SOME EFFECTS OF THE AMINOGLYCOSIDE ANTIBIOTIC AMIKACIN ON NEUROMUSCULAR AND AUTONOMIC TRANSMISSION

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SUMMARY

The effects of the new aminoglycoside antibiotic amikacin on neurohumoral transmission were tested in the anaesthetized cat, and in mouse, rat and chick isolated nerve-muscle preparations. Amikacin had blocking actions on both autonomic and neuromuscular transmission. The autonomic effects were caused mainly by ganglion blockade and were reversed by calcium. The amikacin-induced neuromuscular blockade resulted from a decreased release of acetylcholine and a reduced postjunctional sensitivity. Intracellular recording from end-plates in the rat diaphragm demonstrated that amikacin had magnesium-like effects on acetylcholine release. The blockade was reversed completely by calcium, 4-aminopyridine and 3,4-diaminopyridine and partially by neostigmine. The neuromuscular effects of amikacin in vivo were augmented greatly after pretreatment with tubocurarine. It is concluded that care should be exercised if amikacin is administered during surgery in conjunction with tubocurarine.

Neuromuscular blockade is a recognized clinical side-effect of the use of aminoglycoside antibiotics, and prolonged respiratory depression may occur when aminoglycosides are used in conjunction with anaesthetic agents or neuromuscular blocking drugs (Pittinger and Adamson, 1972). Most of the experimental evidence indicates that the aminoglycosides possess both pre- and postjunctival blocking actions (Elmqvist and Josefsson, 1962; Vital Brazil and Prado-Franceschi, 1969), but the reversal of the blockade by either calcium or anticholinesterase agents is unpredictable.

Amikacin is a recently-introduced aminoglycoside antibiotic possessing a powerful action on resistant Gram-negative bacteria (Finland, Brumfitt and Kass, 1976). There have been no clinical reports of adverse neuromuscular blocking effects. However, it seemed important to establish the degree and mechanism of any neuromuscular blocking activity under experimental conditions. Therefore we have tested the effects of amikacin on neuromuscular and autonomic transmission in the anaesthetized cat and in isolated nerve-muscle preparations of mice, rats and chicks.

METHODS

Anaesthetized cats

Twelve mongrel cats of both sexes (weight 2–3.75 kg) were anaesthetized with a mixture of α-chloralose 80 mg kg⁻¹ and pentobarbitone sodium 5 mg kg⁻¹ injected i.p. The lungs were ventilated through a tracheostomy with air at a rate of 26 b.p.m. and a tidal volume of 18 ml kg⁻¹.

Drugs were administered i.v. through a polythene cannula placed in a femoral vein. Arterial systemic pressure was recorded via a polythene cannula placed in a femoral artery and connected to a Statham P23AC pressure transducer. The pulse pressure was used to trigger a Grass 7P4F EKG tachograph which measured heart rate.

Both vagus nerves were separated from the cervical sympathetic nerves and ligated. One vagus nerve was stimulated by trains of impulses (0.5 ms pulse duration at a frequency of 10 Hz for 10 s every 100 s) applied on the cardiac side of the ligation. The stimulation strength was adjusted to produce a decrease in heart rate of approximately 50%. In some experiments, acetyl-β-methylcholine was injected in a dose (5–9 μg kg⁻¹) which produced bradycardia approximately equal to that produced by vagal stimulation.

The cervical sympathetic nerves were ligated centrally to the superior cervical ganglion and stimulated unilaterally with trains of impulses (0.5 ms pulse duration at a frequency of 10 Hz for 10 s every 100 s). The stimulus strength was adjusted to produce a maximal contraction of the nictitating membrane. Contractions of the nictitating membrane were recorded using a Grass FTO3C force displacement transducer.

The sciatic nerve in the popliteal space was stimulated by rectangular pulses of 0.2 ms duration at a frequency of 0.1 Hz. The stimulation strength was adjusted to be in excess of that required to produce...
maximal twitches of the tibialis anterior and soleus muscles. Contractions of these muscles were recorded using Grass FT10C force displacement transducers.

