Anesthesiology
71:57–61, 1989

Differential Effects of Pancuronium on Masseter and Adductor Pollicis Muscles in Humans

Charles E. Smith, M.D., F.R.C.P.C., François Donati, Ph.D., M.D., F.R.C.P.C.,† David R. Bevan, M.B., M.R.C.P., F.F.A.R.C.S.‡*

The sensitivity of the masseter, one of the muscles of the upper airway, to pancuronium was measured in ten adults undergoing elective surgery and compared with that of the adductor pollicis. During thiopental–nitrous oxide–enflurane (end-tidal concentration < 0.25%) anesthesia, supramaximal nerve stimulation was applied to the ulnar nerve at the elbow and to the nerve to the masseter, at a point inferior to the zygomatic arch, anterior to the mandibular condyle. Jaw closure was measured by a force transducer system attached to both an oral airway and a metal frame fixed to the operating table 10 cm caudad to the chin. Cumulative dose–response curves for pancuronium (initial dose = 0.02 mg/kg, incremental doses = 0.01 mg/kg) were determined. Control twitch tensions were (mean ± SEM) 473 ± 75 g at the masseter and 660 ± 118 g at the adductor pollicis. The masseter was slightly more sensitive to pancuronium, the ED_{50} being 0.024 ± 0.001 mg/kg compared with 0.028 ± 0.001 mg/kg for the adductor pollicis ($P < 0.05$). Corresponding values for the ED_{90} were 0.038 ± 0.004 and 0.043 ± 0.002 mg/kg, respectively ($P < 0.05$). The time from injection of the first dose of pancuronium to maximum blockade was 3.2 ± 0.2 min at the masseter and 3.8 ± 0.2 min at the adductor pollicis ($P < 0.01$). Following incremental doses, this time was 1.8 ± 0.1 and 2.6 ± 0.1 min, respectively ($P < 0.01$). It is concluded that after injection of pancuronium, neuromuscular blockade is greater at the masseter and occurs sooner than at the adductor pollicis. Jaw relaxation can be achieved with relatively small doses of pancuronium. This suggests that return of adductor pollicis function may not imply complete masseter muscle recovery. (Key words: Monitoring, neuromuscular function: train-of-four. Neuromuscular relaxants: pancuronium. Skeletal muscle: adductor pollicis; masseter.)

NONDEPOLARIZING relaxants are employed to facilitate tracheal intubation and provide surgical relaxation. Although several factors may influence the ease of tracheal intubation, such as depth of anesthesia, anatomic configuration of the airway, and skill of the anesthesiologist, the degree of jaw relaxation appears important.

In the clinical and research settings, stimulation of the ulnar nerve and observation or recording of the force of contraction of the adductor pollicis muscle is the most common method of monitoring neuromuscular function.[1,2] However, different muscle groups may exhibit different sensitivities to nondepolarizing relaxants. For example, the orbicularis oculi muscle is less easily paralyzed than is the adductor pollicis muscle.[3,4] Compared with peripheral muscles, respiratory muscles are more resistant to the action of nondepolarizing blocking agents.[5–9] Similarly, vocal cords require more vecuronium than the adductor pollicis for an identical degree of blockade.[10] In cats the masseter was found to be more sensitive than respiratory or limb muscles to a variety of nondepolarizing agents including pancuronium, pipecuronium and *d*-tubocurarine (*d*Tc).[11] Comparable human data are not available.

Moreover, the onset of neuromuscular blockade is not simultaneous in all muscles. For example, blockade of the diaphragm[12,13] and of the jaw muscles[14] was reported to occur before that of the adductor pollicis.

Because of the importance of jaw muscle function for the provision of adequate intubating conditions and for the maintenance of a patent airway, the sensitivity of the masseter muscle to pancuronium was investigated and compared with that of the adductor pollicis.

Methods

After approval of the Hospital Ethics Committee and written informed consent, ten adult patients, ASA physical status 1 or 2 undergoing elective surgical procedures were studied. Patients with any evidence of neuromuscular, renal, hepatic, or electrolyte disorders were excluded as well as those taking any medication whose interaction with neuromuscular function is known or suspected. Other exclusion criteria were trigeminal nerve dysfunction, abnormal dentition, abnormal mandibular/maxillary configuration, or anticipated difficult airway.

