction was unaffected. These studies rule out a significant direct effect of the drug on the muscle. The neuromuscular block of streptomycin is at least partially reversed with calcium and neostigmine with calcium being the more effective of the two.

The available information implies the existence of three possible modes of action of streptomycin on neuromuscular conduction. They are: 1) a post-
synaptic receptor blockade, 2) inhibition of Ach release from the nerve terminal, and 3) a minor non-specific local anesthetic type of action. This suggests that a neuromuscular block caused by streptomycin should be at least partially reversible by calcium and neostigmine as has been demonstrated by Singh et al.\textsuperscript{16}

\textit{Neomycin.} Neomycin is structurally related to streptomycin and shares in many of that drug's properties qualitatively but not necessarily quantitatively. For example, Wright and Collier\textsuperscript{27} found in the rat phrenic hemidiaphragm preparation that neomycin, as is the case with streptomycin, decreased the muscle response to indirect stimulation as well as to close intra-arterial injection of Ach. They also found that with neomycin, a large percentage of the block appeared to be presynaptic in origin in that the indirect muscle response was more easily blocked by neomycin than was the response to intra-arterially injected Ach. Elmqvist and Josefsson\textsuperscript{31} noted that the amplitude of the Epp was well maintained during a tetanic stimulus in the neomycin-blocked preparation, a phenomenon not characteristic of a nondepolarizing neuromuscular block, but characteristic of magnesium-blocked preparations.\textsuperscript{32} All of these phenomena were observed in the presence of normal concentrations of calcium, suggesting that calcium chelation is not the mechanism of block, but that blockade of calcium entry into the nerve terminal may be involved.\textsuperscript{37}

Additionally, Wright and Collier\textsuperscript{27} found that the antibiotic decreased induced Ach release, an action not seen by Dretchen et al.\textsuperscript{13} Species difference and differing assay techniques could account for these divergent results. Neomycin and streptomycin also differed in the effect produced by prolonged administration.\textsuperscript{33} The ability of neomycin to alter specific parameters of Ach release from the nerve terminal has been studied in the rat phrenic hemidiaphragm preparation by McQuillen and Engbaek\textsuperscript{34} who noted that neomycin decreased the probability of release of quanta of Ach but not the size of the releasable store. When administered to cats for 22–28 hours, the blockade produced by neomycin came to resemble a curare-induced blockade.\textsuperscript{35} Another observed difference is that with neomycin, a tetanic stimulus is followed by posttetanic facilitation and then posttetanic exhaustion. Several similarities exist between neomycin or streptomycin including a well sustained tetanic response and a train-of-four ratio approximating 1.0 in the face of a markedly inhibited twitch response and the absence of fasciculation.\textsuperscript{35,36}

Elmqvist and Josefsson\textsuperscript{31} observed a decreased depolarization of the end-plate region of the frog sartorius muscle after neomycin application, as well as decreased contracture of the denervated rat diaphragm and decreased MEPP and EPP amplitudes with no change in MEPP frequency. Although, as previously mentioned, Dretchen et al.\textsuperscript{13} saw no significant drug-induced change in Ach rebase, they did note a dose-related decrease in indirectly stimulated muscle contraction.

Both calcium and neostigmine have been utilized to reverse a neomycin-induced block.\textsuperscript{35,37–39} Most of these sources report that calcium is a more effective reversal agent than is the anticholinesterase. This concept is shared by Singh et al.\textsuperscript{16} who reported a 55–65 per cent reversal with 5 mm calcium, but only a 20–30 per cent reversal with 3 mm neostigmine. It is unfortunate that the ability of higher doses of neither calcium nor neostigmine to reverse the NMB of all antibiotics studied by these authors were evaluated.

To summarize, the available information suggest that neomycin blocks neuromuscular transmission by a prominent depressant effect on the nerve terminal inhibiting Ach release, and by a weaker postsynaptic blocking action.

The kanamycin-induced block has been shown repeatedly to be more easily and completely antagonized by calcium than by neostigmine.\textsuperscript{10,44} Molgo\textsuperscript{43} reported that 4-AP also antagonized the block produced by kanamycin.

