REVIEW ARTICLE

Muscle Relaxants in Anesthesia Practice: A Narrative Review

Zahid Hussain Khan*, Asghar Hajipour, Jayran Zebardast, Sami Raheem Hasan

Background: The objective of this study is to review the literature about the muscle relaxants in anesthetic practice.

Methods: In this review, our search includes, the studies performed and applied between 2000 and 2016. Therefore, for review of muscle relaxants in anesthesia practice in major surgeries, we referred to Google scholar, UpToDate, science direct, Ovid MEDLINE, Springer, free journals and the references of reviewed articles in the English language.

Results: Neuromuscular blocking agents are a chore and essential part of balanced anesthesia. These are used to facilitate endotracheal intubation and provide skeletal muscle relaxation during surgery. The main disadvantage, i.e. residual paralysis, can be treated or prevented by reversing of such a block.

Conclusion: The muscle relaxant plays an important role in adequate muscle relaxation, which allows efficient and safe surgery, requiring automated ventilatory control.

Keywords: Muscle relaxant; Anesthesia practice

Provision of anesthesia is an essential component of health services the worldwide. Access to safe anesthesia is considered an essential individual's right, and there are global standards for its safe practice [1]. Therefore, it is important for a health system to be able to provide safe and efficient anesthesia for a wide range of surgical procedures in children and adult. However, there are many challenges being faced in providing anesthesia particularly in developing world where facilities, equipment, and staff training are often inadequate [2]. In general anesthesia, the patients are unconscious and do not realize their surroundings, but in practice, general anesthesia is more than just a state of unawareness. Analgesia, amnesia, muscle relaxation, and limiting the autonomic reflexes are also important components [3]. There is no single drug used for general anesthesia that provides all elements of general anesthesia goals. Therefore, during general anesthesia, a combination of medicine including the volatile anesthetics, opiates, and not the least the muscle relaxants are used [3]. The availability of a number of different agents to produce each of desired components of general anesthesia is recommended in (World health organization) (WHO) guidelines on aesthetic infrastructures [2].

Classification of muscle relaxants

A-Non-depolarizing neuromuscular agents: These agents form most of the clinically related neuromuscular blockers. They act by competitively blocking the binding of acetylcholine to its receptors, and in some cases, they also directly block the ionotropic activity of the acetylcholine receptors [4]. They are a type of neuromuscular inhibitors that do not remove the polarization of the motor ending plate [4]. Nondepolarizing neuromuscular blocking drugs bind to the postsynaptic receptor in a competitive fashion by binding to one of the α subunits of the receptor [5]. The two extensively studied chemical series of synthetic nondepolarizing muscle relaxants are the benzylisoquinolinium series, in which the distance is maintained by linear diester-containing chains and the aminosteroid (steroidal) in which the distance is maintained by an androstane skeleton [6].

I-According to the chemical structures

A-The benzylisoquinolines nondepolarizing muscle relaxants

The structure activity relationships of bisbenzylisoquinolines have been described by Waser [7] and by Hill and associated [8] as follows:

1-The nitrogen atoms are incorporated into isoquinoline ring system. This bulky molecule favors nondepolarizing rather than depolarizing activity.

2- The interonium distance (distance between charged amines) is approximately 1.4 nm.

3- Both the ganglion- blocking and the histamine-releasing properties of dTc are probably due to the presence of the tertiary amine function.

4- Bisquaternary compounds are more potent than their monoquaternary analogs [9].

5- Substitution of the methyl groups on the quaternary nitrogen with bulkier groups causes a reduction in both potency and duration of action. The nondepolarizing muscle relaxants benzylisoquinolinium are d-tubocurarine, metocurine, doxacurium which are long acting, atracurium and cisatracurium that are intermediate acting and finally

mivacurium which is short acting [10]. They consist of two quaternary ammonium groups joined by a thin chain of methyl groups. They are more liable to a breakdown in the plasma than the aminosteroid compounds. They lack any vagolytic effect but are more likely to release histamine [11]. The methyl chain contains one or more chiral atoms, which lead to the existence of several stereoisomers of these drugs.

I- Atracurium: It is a bisquaternary ammonium benzylisoquinoline compound of the intermediate duration of action. It is degraded via two metabolic pathways. One of these pathways is the Hofmann reaction, a non-enzymatic degradation with a rate that increases as temperature and/or pH increases [12]. The second pathway is nonspecific ester hydrolysis. The enzymes involved in this metabolic pathway are a group of tissue esterases, which are distinct from plasma or acetylcholinesterase [13]. The same group of enzymes is involved in the degradation of esmolol and remifentanil. It has been estimated that two-thirds of atracurium is degraded by ester hydrolysis and one-third by Hofmann reaction. Subjects with abnormal plasma cholinesterase have a normal response to atracurium. No deleterious effect of laudanosine has been demonstrated conclusively in humans [13].