Isolated nerve–muscle preparations

(a) Mouse phrenic nerve–hemidiaphragm. Phrenic nerve–hemidiaphragm preparations from Balb/c mice (25–40 g) were mounted in Krebs–Henseleit (1932) solution to which 2 g litre⁻¹ dextrose was added, maintained at 32 °C and bubbled with 5% carbon dioxide in oxygen. The phrenic nerve was stimulated at a frequency of 0.1 Hz with rectangular pulses of 0.2 ms duration and of strength greater than that required to elicit maximal twitches of the hemidiaphragm. For direct muscle stimulation, neuromuscular transmission was abolished either by tubocurarine 4 μmol litre⁻¹ or by the irreversible cholinesterase blocking agent erabutoxin b 0.9 μmol litre⁻¹. The hemidiaphragm was stimulated through a hook electrode inserted into the rib tissue with rectangular pulses of 1 ms duration at a frequency of 0.1 Hz and of strength greater than that required to elicit maximal twitches.

To construct concentration–effect curves test compounds were allowed to remain in contact with the preparation for 5 min before washing. Further concentrations of the test compounds were added to the preparation at least 5 min after the twitch height had returned to the control. Each preparation was exposed to only one test compound.

To assess reversibility of neuromuscular paralysis, an 80–90% block of twitch height was established and calcium chloride (to a final calcium concentration of 5 mmol litre⁻¹), neostigmine 3 μmol litre⁻¹, 4-aminoypyridine or 3,4-diaminopyridine 0.1 mmol litre⁻¹ was added to the tissue bath. The extent of reversal was measured 5 min after addition of the antagonizing agent.

(b) Chick biventer cervicis muscle. Biventer cervicis muscles (Ginsborg and Warriner, 1960) from chicks aged 3–10 days were mounted and stimulated under the same conditions as those used for indirect stimulation of the mouse hemidiaphragm. At intervals nerve stimulation was stopped and either acetylcholine or carbachol was added to the tissue bath. Acetylcholine and carbachol were allowed to remain in contact with the tissue for 30 s and 90 s respectively before washout.

(c) Rat phrenic nerve–hemidiaphragm. Phrenic nerve–hemidiaphragm preparations from CFHB rats (150 g) were pinned to the base of a 10-ml tissue bath. The bath was perfused at a rate of 2.5–5 ml min⁻¹ with a physiological saline of the following composition:

NaCl 110 mmol litre⁻¹; KCl 5 mmol litre⁻¹; CaCl₂ 2 mmol litre⁻¹; MgSO₄ 7H₂O 1 mmol litre⁻¹; KH₂PO₄ 1.2 mmol litre⁻¹; BES (N,N-bis[2-hydroxyethyl]-2-aminoethane sulphonic acid) 5 mmol litre⁻¹; dextrose 10 mmol litre⁻¹ and previously aerated with oxygen containing 5% carbon dioxide.

The muscle was maintained at a temperature of 28–30 °C.

End-plates were observed under 400× magnification using a standard binocular microscope fitted with a Leitz UM 20/0.33 long-working-distance objective. Intracellular recordings of membrane potential, end-plate potentials and miniature end-plate potentials were made with conventional recording techniques from 8–10 mΩ glass microelectrodes. Potentials were either recorded continuously on 35-mm film or photographed from a storage oscilloscope on to Polaroid film.

Drugs

The drugs used were tubocurarine chloride, chloralose, acetyl-β-methylcholine chloride, acetylcholine chloride, carbachol chloride, 4-aminoypyridine, noradrenaline hydrochloride and neomycin sulphate (Sigma), amikacin sulphate (Mead Johnson), pentobarbital sodium (Abbott), 3,4-diaminopyridine (Koch–Light) neostigmine methyl sulphate (Roche), dimethylphenylpiperazinium (supplied by Dr A. L. Green, Department of Biochemistry, University of Strathclyde) and erabutoxin b (supplied by Professor N. Tamiya, Tohoku University, Sendai, Japan). All drugs were dissolved in 0.9% sodium chloride solution.

RESULTS

Anaesthetized cats

Two types of experiment were performed in the anaesthetized cat. Amikacin was injected in a cumulative fashion at 100 or 200-s intervals either into cats in which neuromuscular transmission was unimpaired or into cats in which neuromuscular transmission was partially blocked with tubocurarine. In all cats studied, the effects of amikacin were qualitatively similar.