The preponderance of evidence suggests that a kanamycin-induced block is of presynaptic origin on the basis of microelectrode studies and reversibility with calcium and 4-AP. A postsynaptic component, if it exists, appears to be minor.

\textit{Kanamycin.} As with the other aminoglycosides, the site of action of kanamycin at the neuromuscular junction has been the focus of debate. Using the dog sciatic nerve—tibialis anterior muscle preparation, Chinyanga and Stoyka\textsuperscript{40} suggested that the drug produced at least some Ach release inhibition. Unfortunately, the authors also used pancuronium in addition to antibiotics and observed the combined effects. They also used varying stimuli rather than a supramaximal stimulus used by most investigators. Singh et al.\textsuperscript{16} and Paradellis et al.,\textsuperscript{41} however, demonstrated that a kanamycin-induced NMB could be almost completely reversed by calcium, thus suggesting that the prime mode of action of the drug was to inhibit release of the Ach from the nerve terminal. Prado\textsuperscript{42} studied the effect of kanamycin on quantal content as related to drug concentration in rat phrenic nerve diaphragm and toad sciatic nerve-sartorius nerve muscle preparation, and concluded...
that the drug had an action that was competitive with calcium at the nerve terminal. These observations were supported by Molgo et al., who performed more complete microelectrode experiments involving the action of kanamycin the frog sciatic nerve-sartorius muscle preparation. They observed little effect on MEPP amplitude concomitant with a decrease in EPP amplitude and quantum content of the EPP, suggesting an almost complete presynaptic effect on transmission. The stimulation rates used in both of these studies were low (0.1 and 0.2 Hz) and the muscle twitch was inhibited by using low calcium and high magnesium ion concentrations, thus somewhat confusing interpretation of the data. The use of faster stimulus rates and methods other than decreasing calcium or increasing magnesium to suppress muscle twitch would aid in the interpretation of the data.

Timmerman originally attributed kanamycin-induced NMB to a postsynaptic action since he could demonstrate no change in Ach release. This finding was supported by Dretchen et al. who also demonstrated a dose-related decrease in indirectly elicited tetanic response.

Gentamycin. In 1969, Vital Brazil and Prado-Franceschi and Barnett and Ackerman demonstrated the neuromuscular blocking properties of gentamycin which had been forecast by Finland in the same year. The former authors, using the rat phrenic nerve diaphragm and the cat sciatic nerve-tibialis anterior muscle preparations concluded that the antibiotic had presynaptic blocking effects. These were manifest in a sustained response to tetanic stimulation at the same time that twitch tension was depressed at slow rates of stimulation. This effect mimics that of increased magnesium concentration at the neuromuscular junction. Dretchen et al. demonstrated a dose-related decrease of Ach release and a concomitant decrease in indirectly induced tetanic response.

Barnett and Ackerman, using the cat peroneal nerve-tibialis anterior muscle preparation, also suggested a “curare-like” blockade in that the antibiotic potentiated the effect of curare, a phenomenon also observed by Drury and Healey in the rat phrenic nerve hemidiaphragm preparation. A gentamycin-induced NMB has been noted by many authors to be more easily and completely reversed by calcium than by neostigmine.

The preponderance of currently available data suggests a major presynaptic site of action of gentamycin in producing NMB. This is evidenced by the depressed Ach release and antagonism of the block by calcium. Despite the inadequate partial reversal of a gentamycin-induced block by neostigmine, there is no concrete evidence of a postsynaptic component to the block.

In addition to the specific aminoglycosides antibiotics discussed above, a number of others have been synthesized, including kanamycin, amikacin, netilmicin, tobramycin, ribostamycin, dibecacin, sisomicin, and spectinomycin. Of these drugs, amikacin has been well investigated by Singh et al. They observed a NMB which was most profound in fast muscle and correlated with a decrease in EPP amplitude while MEPP amplitude was apparently unaffected. Amikacin enhanced the effect of d-tubocurarine on skeletal muscle. The NMB induced by amikacin was well reversed by calcium, but only partially by neostigmine. This data suggests a primary presynaptic site of action of the drug.