II- Cisatracurium: In an attempt to increase the margin of safety between the neuromuscular blocking dose and the histamine-releasing dose, a potent isomer of atracurium, cisatracurium, was identified. Like atracurium, its cardiovascular effects are manifested only at doses exceeding 0.4 mg/kg, but it's ED95 (0.05 mg/kg) is much lower. As a result, manifestations of histamine release are not seen in practice. The metabolism of cisatracurium is similar to that of atracurium, with Hofmann and ester hydrolysis both playing a role [13].

III- Doxacurium: It is a potent, long-acting bis-quaternary benzylisoquinoline compound that is not degraded by Hofmann elimination or ester hydrolysis. It has a prolonged elimination half-life (1 to 2 hours) and depends on the kidney and the liver for its disposition. Thus, duration of action is prolonged in the elderly and in subjects with impaired renal or hepatic function [14]. Doxacurium has a limited place in clinical practice because of its very slow onset and long duration of action. Nevertheless, its cardiovascular stability may be useful in patients with ischemic heart disease who are undergoing prolonged anesthesia or long-term mechanical ventilation of the lungs [15]. When infused for several days to patients in the ICU, recovery after stopping the infusion exceeded 10 hours.

IV- Mivacurium: It is a benzylisoquinoline derivative with a short duration of action that is hydrolyzed by plasma cholinesterase, like succinylcholine [16]. Contrary to succinylcholine, however, mivacurium produces nondepolarizing blockade. The drug is presented as a mixture of three isomers. Intubating doses are 0.2 or 0.25 mg/kg but intubating conditions are not as good as with succinylcholine [17].

B- Steroider nondepolarizing muscle relaxants

In these compounds, it is probably essential that one of two nitrogen atoms in the molecule be quaternized [18]. The presence of acetyl ester (acetylcholine- like moiety) is thought to facilitate its interaction with nACHRs at the postsynaptic muscle membrane [19-20].

I- Vecuronium: It is an intermediate-duration aminosteroid

neuromuscular relaxant without cardiovascular effects [21]. Vecuronium undergoes spontaneous deacetylation to produce 3-OH, 17-OH, and 3,17-(OH)2 metabolites. The most potent of these metabolites, 3-OH vecuronium, with about 60% of the activity of vecuronium, is excreted by the kidney and may be responsible, in part, for prolonged paralysis in patients in the ICU [12]. Vecuronium usually produces no cardiovascular effects with clinical doses [22]. It does not induce histamine release. Allergic reactions have been described, but no more frequently than after the use of other neuromuscular blocking drugs [23-24].

II- Pancuronium belongs to a series of bis-quaternary aminosteroid compounds. It is metabolized to a 3-OH compound, which has one-half the neuromuscular blocking activity of the parent compound. The ED95 of pancuronium is 0.07 mg/kg. The duration of action is long, being 1.5 to 2 hours after a 0.15 mg/kg dose. Clearance is decreased in renal and hepatic failure, demonstrating that excretion depends on both organs. The onset of action is more rapid in infants and children than in adults, and recovery is slower in the elderly [25].

III- Pipecuronium: Like pancuronium, it is a bis-quaternary compound. Its ED95 is slightly less (0.05 mg/kg) than that of pancuronium, and it is virtually without any cardiovascular effects. However, pipecuronium soon became obsolete because it had the drawbacks of versatility), and the absence of cardiovascular effects was also seen with the shorter-acting vecuronium and rocuronium [26].

IV- Rocuronium: Is an aminosteroid compound with structural similarity with vecuronium and pancuronium. Its duration of action is comparable with that of vecuronium, but its onset is shorter [27]. Rocuronium and rapacuronium are about 6 and 10 times less potent than vecuronium [28], Rocuronium has one-sixth the potency of vecuronium, a more rapid onset, but a similar duration of action and similar pharmacokinetic behavior. Most of the drug is excreted unchanged in the urine, bile, or feces [29]. No hemodynamic changes (blood pressure, heart rate, or ECG) were seen in humans. Anaphylactic reactions have been described, and a French study indicated that these events occurred more frequently with rocuronium than with other neuromuscular blocking agents [23].

V- Rapacuronium: It is also an aminosteroid compound that was introduced for clinical use in 1999. It was withdrawn in 2001 because of a high incidence of respiratory complications [30-33]. Being less potent than rocuronium, it had a more rapid onset of action. Following 1.5 mg/kg, good-to-excellent intubation conditions were produced at 60 seconds, mean clinical duration was 17 minutes, and spontaneous recovery to the train of four ratio of 0.7 occurred in 35 minutes [34].