In cats which had not received tubocurarine, the autonomic responses measured were depressed at concentrations of amikacin below those which reduced the amplitude of skeletal muscle twitches. Doses as small as 10 mg kg⁻¹ of amikacin produced a decrease in arterial pressure and heart rate (fig. 1).
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Slightly larger doses (20–40 mg kg\(^{-1}\)) depressed responses of the preganglionic-stimulated nictitating membrane and produced a depression of the response to vagal stimulation. Neuromuscular block was detectable only at doses larger than 40–80 mg kg\(^{-1}\) (fig. 1).

The neuromuscular block produced by amikacin was preceded occasionally by twitch augmentation but no muscle fasciculations were seen. As noted with other aminoglycoside antibiotics (Adams et al., 1976), the fast-contracting tibialis anterior muscle was always blocked to a greater extent than was the slow-contracting soleus muscle. At a dose producing 75–80% depression of the twitches of the tibialis anterior muscle, the time from injection to maximal twitch depression was about 4 min and the time of recovery from 75% depression to 25% depression was 10 min. The neuromuscular block was partially removed by calcium chloride 10 mg kg\(^{-1}\) (0.08 mmol kg\(^{-1}\)) (fig. 1) and by neostigmine 100 \(\mu\)g kg\(^{-1}\), but was completely removed by calcium chloride 20 mg kg\(^{-1}\) (fig. 2).

Doses of amikacin that reduced responses of the heart rate to vagal stimulation did not depress responses of the heart rate produced by acetyl-\(\beta\)-methylcholine 5–9 \(\mu\)g kg\(^{-1}\). However, the increase in heart rate and arterial pressure, and the contractions of the nictitating membrane produced by the ganglion stimulant dimethylphenylpiperazinium 8–15 \(\mu\)g kg\(^{-1}\) were reduced by amikacin 80–160 mg kg\(^{-1}\), whereas similar responses produced by noradrenaline 3\(\mu\)g kg\(^{-1}\) were unaffected.

The depression of the heart rate, arterial pressure and responses to vagal stimulation produced by amikacin were antagonized partially by calcium chloride 10–20 mg kg\(^{-1}\) (fig. 1). The amikacin-depressed responses of the nictitating membrane to preganglionic stimulation and to dimethylphenylpiperazinium were restored by calcium chloride 20 mg kg\(^{-1}\).

In cats pretreated with tubocurarine 0.3–0.5 mg kg\(^{-1}\), amikacin was injected when the twitches of the tibialis anterior had recovered to 50% of their control height after the dose of tubocurarine. At this time, the twitches of the soleus muscle were blocked to a greater extent than those of the tibialis anterior (fig. 3). Under these conditions, the neuromuscular blocking action of amikacin could be detected at doses of 5 mg kg\(^{-1}\) which was 16 times less than that used in animals not pretreated with tubocurarine. The neuromuscular block resulting from the combination of tubocurarine and amikacin was reversed completely within 5 min by calcium chloride 20 mg kg\(^{-1}\) in the
tibialis anterior muscle, but was reversed only partially in the soleus muscle (fig. 3). In contrast, neostigmine 100 μg kg⁻¹ injected during the block resulting from tubocurarine and amikacin reversed the blocks in both tibialis anterior and soleus muscles within 5 min (fig. 3).

Pretreatment of cats with sub-neuromuscular blocking doses (50 μg kg⁻¹) of tubocurarine also augmented greatly the blocking action of amikacin (fig. 4).

Isolated nerve–muscle preparations

At concentrations above 3 mmol litre⁻¹, amikacin depressed indirectly elicited twitches of the mouse hemidiaphragm (fig. 5). Increasing the calcium concentration of the bathing solution from 2.5 to 5 mmol litre⁻¹ rapidly restored twitch height to 73 ± 1% of control in preparations in which twitch height was reduced to 15% of control by 5.5 mmol litre⁻¹.
of amikacin (fig. 6). Neostigmine 3 μmol litre⁻¹ produced a reversal to only 40 ± 4% of control twitch height, whereas 4-aminopyridine 0.1 mmol litre⁻¹ and 3,4-diaminopyridine 0.1 mmol litre⁻¹ completely restored twitch height (fig. 6). In some preparations treated with aminopyridines, twitch height returned to a level 10–20% greater than control. At concentrations of amikacin that abolished responses to indirect stimulation, there was no depression of directly elicited twitches.