Lincomycin. Although Adamson and Dixon were unable to demonstrate neuromuscular blocking properties of lincomycin using rabbit sciatic nerve-gastrocnemius muscle preparation, Straw et al. using more rapid stimulus frequencies in a similar preparation, were able to demonstrate such effect. Tang and Schroeder confirmed Straw’s observations using the same preparation as well as in the chicken in vivo. Samuelson and co-workers made the clinical observation that lincomycin potentiated a d-tubocurarine-induced blockade. Booij et al. confirmed this potentiation with pancuronium, also in anesthetized patients. Gergis et al. described a prolongation of the recovery phase of a d-tubocurarine-induced blockade by lincomycin in the cat. In the frog sciatic nerve-gastrocnemius muscle preparation, Rubbo et al. described a depression of Ach release. They also noted an increased twitch height on drug application in the sciatic nerve-sartorius muscle preparation, a finding also noted by Wright and Collier in the rat. The increased twitch tension suggests nerve terminal stimulating properties of the drug.

Rubbo et al. also observed a decrease in MEPP amplitude, suggesting an additional postsynaptic element of the drug’s action. Wright and Collier observed a parallel blockade of both indirectly and directly elicited muscle contraction in the rat. This suggests an interference with the process of excitation of the muscle membrane or muscle contraction. A lincomycin-induced block does not appear to be depolarizing in nature since flaccid paralysis was produced in chicken and no initial stimulation was noted in the rabbit preparation.

Reversal of lincomycin blockade has been somewhat unpredictable. Straw et al. were unable to observe any alteration in the recovery pattern of a lincomycin-induced blockade by the administration.
of neostigmine. Tang and Schroeder, however, found variable responses to neostigmine, ranging from partial reversal to enhancement of the block. They did observe a consistent, though partial, reversal with edrophonium. Calcium did not antagonize this blockade. Wright and Collier were unable to reverse the neuromuscular block with either calcium or physostigmine. In their clinical observation Booij et al. found that neostigmine or 4-AP effectively antagonized a blockade caused by a combination of pancuronium and lincomycin. The neostigmine-induced reversal might occur if a great proportion of the blockade with which they were dealing was due to the pancuronium and not to lincomycin.

Analysis of the available information indicates the primary site of action of lincomycin as a neuromuscular blocker is directly on the muscle. The exact site of this action has not been investigated. The drug also has slight pre- and postsynaptic inhibitory effects. The pure lincomycin-induced blockade is poorly reversed by calcium or anticholinesterase. Reversal with 4-AP has not been adequately studied.

**Clindamycin.** Clindamycin is closely related structurally to lincomycin but differs qualitatively and quantitatively in its action. Wright and Collier demonstrated a local anesthetic action of clindamycin on the desheathed frog sciatic nerve. Rubbo et al. observed that clindamycin increased MEPP frequency and Ach release over a wide range of concentrations in the nerve muscle preparation. This coincides with the observations of Becker and Miller using guinea pig lumbrical nerve muscle preparation. Wright and Collier and Singh et al. all of whom observed an increase in twitch tension at low concentrations of clindamycin, noted a decrease in MEPP amplitude and sensitivity of the end-plate to iono-photoretically applied Ach at higher drug concentrations at which MEPP frequency is still elevated. This observation of nerve terminal stimulation at low drug concentrations and NMB at higher drug concentrations was also noted by other investigators. Similar to lincomycin, clindamycin also has a marked direct depressant effect of the muscle.

Clindamycin-induced NMB is difficult to reverse. No reversal could be obtained using either calcium or neostigmine by Wright and Collier. The partial reversal obtained by Becker and Miller may have been due to their use of d-tubocurarine in the preparation and the resultant effect of calcium and neostigmine on the blockade caused by this drug rather than an effect on the clindamycin-induced NMB.

In summary, the mode of action of clindamycin on neuromuscular function is complex. Although it has a local anesthetic effect on myelinated nerves it also stimulates the nerve terminal and simultaneously blocks the postsynaptic cholinergic receptor. It appears that the major neuromuscular blocking effect is its direct depressant action on the muscle. This latter effect is a property of the unionized form of clindamycin. This unionized form of clindamycin is approximately four times as potent as lincomycin as a neuromuscular blocker.