B-Depolarizing blocking agents

A depolarizing neuromuscular block agent is a type of neuromuscular inhibitor which depolarizes the motor end plate [5]. These agents act by removing the polarization in the sarcolemma from skeletal muscle fiber. This continuous depolarization makes the muscle fiber impedance to further stimulation through acetylcholine [35]. Depolarizing blocking agents act through depolarizing a plasma membrane from muscle fiber, Look like acetylcholine [36]. However, these factors are more resistant to Deterioration by acetylcholinesterase, the responsible enzyme for degrading

acetylcholine, and thus can more persistently depolarize the muscle fibers [37]. The depolarization block has two phases. During the first phase (depolarizing stage), they cause muscular sclerosis (muscle twitches) whilst they are depolarizing the muscle fibers [38]. Eventually, after adequate depolarization has occurred, the second phase (desensitizing phase) sets in and the muscle is no longer responsive to acetylcholine released via the moto neurons. At this dot, a complete neuromuscular block has been realized. The ideal depolarizing block drug is succinylcholine (suxamethonium). This is the single drug that is used clinically. It has a quick start (30 seconds) but a very low duration of efficacy (5–10 minutes) due to of hydrolysis by various cholinesterases (such as butyrylcholinesterase in the blood) [39]. Succinylcholine was known as diacetyl choline because structurally it consisted of two acetylcholine molecules joined with a methyl group. Decamethonium is seldom used in the clinical practice.

Mechanism of action

Quaternary muscle relaxants are chemically related to nicotinic acetylcholine receptor and prevent or interfere with the linkage and influence of acetylcholine on a receptor. Each acetylcholine-receptor has two receptor sites and activation of a receptor requires that drug to be linked to both of them. Each receptor site is located at one of the two α-subunits of the receptor. Each of receptor site contains two subsidies, an anionic site that links to the cationic ammonium head and a location which links to the blocking agent via donating a hydrogen bond [40]. Nondepolarizing agents, a decrease in connecting of acetylcholine leads to a reduction in its influence and neuron transmission to the muscle. In general, it is acceptable that non-depolarizing agent blockage happens by as reversible competitive inhibition. That is, they link to the receptor as agonist and thus leaving few receptors available for acetylcholine to link [40-41]. Depolarizing agents generate their block through connecting and stimulating the acetylcholine receptor, initially, causing muscle contraction followed by paralysis [42]. They link to the receptor and cause depolarization through unlocking channels only such as acetylcholine does. This causes repetitive excitation that continues lengthier than a normal acetylcholine excitation and is most likely explained via the resistance of depolarizing agents to the enzyme acetylcholinesterase. The continuation depolarization and triggering of the receptors make the endplate impedance for activation via acetylcholine. Therefore, a normal neuron transition to muscle cannot cause constriction of the muscle because the endplate is depolarized and thereby the muscle paralyzed [40-41]. Connecting to the nicotinic receptor shorter molecules such as acetylcholine needs two molecules to stimulate the receptor, one at each receptive site. Decamethonium congeners, which prefer matching straight line (lowest energy state), typically extend the two receptive locations with a single molecule (linked inter-site). The maximal energy a molecule needs to bend and suit generally results in less potency [43].

Factors that are considered in selecting the muscle relaxants

Determining suitable situations for endotracheal intubation partially depends on the clinical condition presented to the anesthesiologist. In the case of an elective surgical procedure and if the patient did not have anything to eat for a suitable amount of time before surgery, the speed with which endotracheal intubation is achieved is less important. However, a case for which fast induction of anesthesia and endotracheal intubation is required, the option of muscle relaxant becomes more important [44]. It will be the latter situation that will dominate this summary. Regardless of the choice of muscle relaxant, there are five conditions that should be met in the whole situations:

1. The lungs should be full of oxygen,
2. An adequate dose of inhalation or agent intravenously administered drug, must be present to guarantee that the patient is adequately anesthetized.
3. Endotracheal intubation must be accomplished within 60 seconds, 4. Attention should be given for enacting those maneuvers that would shorten the onset of a muscle relaxant,
4. Cricoid pressure must is applied after injection of either the muscle relaxant or anesthetic if NPO period is inadequate [45].