In the chick biventer cervicis muscle preparation, amikacin 5–6 mmol litre⁻¹, neomycin 1.1–1.3 mmol litre⁻¹ and magnesium 20–25 mmol litre⁻¹ reduced responses both to nerve stimulation and to the added agonists acetylcholine $5 \times 10^{-5} - 1 \times 10^{-4}$ mol litre⁻¹ and carbachol $5 \times 10^{-6} - 10^{-5}$ mol litre⁻¹ (fig. 7). Single doses of carbachol were always reduced to a greater extent than those of acetylcholine by all three agents.

**Fig. 6.** Reversibility of amikacin-induced blockade of indirectly elicited twitches of the mouse hemidiaphragm preparation. A: (amikacin 5.5 mmol litre⁻¹) reversibility by calcium 5 mmol litre⁻¹. B: (amikacin 5.6 mmol litre⁻¹) reversibility by neostigmine 3 μmol litre⁻¹. C: (amikacin 5.1 mmol litre⁻¹) reversibility by 3,4-diaminopyridine 0.1 mmol litre⁻¹.

**Fig. 7.** Effects of magnesium (top records), amikacin (middle records) and neomycin (bottom records) (all concentrations mmol litre⁻¹) on responses of the chick biventer cervicis preparation to indirect stimulation, to acetylcholine (ACh—left-hand records—mol litre⁻¹) and to carbachol (Car—right-hand records—mol litre⁻¹).

**Intracellular recording**

In the rat phrenic nerve–hemidiaphragm preparation, control membrane potentials and miniature end-plate potentials were recorded from several end-plate regions before introduction of the amikacin to the perfusing fluid. Stimulation of the phrenic nerve produced junctional action potentials and muscle twitching. Amikacin was then introduced into the perfusing fluid and the nerve stimulated until no contractions could be observed microscopically. At this stage, end-plate regions were sampled for end-plate potentials and miniature end-plate potentials.

Amikacin 4.2 mmol litre⁻¹ abolished muscle twitching after 15–30 min of contact with the tissue. At this stage end-plate potentials were recorded which were too small to trigger action potentials. The recorded end-plate potentials fluctuated randomly in amplitude with many stimuli failing to elicit a response. However, miniature end-plate potentials were still recorded (fig. 8).

**DISCUSSION**

The aminoglycoside antibiotic amikacin has significant neuromuscular and autonomic blocking actions.
Fig. 8. End-plate potentials (left panel) and miniature end-plate potentials (right panel) recorded intracellularly from a rat diaphragm preparation after treatment with amikacin 4.2 mmol litre\(^{-1}\). Ten superimposed end-plate potentials are shown—note the variation in amplitude and the failure of some stimuli to produce an end-plate potential. A miniature end-plate potential is indicated at the arrow. The miniature end-plate potential record shows successive oscilloscope sweeps recorded on moving film.

which are pronounced after administration of tubocurarine. The neuromuscular block produced by amikacin was not of the depolarizing type since there was no muscle fasciculation in the cat and there was no contracture of the chick biventer cervicis muscle. Amikacin did not appear to have a direct depressant effect on muscle contractility. Hence, the possibilities of a prejunctional, magnesium-like action and of a postjunctional, curare-like action were investigated.

In the mouse hemidiaphragm, amikacin was five times less potent than neomycin (Singh, Harvey and Marshall, 1978) in depressing indirectly elicited twitches. The neuromuscular blockade of amikacin was reversed completely by calcium, whereas neostigmine was less effective. These actions of calcium and neostigmine are similar to those observed when these substances are injected during neomycin- or magnesium-induced neuromuscular blockades (Singh, Harvey and Marshall, 1978). In contrast, tubocurarine-induced blockade of the mouse hemidiaphragm is antagonized completely by neostigmine whereas calcium is almost totally inactive as a reversal agent (Singh, Harvey and Marshall, 1978). Magnesium is known to depress acetylcholine release (del Castillo and Engbaek, 1954) by competing for active sites on the presynaptic terminals (Dodge and Rahamimoff, 1967). In the presence of increased concentrations of magnesium ions, end-plate potentials are reduced below the threshold and they fluctuate randomly in amplitude with many failures (Liley, 1956). Miniature end-plate potential amplitude, however, is not greatly affected by high magnesium concentrations, indicating that magnesium acts mainly prejunctionally. On the other hand, a similar reduction in end-plate potential amplitude by tubocurarine is accompanied by the abolition of miniature end-plate potentials, and the end-plate potentials, although reduced, do not vary greatly in amplitude. Use of intracellular recording techniques demonstrated that amikacin produced effects that were very similar to those of increased concentrations of magnesium ions. Thus, amikacin appears to have an inhibitory action on transmitter release at the neuromuscular junction.