Preanesthetic medication consisted of intramuscular morphine, 0.1 mg/kg, and glycopyrrolate, 0.003 mg/kg, 1 h before surgery. After application of an automatic arterial blood pressure cuff, electrocardiograph, and pulse oximeter, anesthesia was induced with thiopental, 3–5 mg/kg, and fentanyl, 1–2 μg/kg, intravenously. Nitrous oxide, 66%, and enflurane, 1.5–2.5% end-tidal (mass spectrometer), was given *via* a face mask. End-tidal CO_2 partial pressure was maintained between 30 and 35 mmHg (mass spectrometer). After tracheal intubation, which was performed without the use of neuromuscular relaxants, enflurane was discontinued and mechanical ventilation was instituted. Anesthesia was maintained with

* Assistant Professor of Anaesthesia.
† Associate Professor of Anaesthesia.
‡ Professor of Anaesthesia and Chairman.
Received from the Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal, Quebec, Canada. Accepted for publication February 27, 1989.
Address reprint requests to Dr. Donati: Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

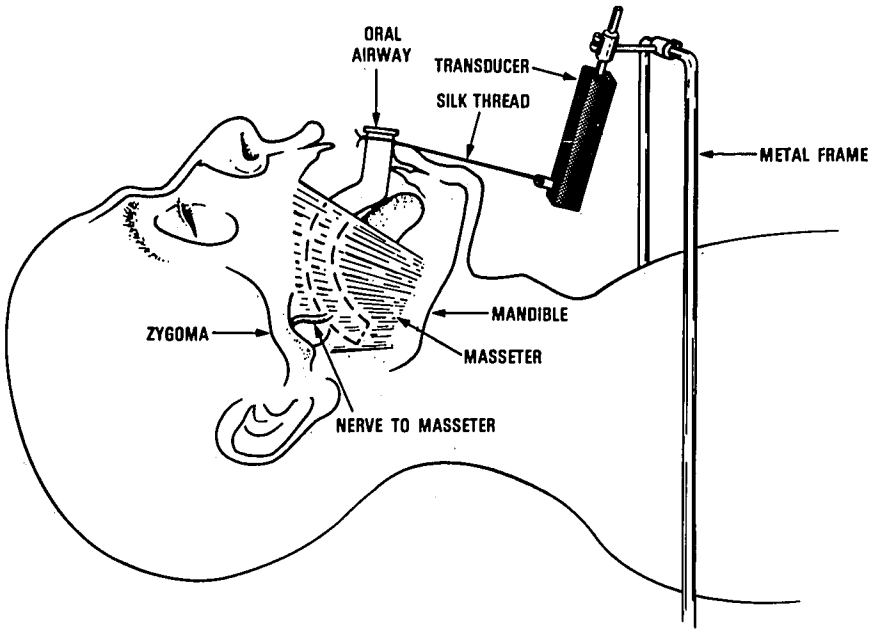

FIG. 1. The assembly used to measure isometric jaw tension. An oral airway is inserted into the mouth. A piece of heavy silk thread connects it to a force transducer, which is held in place by a bar fixed to the operating table. The thread and airway are taped to the patient between the lower lip and the chin (not shown).

nitrous oxide, 66%, in oxygen, and incremental doses of fentanyl.

Supramaximal stimulation was applied to the ulnar nerve at the elbow. Four consecutive 0.2-ms pulses were delivered at a frequency of 2 Hz every 12 s, using a Grass S88 stimulator and a SIU5 isolation unit. The hand and forearm were immobilized in a splint, and the evoked force of contraction of the adductor pollicis muscle was measured with a Grass FT-10 force displacement transducer and recorded on paper. A preload of 200–300 g was applied.

The nerve to the masseter muscle, which originates from the mandibular branch of the trigeminal nerve, was also stimulated supramaximally with silver–silver chloride electrodes positioned bilaterally on the skin overlying the space formed by the zygomatic arch superiorly and the mandibular notch inferiorly. The anterior or motor division of this nerve supplies the masseter muscle, which consists of three overlapping layers that arise from the zygomatic process of the mandible and the zygomatic arch and are inserted into the lateral surface of the angle, ramus, and coronoid process of the mandible.[15] Isometric contraction of the masseter was measured by a Grass force displacement transducer (FT-10) which was attached to a metal frame fixed to the operating table 10 cm caudad to the chin and connected with a heavy silk thread to an oral airway taped to the chin (fig. 1). A preload of 100–200 g was applied. The force registered was therefore proportional to the isometric tension developed in the masseter muscle. Supramaximal stimulation was achieved by increasing the voltage until the jaw response was stable, and setting it 15% higher. The position of the oral airway and the tracheal tube was assessed carefully to protect the teeth, tongue, and lips. Train-of-four stimulation was applied to the nerve to the masseter every 12 s.

