Neuromuscular Blocking Property of Amikacin in Man

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HASHIMOTO, Y., SHIMA, T., MATSUKAWA, S. and SATOU, M. *Neuromuscular Blocking Property of Amikacin in Man.* Tohoku J. exp. Med., 1978, 125 (1), 71-75 — The effect of amikacin on the neuromuscular junction was studied in man during anesthesia and surgery. Amikacin alone did not show any neuromuscular blocking action in normal man in therapeutic doses (100-200 mg). However, during recovery from either d-tubocurarine block or phase II block with succinylcholine, the intravenous administration of 200 mg of amikacin caused a decrease in twitch tension. This neuromuscular block aggravated by amikacin was antagonized by edrophonium (10 mg) or calcium chloride (400 mg). Data obtained from the peroneal nerve-anterior tibial muscle preparation of rabbits suggested that the neuromuscular blocking potency of amikacin was one-twelfth of that of kanamycin in therapeutic doses. Although amikacin is thus less potent than kanamycin, caution should be taken in its use for patients with myasthenic state. — amikacin; neuromuscular blockade

Since the first report of respiratory arrest following the intraperitoneal administration of neomycin under ether anesthesia (Pridgen 1956), many other antibiotics having aminoglycoside structures were shown to have similar action by clinical and experimental studies. We previously reported that bekanamycin, ribostamycin and dibekacin potentiated the neuromuscular blocking action of d-tubocurarine (dTC) in man (Hashimoto et al. 1971, 1975). Amikacin (1-N-[L(-)- γ -amino- α -hydroxybutyryl] kanamycin A) is structurally related to the aminoglycoside group of antibiotics (Fig. 1). However, we have so far been unaware of

Fig. 1. Amikacin.

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any adverse clinical effects resulting from the neuromuscular blocking action of amikacin. Therefore, in the present study, it was attempted to determine the potency and to examine the property of the neuromuscular blocking action of amikacin in anesthetized man.

METHODS

Nineteen adult patients of both sexes from 26 to 60 years of age without known neuromuscular diseases were studied during anesthesia and genito-urinary surgery. Pre-anesthetic medication consisted of meperidine (50–70 mg) and atropine (0.4–0.5 mg), given intramuscularly 1 hr prior to anesthesia. After peridural analgesia, anesthesia was induced with thiamylal sodium (200–300 mg), and maintained with nitrous oxide (5 liters/min) and oxygen (2 liters/min) supplemented with pentazocine (30–60 mg) administered intravenously. Succinylcholine (SCh) (1 mg/kg) was given intravenously and lidocaine 8% spray was applied to the trachea and vocal cords, and intubation performed. Ventilation was either assisted or controlled as the occasion demanded to provide an adequate respiratory exchange. Prior to the study, the patient's forearm and hand were fixed firmly to a specially designed metal armboard.

The median nerve was stimulated at the elbow through the subcutaneous needle electrodes with supramaximal square-waves of 0.2 msec duration using a Nihon Kohden SEN-1101 stimulator and a stimulus isolation unit. The electrical stimuli were applied either continuously with 0.2 Hz or 2 Hz for 2 sec (train-of-four stimuli). The resultant force of adduction of the middle finger was measured with a force-displacement transducer (Shinkoh U-gage) and recorded on a Nihon Kohden polygraph.

When a steady twitch height was obtained, amikacin (100 or 200 mg) was administered intravenously (7 patients). Twelve patients were given amikacin (100 or 200 mg) intravenously during recovery from dTC or SCh block (phase I and phase II). To obtain phase II block, SCh (6 mg/kg) was administered intravenously by continuous infusion (0.3 mg/kg/min). After the twitch height had recovered fully to pre-drug height, SCh (1 mg/kg) was administered intravenously. The total cumulative dose of SCh was 8 mg/kg and this dose was sufficient to produce phase II block. Phase II block was determined by the train-of-four ratio at a twitch height 25, 50 and/or 75% of the initial value. Train-of-four ratio was expressed as a percentage of the ratio of the 4th response to the first. Phase II block was considered present when the train-of-four ratio was close to that of dTC block (Shima et al. 1977). The antagonizing effects of edrophonium and calcium chloride were also studied.

RESULTS

Amikacin (100 or 200 mg) alone did not depress the twitch height and train-of-four ratio in 6 of 7 patients. In one patient the intravenous administration of 100 mg amikacin caused a fair decrease in the twitch tension (Fig. 2). The train-of-four ratio of this patient before amikacin was exceptionally low, 75%, which was not the case in all the other 18 patients in this study. This indicated (Slomić et al. 1968) that the patient was in the "mild myasthenic state" (Rogoff et al. 1974; Lieding and Waldman 1975). Calcium chloride antagonized this neuromuscular blockade by amikacin (Fig. 2).

No change was found in the twitch height when amikacin was given intravenously during recovery from a neuromuscular block produced by SCh (phase I block). However, when the twitch height after dTC had recovered to 50%

Fig. 2. Neuromuscular block by amikacin (100 mg) in a patient thought to be "mild myasthenic state" and its antagonism by calcium chloride. AMK: amikacin.

Fig. 3. Effect of amikacin on the action of d-tubocurarine (dTC) and antagonism of this effect by calcium chloride and edrophonium (Ed). Right side bars represent 500 g of tension.