**Clinical Management**

Neuromuscular blockade induced or potentiated by antibiotics can be modified by many factors: 1) total dosage and route of administration, 2) metabolism and excretion; 3) patient sensitivity; 4) the concurrent administration of other drugs; and 5) other disease states.

The dose of antibiotic and its route of administration are important factors in determining the drug uptake and hence the blood level and the magnitude of its action. For most drugs, oral administration results in limited uptake and low blood levels. Despite this, cases have been reported where the oral administration of neomycin for a number of days has resulted in apparent antibiotic-induced NMB. The parenteral administration of antibiotics results in higher blood levels. With intramuscular administration, NMB has been noted with streptomycin and dihydrostreptomycin (as little as 1 g daily for 3 days) kanamycin, polymyxin (50 mg given once), and colistin (75 mg for 4 doses). The time between the last dose and the onset of clinical symptoms of neuromuscular blockade is erratic and has been reported to be as short as one hour and as long as 26 hours. Because of the higher peak blood levels that might be expected to result from intravenous as compared to intramuscular administration, the incidence of antibiotic-induced NMB would be expected to be greater and the onset of symptoms faster.

The aforementioned modes of administration of these antibiotics are used principally outside the operating room. In addition to these in the operating room, it is a common surgical practice to irrigate the operation field with antibiotic-containing solutions. The potential for the development of NMB with this practice will depend on the total dose retained within the body. Thus the irrigation of an extremity incision would be expected to have little effect since only small amounts of the drug would be retained while the irrigation of the peritoneal or pleural cavities with larger volumes of antibiotic-containing solution may have a significant effect. The magnitude of this effect is directly related to the total dose of drug retained within the body. Onset of drug effect may
be rapid (30–45 min/cm) since absorption from the peritoneal or pleural surfaces, particularly if they are inflamed, approaches that of the intravenous route.

With the exception of lincomycin and clindamycin which are primarily inactivated by the liver, the drugs discussed here rely principally on the kidney for their elimination. In the presence of impaired renal function, blood concentrations of these antibiotics may more easily reach those having neuromuscular effects. In this circumstance, renal dialysis may be required to terminate the NMB.

Not all patients to whom these antibiotics are administered develop NMB, the response of the susceptible groups of patients is most likely an expression of variable sensitivity of the neuromuscular junction to blocking agents. In addition to these patients, those having myasthenia gravis are also very susceptible to antibiotic-induced NMB. As with the above group, the NMB has been noted to occur without the concomitant administration of other drugs interfering with neuromuscular transmission. Patients having other neuromuscular diseases characterized by weakness may also be adversely affected by these drugs.

Although the antibiotics do not have pronounced effects on neuromuscular transmission, they can potentiate the muscle relaxant effects of the anesthetics and muscle relaxants used during surgical procedures. It is this interaction which is of importance to the anesthesiologist.

The anesthesiologist must suspect a possible interaction between the antibiotic and the anesthetic agents and/or muscle relaxants when there is: 1) a delayed recovery from a nondepolarizing NMB; 2) an increased depth of NMB following antibiotic administration; 3) difficulty reversing a nondepolarizing NMB with anticholinesterases administered in usual doses when antibiotics have been used concomitantly; and 4) a recurvarization following the administration of antibiotics in the postoperative period.

The ultimate life threatening symptom of an antibiotic-induced or potentiated NMB is hypventilation. It is most important in the initial stages of the treatment of this NMB to support the patients ventilation. Since pharmacologic reversal of this type of blockade is difficult and often incomplete, it is necessary to document the adequacy of the reversal. After insuring the adequacy of ventilation, the anesthesiologist should proceed with further evaluation of the NMB by observing the response to a tetanic stimulus or to a train-of-four in the anesthetized patient. The anesthesiologist should be aware that, at least with streptomycin and neomycin, tetanic tension can be well sustained and the train-of-four approach 1.0 in the face of a markedly depressed twitch response; hence, suggesting significant neuromuscular block resembling that of magnesium or a phase 1 depolarizing block. This stresses the necessity for the clinical evaluation of the patient in addition to the used electrophysiologic criteria of reversal of NMB. If the patient is awake, then the train-of-four and/or maximum inspiratory force or head lift tests may be useful.