After a stable baseline was obtained, cumulative doses of pancuronium (initial dose = 0.02 mg/kg, incremental doses = 0.01 mg/kg) were given until at least 95% first twitch (T1) depression of both the masseter and adductor pollicis muscles was observed. Each dose increment was given only after the response following the previous dose had become stable, defined as three equal consecutive first twitches at both muscles. Linear regressions were obtained between the logit transformation of T1 depression at the adductor pollicis and masseter muscles and the logarithm of the dose.[16] A regression line was obtained for each patient and for each muscle from which a mean dose–response curve was constructed. The slope of the curves and the doses corresponding to 50% and 90% first twitch depression (ED_{50} and ED_{90}) were derived. Statistical comparisons between muscles were performed with a paired Student's *t* test. Results are expressed as mean values ± SEM. A *P* value of 0.05 or less was considered to indicate statistically significant differences.

Results

The patients' mean age was 45 ± 5 yr, weight 64 ± 3 kg, and height 162 ± 2 cm. Indirect masseter muscle stimulation was achieved easily in all subjects. No direct stimulation of the muscle was observed because appropriate doses of pancuronium abolished twitch response entirely. Control twitch tensions were 473 ± 75 g at the masseter and 660 ± 118 g at the adductor pollicis. Mean

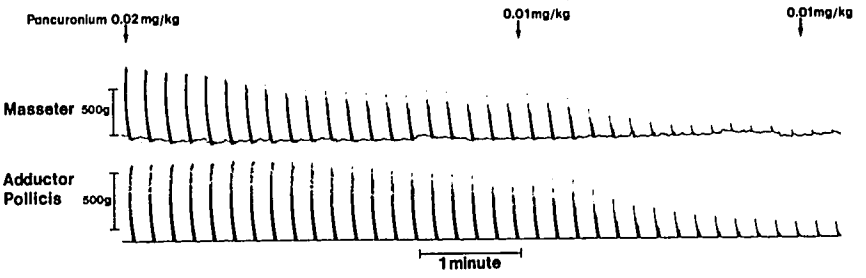

FIG. 2. Tracings from an individual patient showing evoked train-of-four responses obtained from the masseter (top) and the adductor pollicis (bottom).

end-tidal enflurane concentration was 0.21% when pancuronium was first administered and 0.06% when the maximum effect of the last dose was measured.

A total of 3.6 ± 0.2 doses was required to complete the study, and this required 12.2 ± 0.6 min. The masseter response to train-of-four stimulation was characterized by fade similar to that observed at the adductor pollicis muscle. In all but two patients, the jaw response was depressed more than that of the thumb. An example of an individual patient's response is shown in figure 2. The number of twitches which were recorded always corresponded to the number of contractions observed visually at the jaw.

The masseter was more sensitive to pancuronium than the adductor pollicis muscle and the curves did not deviate significantly from parallelism (fig. 3). The slopes were 5.44 ± 0.43 at the masseter and 5.42 ± 0.29 at the adductor pollicis. The ED_{50} were 0.024 ± 0.001 and 0.028 ± 0.001 mg/kg, respectively ($P < 0.05$). Corresponding values for the ED_{90} were 0.038 ± 0.004 and 0.043 ± 0.002 mg/kg, respectively ($P < 0.05$). The ED_{50} was greater at the masseter than at the adductor pollicis in only two instances (by 3% and 4%, respectively). The discrepancy was greater than 20% in only two patients, the ED_{50} at the masseter being 63% and 79% of the value at the adductor pollicis, respectively.

The onset of neuromuscular blockade was more rapid at the masseter. The time from injection of the initial dose to maximum masseter blockade was 3.2 ± 0.2 min compared with 3.8 ± 0.2 min at the adductor pollicis ($P < 0.01$). Following incremental doses, maximum blockade occurred in 1.8 ± 0.1 and 2.6 ± 0.1 min, respectively ($P < 0.01$). Both muscles exhibited a similar degree of train-of-four fade at comparable intensities of first twitch blockade. However, because train-of-four fade took longer to stabilize than the T1 response, dose–response relationships for T4/T1 could not be obtained.