It has been proposed previously that other aminoglycoside antibiotics have prejunctional, magnesium-like actions (Vital Brazil and Corrado, 1957; Elmqvist and Josefsson, 1962; Vital Brazil and Prado-Franceschi, 1969). While confirming that amikacin also possesses such an action, we have provided evidence that amikacin has additional postjunctional effects. At concentrations that reduced twitch height in the chick biventer cervicis muscle, amikacin decreased responses to added agonists. Since magnesium and neomycin depressed postjunctional sensitivity also in this preparation, the postjunctional blocking action of amikacin and neomycin also may probably be termed magnesium-like.

The reversal of the amikacin-induced neuromuscular blockade in vitro by 4-aminopyridine and 3,4-diaminopyridine is of interest. The aminopyridines are potent neuromuscular facilitatory compounds (Lemeignan and Lechat, 1967; Sobek et al., 1968; Bowman, Harvey and Marshall, 1977; Harvey and Marshall, 1977a, b, c) that have been shown to increase acetylcholine release (Molgo Lemeignan and Lechat, 1975; Lundh and Thesleff, 1977). Since the aminopyridines reverse both curare-like and magnesium-like blockades, it is possible that these compounds are potentially useful in reversing antibiotic-induced neuromuscular blockade.

Autonomic and cardiac depressant actions of aminoglycoside antibiotics have been noted previously (Corrado, 1958; Adams, Teske and Mercer, 1976). In both the parasympathetic and sympathetic systems the main action of amikacin appeared to be at the ganglia, as responses of acetyl-β-methylcholine and noradrenaline which act at the respective postganglionic neuroeffector junctions were unimpaired. Thus the decrease in arterial pressure and heart rate and the depression of responses to vagal stimulation and preganglionic cervical sympathetic stimulation may be explained in terms of ganglion blockade although a direct cardiac depressant action as seen with other
aminoglycosides (Adams, Teske and Mercer, 1976) may contribute to the hypotension. A ganglion blocking action of streptomycin has been demonstrated previously by Corrado (1958). However, the site of action of amikacin at ganglia is unclear. The amikacin-induced block of the responses of the preganglionic-stimulated nictitating membrane was reversed by calcium, suggesting a prejunctional action of amikacin. A prejunctional action of neomycin on the superior cervical ganglion has been demonstrated previously by Wright and Collier (1974). Nevertheless, amikacin also reduced responses to the nicotinic agonist, dimethylphenylpiperazinium, an action that was also reversed by calcium. A similar reversal was seen in atropinized cats when acetylcholine responses were inhibited by streptomycin (Corrado, 1958). Two possibilities exist to explain this action of calcium.

The first is that calcium ions may increase post-junctional sensitivity to both transmitter and added agonists at ganglia, although this does not seem to take place at the neuromuscular junction. The second and more likely explanation is that at autonomic ganglia nicotinic agonists act partially through a prejunctional action to release acetylcholine (McKinstry and Koelle, 1967). Thus, at ganglia, antibiotic-induced depression of transmitter release would affect both responses to nerve stimulation and to added agonists. However, this cannot account for the observed depression of the responses to added agonists in the chick biventer cervicis muscle preparation as it has been shown that agonists act postjunctionally in this preparation (Marshall, 1971; Gandiha and Marshall, 1973).

We conclude that amikacin blocks nicotinic transmission at both the neuromuscular junction and autonomic ganglia by a mixture of pre- and postjunctional blocking actions, closely resembling those of an excess of magnesium ions. Although our results indicate that the neuromuscular blocking activity of amikacin per se is weak (occurring at 20–25 times the human dose), pretreatment with tubocurarine greatly enhances the neuromuscular blocking potency of the antibiotic. Wright and Collier (1976) have demonstrated a similar phenomenon with lincomycin and have explained the increase in potency in terms of Paton and Waud's (1967) finding that over 70–80% of acetylcholine receptors must be occupied for a depression of twitch height to be seen. Thus, in our experiments when amikacin was injected at 50% switch depression after tubocurarine, the margin of safety in transmission would be low and any occupation of pre- or postjunctional sites, or both, by amikacin would be expected to produce a reduction of twitch height. This result indicates that care should be exercised when using amikacin with tubocurarine.