Fig. 4. Effect of amikacin (AMK) on the phase II block of succinylcholine (SCh) and antagonism of this effect by calcium chloride. Right side bar represents 500 g of tension.

of the control level, a single intravenous injection of 200 mg amikacin caused a decrease in the twitch height (Fig. 3). Amikacin 200 mg given intravenously during recovery from phase II block by SCh resulted in a decrease in the twitch height, while amikacin 100 mg did not show a potentiating effect (Fig. 4). This

neuromuscular block aggravated by amikacin could be antagonized promptly by edrophonium (10 mg) and more slowly by calcium chloride (400 mg) (Figs. 3, 4).

DISCUSSION

Many antibiotics have been reported to block neuromuscular transmission and to enhance the neuromuscular blocking effects of anesthetics and various neuromuscular blocking agents. The aminoglycoside group of antibiotics includes bekanamycin, dibekacin, dihydrostreptomycin, kanamycin, neomycin, ribostamycin, streptomycin and tobramycin (Pittinger et al. 1970; Hashimoto et al. 1971, 1975; Waterman and Smith 1977). The main pharmacological mechanism of the neuromuscular blocking action by this group of antibiotics is inhibition of the release of acetylcholine from nerve endings, an effect similar to that of low calcium or high magnesium concentration (Elmqvist and Josefsson 1962; Vital Brazil and Prado-Franceschi 1969; Pittinger and Adamson 1972). The neuromuscular blockade of this group of compounds is reversible with calcium and with neostigmine when the block is incomplete (Vital Brazil and Prado-Franceschi 1969). In the present study, we failed to demonstrate the neuromuscular blocking effect of amikacin itself in the therapeutic doses in normal patients, but did show the potentiating effect of amikacin on dTC and SCh-phase II blocks. Our results suggested that the characteristic of the neuromuscular blocking property of amikacin is similar to that of the block caused by other members of the aminoglycoside group.

For comparing the neuromuscular blocking potencies of amikacin, kanamycin and dTC, these drugs were studied in rabbits. The cumulative ED_{50} for neuromuscular blocking action of amikacin, kanamycin and dTC were 102, 85 and 0.19 mg/kg, respectively (Fig. 5). On the basis of therapeutic doses in man, amikacin is 10

Fig. 5. Log-dose-response curves for amikacin (AMK), kanamycin (KM) and d-tubocurarine (dTC). These drugs were studied in 18 rabbits anesthetized with sodium pentobarbital applied intravenously. The peroneal nerve-anterior tibial muscle preparation was used. The nerve was stimulated with single stimuli of 0.2 msec duration at a rate of 0.2 Hz.

times as potent an antibiotic as kanamycin. The relative neuromuscular blocking potency of amikacin in therapeutic doses is, therefore, one-twelfth of that of kanamycin. It would seem that amikacin may not cause a neuromuscular block leading to respiratory depression even if this antibiotic is used in combination with anesthetics or muscle relaxants. However, we have observed a "mild myasthenic state" patient with a fair decrease in twitch tension after 100 mg amikacin was administered intravenously. Therefore, it is conceivable that amikacin could produce undesirable clinical effects under circumstances of overdosage or excessive absorption in patients with myasthenic state.

References

- 1) Elmqvist, D. & Josefsson, J.O. (1962) The nature of the neuromuscular block produced by neomycin. *Acta physiol. scand.*, **54**, 105-110.
 - 2) Hashimoto, Y., Iwatsuki, N., Shima, T. & Iwatsuki, K. (1971) Neuromuscular blocking properties of lincomycin and kanamycin in man. *Jap. J. Anesthesiology*, **20**, 407-411.
 - 3) Hashimoto, Y., Shima, T., Matsukawa, S. & Iwatsuki, K. (1975) Neuromuscular blocking properties of some antibiotics in man. *Tohoku J. exp. Med.*, **117**, 399-400.
 - 4) Lieding, K.G. & Waldman, J. (1975) The "mild myasthenic state" *Anesthesiology*, **42**, 513.
 - 5) Pittinger, C.B. & Adamson, R. (1972) Antibiotic blockade of neuromuscular function. *Ann. Rev. Pharmacol.*, **12**, 169-184.
 - 6) Pittinger, C.B., Eryasa, Y. & Adamson, R. (1970) Antibiotic-induced paralysis. *Anesth. Analg.*, **49**, 487-501.
 - 7) Pridgen, J.E. (1956) Respiratory arrest thought to be due to intraperitoneal neomycin. *Surgery*, **40**, 571-574.
 - 8) Rogoff, R.C., Lippmann, M. & Walts, L.F. (1974) Anusual sensitivity of d-tubocurarine. *Anesthesiology*, **41**, 397-398.
 - 9) Shima, T., Hashimoto, Y. & Iwatsuki, K. (1977) Assessment of residual curarization by train-of-four nerve stimulation. *Jap. J. Anesthesiology*, **26**, 155-161.
 - 10) Slomić, A., Rosenfalck, A. & Buchthal, F. (1968) Electrical and mechanical responses of normal and myasthenic muscle. *Brain Res.*, **10**, 1-78.
 - 11) Vital Brazil, O. & Prado-Franceschi, J. (1969) The neuromuscular blocking action of gentamicin. *Arch. int. Pharmacodyn.*, **179**, 65-77.
 - 12) Waterman, P.M. & Smith, R.B. (1977) Tobramycin-curare interaction. *Anesth. Analg.*, **56**, 587-588.
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