Extrapolation from in vitro studies of calcium and neostigmine reversal of antibiotic-induced NMB suggest that calcium is more effective. Of the antibiotics currently in use which possess neuromuscular blocking properties, in vitro blockade produced by streptomycin, kanamycin, ribomycin, gentamycin, and oxytetracycline are reasonably well reversed (>70 per cent) by the administration of calcium. Calcium, however, has only slight (about 30 per cent) reversing effect on a lincomycin-induced block and essentially no effect on a block produced by clindamycin, polymyxin, or colistin.

Neostigmine produces only about a 65 per cent reversal of a gentamycin-induced block and 45 per cent reversal in the case of neomycin. Blockades induced by streptomycin and kanamycin are poorly (about 20 per cent) reversed. There is no reversal of a block produced by lincomycin, clindamycin, polymyxin, and colistin.

In the clinical circumstance, since nondepolarizing relaxants will often have preceded the administration of the antibiotic, it appears logical to begin the reversal of the block with neostigmine in increments to a total dose not exceeding 0.07 mg/kg or a maximum total dose of 5 mg. Equivalent doses of other anticholinesterase agents may be used. If the antibiotic used was polymyxin or lincomycin, the response to each incremental dose of neostigmine must be observed since neostigmine and edrophonium have been reported to increase the depth of the block produced by these antibiotics. If with any incremental dose of neostigmine, there is no further improvement or there is a lessening of neuromuscular function, then anticholinesterase administration should be discontinued at that point.

If the antibiotic-induced NMB is one of those amenable to reversal with calcium, then calcium chloride or calcium gluconate may be administered intravenously. Because of its potent cardiac effect, calcium should be administered slowly with constant ECG monitoring. Calcium chloride or calcium gluconate should be administered at the rate of 14
mg/kg or 28 mg/kg to a total maximum dose of 1 or 2 g, respectively. Although 4-AP has been used with varying degrees of success to reverse antibiotic-induced block in vitro, it is not available for clinical use. Should the patient still demonstrate inadequate reversal, electrophysiologically or clinically, then respiratory support should be continued. The patient’s condition should be reassessed at least every 2–3 hours. Should further antibacterial therapy be indicated, a different antibiotic should be recommended.

**Summary**

A drug may effect neuromuscular conduction at any one of a number of steps: 1) interference with neuro-axonal conduction, most likely at the node of Ranvier; 2) inhibition of acetylcholine release from the nerve terminal; 3) interference with the interaction of the transmitter with the postsynaptic cholinergic receptor; 4) alteration of the state of excitability of the cholinergic receptor; 5) direct action on the muscle membrane; or 6) interference with contractile mechanisms within the muscle.

The antibiotics discussed cover a wide range of compounds and have multiple actions on neuromuscular transmission. The primary action of the penicillins is to stimulate the nerve terminal causing the development of postdrug repetitive activity. The polymyxins and colistin cause neuromuscular block which is not reversible with either calcium or neostigmine but does appear to be reversed by dexamethasone. The tetracyclines cause neuromuscular block, but only in extremely high concentrations. This block is most likely related to a direct effect on the muscle. The aminoglycoside antibiotics show a wide range of activities. Most of these drugs have combined actions on both the nerve terminal and the cholinergic receptor, although in some, such as amikacin, the site of action appears to be primarily on nerve terminal. Most of these compounds can be reasonably well reversed with calcium and partially reversed with neostigmine. Lincomycin and clindamycin, though chemically similar, have somewhat different actions. Lincomycin inhibits nerve terminal activity, whereas clindamycin appears to stimulate this structure. The neuromuscular block of clindamycin is irreversible by either calcium or neostigmine, whereas the lincomycin-induced block can be at least partially reversed by calcium.

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