Reversibility of the combined tubocurarine-amikacin neuromuscular block in vivo would appear to be dependent upon the ratio of the amounts of the two agents in the vicinity of the neuromuscular junction. Thus, if the resultant neuromuscular block is produced mainly by tubocurarine, calcium would be expected to reverse only the amikacin-induced component of block and leave a residual tubocurarine block. Conversely, neostigmine-induced reversal of tubocurarine block should increase the margin of safety in transmission so much that the small reduction in transmission by amikacin is incapable of producing muscle paralysis. In circumstances in which amikacin is the prime cause of the neuromuscular blockade, for example when the muscle strength has returned to normal after tubocurarine but when some receptors may still be occupied by tubocurarine, calcium would appear to be the reversal agent of choice.

ACKNOWLEDGEMENTS

This work was supported by a Medical Research Council project grant. Amikacin and erabutoxin b were gifts from Mead–Johnson Laboratories and Professor N. Tamiya (Tohoku University, Sendai, Japan), respectively. We also thank the Smith Kline and French Foundation for an equipment grant.

REFERENCES


### BRITISH JOURNAL OF ANAESTHESIA

#### QUELLES EFFETS DE L’AMIKACINE

**ANTIBIOTIQUE AMINOGLUCOSIDE SUR LA TRANSMISSION AUTONOME ET NEUROMUSCULAIRE**

**RESUME**

On a procédé à des tests sur les effets de la nouvelle Amikacine antibiotique aminoglycoside sur la transmission neurohumorale d’un chat anesthésié ainsi que sur des préparations de nerfs/muscles isolés de souris, rat et poulet. L’amikacine a eu un effet de blocage sur la transmission autonome et neuromusculaire. Les effets autonomes ont surtout été causés par le blocage des ganglions et ont été inversés par le calcium. Le blocage neuromusculaire provoqué par l’amikacine a été le résultat d’un dégagement diminué d’acétylcholine et de la diminution de la sensibilité après jonction. L’enregistrement intracellulaire effectué à partir de plaques d’extrémité se trouvant dans le diaphragme du rat a prouvé que l’amikacine a des effets semblables à ceux du magnésium sur les dégagements d’acétylcholine. Le blocage a été complètement inversé par le calcium, la 4-aminopyridine et la 3,4-diaminopyridine et partiellement par la néostigmine. Les effets neuromusculaires de l’amikacine in vivo ont grandement augmenté après un pré-traitement à la tubocurarine. On en a conclu qu’il faut faire très attention lorsque l’amikacine est administrée pendant une intervention chirurgicale conjointement avec la tubocurarine.

### EINIGE EFFEKTE DES AMINOGLYKOSID-ANTIBIOTIKUMS AMIKACIN AUF NEUROMUSKULÆRE UND AUTONOME ÜBERTRAGUNG

**ZUSAMMENFASSUNG**

Se comprobaron los efectos de la nueva amikacina antibiótica aminoglicósida en la transmisión neurohumoral en el gato anestesiado, y preparaciones de nervio-musculo aisladas de ratón, rata y pollito. La amikacina presentó de bloqueo tanto en la transmisión autonómica como en la neuromuscular. Los efectos autonómicos fueron causados principalmente por bloqueo de ganglio y fueron revertidos por calcio. El bloqueo neuromuscular inducido por amikacina resultó de una disminuida liberación de acetilcolina y una reducida sensitividad postjuncional. El registro intracelular de placas finales en el diafragma de la rata demostró que la amikacina ejercía efectos semejantes al magnesio sobre la liberación de acetilcolina. El bloqueo fue revertido completamente por el calcio, 4-aminopiridina y 3,4-diaminopiridina y parcialmente por neostigmina. Los efectos neuromusculares de amikacina en vivo fueron aumentados en gran medida después de recibir tratamiento preliminar de tubocurarina. Se concluye que debe tomarse cuidado si se administra amikacina durante la cirugía conjuntamente con tubocurarina.