Discussion

The present study demonstrated that the masseter muscle displayed slightly increased sensitivity and faster onset of blockade following injection of pancuronium compared with that for the adductor pollicis muscle. These results were obtained by injecting cumulative doses of pancuronium in adult patients who had both the ulnar nerve and the nerve to the masseter, a branch of the mandibular division of the trigeminal nerve, stimulated.

Stimulation of the mandibular nerve has been reported previously,[14] but the response was assessed without the use of a force transducer. A quantitative assessment of mouth opening has been described in anesthetized patients by Van Der Spek *et al.*,[17,18] who measured the distance between upper and lower teeth with the mandible held against a constant force. These measurements can only be made intermittently and are not designed to measure the evoked isometric force of contraction in the muscles of the jaw. The arrangement described in the present study (fig. 1) overcomes these two problems: recordings of isometric tension are continuous, allowing force of contraction to be measured quantitatively.

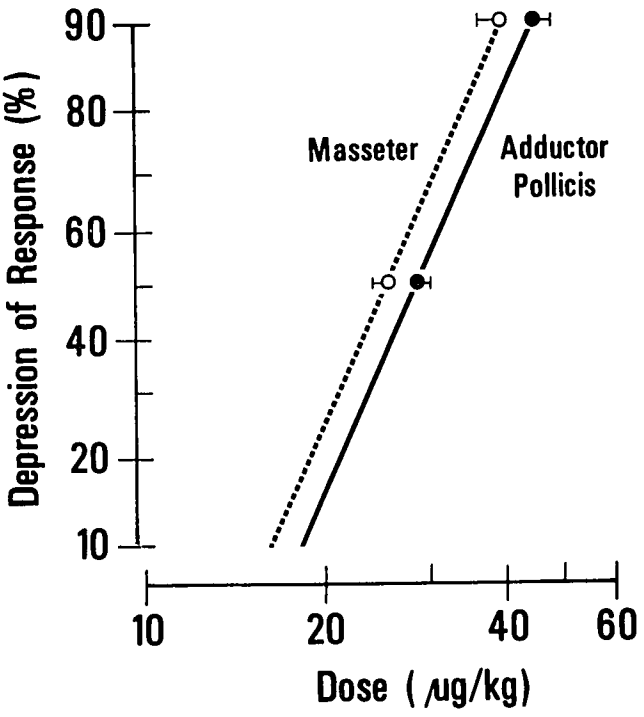

FIG. 3. First twitch depression (logit scale) for the masseter and the adductor pollicis *versus* logarithm of the dose of pancuronium. Bars represent SEM for ED_{50} and ED_{90}.

The masseter is only one of the three muscles that act to close the jaw, the others being the medial pterygoid and the temporalis.[19] All these muscles are supplied by branches of the mandibular nerve. Of these, only the nerve to the masseter has a course that brings it to the lateral (outer) surface of the mandible. Therefore, it is unlikely that the nerves to the temporalis and the medial pterygoid, which are much deeper, were stimulated to any significant extent. The voltage settings on the stimulator for the masseter were 25–35% lower than those required for the ulnar nerve, a superficial nerve at the elbow. This strongly suggests that only the most superficial nerve supplying the muscles of the jaw, *i.e.*, the nerve to the masseter, was stimulated with the apparatus used in this study.

The nondepolarizing relaxant used in this investigation was pancuronium because accurate determinations of its potency can be made with cumulative dose techniques. For long acting relaxants, dose–response curves with the cumulative technique are similar to those obtained with single dose injection technique because little elimination of the drug occurs during the study period.[20,21] Thus, the cumulative dose technique is expected to introduce little bias or error, and valid results can be obtained from a small number of patients.

The factors that determine the sensitivity to neuromuscular blocking drugs of a given muscle or group of muscles are poorly understood. It may depend on which agent is used[11,22] and the type of fibers that make up the muscle[23] because the morphology of the neuromuscular junction is different whether the muscle fiber is classified as red (slow), intermediate, or white (fast).[24] It has been suggested that slow fibers are more sensitive to nondepolarizing relaxants,[23,25] although this has not been a constant finding.[26] The adductor pollicis is made up mostly of slow fibers,[27] whereas the masseter contains a mixture of slow, fast, and intermediate fibers.[28] Part of the difficulty in obtaining a correlation between fiber type and sensitivity to neuromuscular blockers might be the different techniques used to identify the various types and the lack of agreement on the nomenclature.[29]

Irrespective of the mechanism, the masseter appears to be the only muscle that has been reported to be more sensitive than the adductor pollicis to a nondepolarizing relaxant. The diaphragm,[9,12,13] the orbicularis oculi,[4,5] the vocal cords,[10] and probably the muscles of the hypothenar eminence[30] all tend to be more resistant to nondepolarizing blocking drugs. The masseter, which lifts the jaw, is certainly not the only muscle involved in keeping airway patency. Other muscles, such as those of the pharynx and tongue, also play a role.[31] Unfortunately, the sensitivity of these muscles to nondepolarizing relaxants has not been measured. However, the presence of a relatively sensitive muscle, the masseter, supports the contention that upper airway patency may be affected considerably by small doses of nondepolarizing agents.[32]

The faster onset of neuromuscular blockade in the masseter compared with the adductor pollicis observed in this study has also been reported in patients undergoing coronary artery surgery after administration of 0.2 mg/kg vecuronium or a mixture of 0.1 mg/kg vecuronium and 0.1 mg/kg pancuronium.[14] Although differences in sensitivity may play a role in onset times when paralyzing doses are used, as was the case in the previous study,[14] they cannot explain the shorter time to maximum blockade observed in this study. A greater masseter blood flow and/or its shorter distance to the central circulation may account for the shorter onset time. This explanation has been proposed to account for the more rapid diaphragmatic blockade with vecuronium,[12] atracurium,[13] and succinylcholine.[13]

Indirect stimulation of the masseter muscle is easy to perform and could be achieved with most stimulators used in clinical practice. Its use would have three advantages: 1) the extent of jaw relaxation would be measured, 2) the time course of neuromuscular blockade would be probably closer to that of the well-perfused central muscles of respiration and of the upper airway, and 3) the diagnosis of residual paralysis would probably be easier because of the greater sensitivity of the masseter compared with the adductor pollicis. However, such a technique may be inappropriate to predict intubation conditions. This is because the masseter, which is more sensitive than the adductor pollicis, can be blocked with doses insufficient for adequate blockade of the other respiratory muscles, which are more resistant than the adductor pollicis. In addition, the safety of the technique should be evaluated before its clinical use is recommended. Possible damage to teeth, lips, and tongue should be seriously considered. This should be weighed against the consequences of ulnar nerve stimulation, which has not been reported to be associated with any sequelae.

If the effect of pancuronium on the masseter is representative of the action of other nondepolarizing agents, jaw relaxation can be obtained with a dose equal to or less than that required to block the adductor pollicis. Thus, assessment of jaw relaxation is a poor guide to the adequacy of intubating conditions because other, more resistant muscles (vocal cords, diaphragm) must be paralyzed to perform tracheal intubation under ideal conditions. However, the presence near the upper airway of a muscle with considerable sensitivity to neuromuscular relaxants indicates that airway patency might be affected by relatively small doses of relaxant. Because the termination of action of pancuronium is largely dependent on the decrease of plasma concentrations,[33] it is expected

that recovery of masseter neuromuscular function might still be incomplete when full recovery is present at the adductor pollicis.

References

1. Lee C, Katz RL: Neuromuscular pharmacology. A clinical update and commentary. Br J Anaesth 52:173–188, 1980
2. Ali HH, Savarese JJ: Monitoring of neuromuscular function. ANESTHESIOLOGY 45:216–249, 1976
3. Stiffel P, Hameroff SR, Blitt CD, Cork RC: Variability in assessment of neuromuscular blockade. ANESTHESIOLOGY 52:436–437, 1980
4. Caffrey RR, Warren ML, Becker KE: Neuromuscular blockade monitoring comparing the orbicularis oculi and adductor pollicis muscles. ANESTHESIOLOGY 65:95–97, 1986
5. Foldes FF, Monte AP, Brunn HM, Wolfson B: Studies with muscle relaxants in unanesthetized subjects. ANESTHESIOLOGY 22:230–236, 1961
6. Johansen SH, Jorgensen M, Molbech S: Effect of tubocurarine on respiratory and non-respiratory muscle power in man. J Appl Physiol 19:990–994, 1964
7. De Troyer A, Bastenier J, Delhez L: Function of respiratory muscles during partial curarization in humans. J Appl Physiol 49: 1049–1056, 1980
8. Gal TJ, Goldberg SK: Relationship between respiratory muscle strength and vital capacity during partial curarization in awake subjects. ANESTHESIOLOGY 54:141–147, 1981
9. Donati F, Antzaka C, Bevan DR: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. ANESTHESIOLOGY 65:1–5, 1986
10. Gilly H, Redl G, Werba A, Streinzer W, Draxler V, Spiss CK: Pharmacodynamics of vecuronium in two muscle groups: Vocal cord versus thenar neuromuscular blockade in man (abstract). ANESTHESIOLOGY 67:A614, 1987
11. Kharkevich DA, Fisenko VP: The effect of neuromuscular blocking agents on the acetylcholine receptors of different skeletal muscles. Arch Int Pharmacodyn Ther 251:255–269, 1981
12. Chauvin M, Lebreault C, Duvaldestin P: The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 66:117–122, 1987
13. Pansard JL, Chauvin M, Lebreault C, Gauneau P, Duvaldestin P: Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans. ANESTHESIOLOGY 67:326–330, 1987
14. Nakatsuka M, Franks P, Keenan RL: A method of rapid-sequence induction using high-dose narcotics with vecuronium or vecuronium and pancuronium in patients with coronary artery disease. J Cardiothorac Anesth 2:177–181, 1988
15. McMinn RMH, Hutchings RT, Logan BM: Color Atlas of Head and Neck Anatomy. Chicago, Year Book, 1981
16. Norman J: Drug receptor reactions. Br J Anaesth 51:595–601, 1979
17. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA: The effects of succinylcholine on mouth opening. ANESTHESIOLOGY 67:459–465, 1987
18. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA: Increased masticatory muscle stiffness during limb muscle flaccidity associated with succinylcholine administration. ANESTHESIOLOGY 69:11–16, 1988
19. Clemente CD: Anatomy of the Human Body (Gray's Anatomy), 30th American Edition. Philadelphia, Lea & Febiger, 1985, pp 447–451
20. Donlon JV, Savarese JJ, Ali HH, Teplik RS: Human dose–response curves for neuromuscular blocking drugs: A comparison of two methods of construction and analysis. ANESTHESIOLOGY 53: 161–166, 1980
21. Donlon JV, Ali HH, Savarese JJ: A new approach to the study of four non-depolarizing relaxants in man. Anesth Analg 53:934–938, 1974
22. Taylor DB, Prior RD, Bevan JA: The relative sensitivities of diaphragm and other muscles of the guinea pig to neuromuscular blocking agents. J Pharmacol Exp Ther 143:187–191, 1964
23. Day NS, Blake GJ, Standaert FG, Dretchen KL: Characterization of the train-of-four response in fast and slow muscle: Effect of *d*-tubocurarine, pancuronium, and vecuronium. ANESTHESIOLOGY 58:414–417, 1983
24. Padykula HA, Gauthier GF: The ultrastructure of the neuromuscular junction of mammalian red, white, and intermediate skeletal muscle fibers. J Cell Biol 46:27–41, 1970
25. Secher NH, Rube N, Secher O: Effect of tubocurarine on human soleus and gastrocnemius muscles. Acta Anaesthesiol Scand 26: 231–236, 1982
26. Chiu WW, Gergis SD, Sokoll MD: The effects of d-tubocurarine, pancuronium and atracurium on the responses of gastrocnemius and soleus muscles in the cat. Acta Anaesthesiol Scand 28:608–611, 1984
27. Johnson MA, Polgar J, Weightman D, Appleton D: Data on the distribution of fibre types in thirty six human muscles. An autopsy study. J Neurol Sci 18:111–129, 1973
28. Ringqvist M: Histochemical enzyme profiles of fibres in human masseter muscles with special regard to fibres with intermediate myofibrillar ATPase reaction. J Neurol Sci 18:133–141, 1973
29. Close RI: Dynamic properties of mammalian skeletal muscles. Physiol Rev 52:129–197, 1972
30. Kopman AF: The relationship between evoked electromyographic and mechanical responses following atracurium in humans. ANESTHESIOLOGY 63:208–211, 1985
31. Brouillette RT, Thach BT: A neuromuscular mechanism maintaining extrathoracic airway patency. J Appl Physiol 46:772–779, 1979
32. Gal TJ, Goldberg SK: Diaphragmatic function in healthy subjects during partial curarization. J Appl Physiol 48:921–926, 1980
33. Agoston S, Feldman SA, Miller RD: Plasma concentrations of pancuronium and neuromuscular blockade after injection into the isolated arm, bolus injection, and continuous infusion. ANESTHESIOLOGY 51:119–122, 1979