The typical neuromuscular blocking agent

None of the presently available muscle relaxants meet the criteria for the ideal neuromuscular blocking agent as described through Savarese and Kitz [46]. They defined three types of relaxants: fast onset and short duration, intermediate duration, or long duration, all without side effects and with a nondepolarizing mechanism of action [47]. It has been recognized that the start of action of the relaxants depends on the potency of the component; i.e. the less potent the faster the onset [48]. Also, other requirements for typical relaxant have been defined: i.e. nondepolarizing mechanism of action, fast onset, noncumulative, without cardiovascular side effects or histamine release, prompt and complete reversal with anticholinesterases, and fast elimination from the body independent from renal and/or liver function or transformation into inactive metabolites [49]. Muscle relaxants seem to be accountable for 50% of the adverse reactions during anesthesia. The most frequent reactions are tachycardia, cardiovascular collapse, urticaria, and bronchospasm. Such reactions most frequently occur after succinylcholine, followed by the benzylisoquinoline relaxants, whereas they are rarely noticed after steroidal relaxants. Skin tests demonstrated the relative freedom of histamine release with the steroidal relaxants [50], especially pipecuronium, vecuronium are free from adverse effects. With rocuronium pain on injection and a slight hypertensive and tachycardia may happen. With rocuronium, a higher incidence of anaphylactic reactions has been reported than other relaxants reported in France, Norway and New Zealand. It is the substituted ammonium group in the relaxants that raised the allergic reactions. It has been proven that such an effect synchronizes with the use of pholcodine containing drugs [51-52]. Studies detect that pholcodine sensitizes the immune system, leading to increased IgE release. This drug is readily available in the mentioned countries and can explain the higher incidence of anaphylactic reactions to muscle relaxants and especially rocuronium in these countries.

Problem-related to muscle relaxants

Nowadays muscle relaxation is an irreplaceable component

of anesthesia, intensive and emergency care. Its use is indicated for endotracheal intubation, facilitation of surgery and immobilization of patients [53]. When administered appropriately it contributes to the safety of the patient, but when used inappropriately it causes driving to increased morbidity and mortality. A common problem with all relaxants is the vast variability in the pharmacodynamics, behavior that depends on numerous factors:

A-Pharmacological profile of relaxants.

B-Concurrent disease (liver, kidney information, neuromuscular)

C-Concurrent medication (antibiotics, anti-epileptics).

D-Body temperature.

E-Acid-base balance.

F-Type and depth of anesthesia.

G-Gender, age, and weight of patients.

Because all these factors can differ from patient to patient, the variability in effect of muscle relaxants is not surprising. Variability in effects may lead to residual paralysis that in turn may cause postoperative respiratory complications [54-56]. The incidence of postoperative residual paralysis is 40-50% frequently, despite routine administration of neostigmine [57-59]. There are three significant factors in preventing residual paralysis:

1-Only using the shorter acting muscle relaxants.

2-Routinely objective monitoring of neuromuscular block.

3-Routinely reversal of neuromuscular block

Discussion

It may be stated that the use of the muscle relaxants represents a tremendous advance in anesthetic practice. Before their introduction, muscular relaxation, particularly in abdominal surgery, was used to be attained by chloroform or ether anesthesia, but the complications following the use of these factors were so frequent as to warrant the use of other methods, including spinal analgesia, nerve block and infiltration with local anesthesia materials to produce muscular relaxation. The introduction of curare and the closely related set of drugs called as the "muscle relaxants" into anesthesia practice have eliminated these techniques. In anesthetic practice, neuromuscular block agents are used for intubation and operative muscle relaxation. The use of modern inhalational anesthesia such as sevoflurane is usually practiced in pediatric anesthetics for induction and endotracheal intubation. Laryngeal Mask Airway (LMA) is alternative to endotracheal intubation. A supraglottic device is usually used for elective surgical procedures in adults and children population.

Results

In clinical utilization, neuromuscular blockade drugs are used auxiliary to anesthesia to create paralysis, first to cripple the vocal cords and allowing intubation of the trachea, and secondly to improve the surgical field via inhibiting spontaneous ventilation and create relaxation of the skeletal muscles. Because the suitable dose of neuromuscular block drug may cripple muscles wanted for breath (i.e., the diaphragm), mechanical ventilation must be available to maintain sufficient ventilation [60]. Patients are still conscious of ache even after complete conduction block has occurred; thus, general anesthesia and/or analgesia must also be given to prevent awareness under anesthesia [61].

Quaternary ammonium muscle relaxants are the quaternary ammonium salts utilized as medicine for muscle relaxation, more commonly in anesthesia. It is needful to prevent spontaneous motion of muscle during surgical processes. Muscle relaxants block neuron transmission to muscle via preventing the nicotinic acetylcholine receptor. What they have in common, and is needed for their impact, is a structural existence of quaternary ammonium groups, commonly two. Some of them are found in nature and another is synthesized molecules [54,56,62]. Administration of anesthesia has become incredibly safe. The incidence of serious passive morbidity and mortality, just due to anesthesia, is becoming very rare. However, when a condition of morbidity or mortality does occur, it is frequently disastrous [62]. Inability to get a patent airway is the more common cause of dangerous anesthetic-induced morbidity and mortality. Some examples comprise an inadequate check of the airway preoperatively, unusual reactions to medication, like bronchospasm, technique difficulties. It has always been supposed that reducing the time between administration of anesthetic drugs and intubation will reduce the incidence of vomiting and aspiration of stomach contents [63]. Therefore, it seems that the ideal drug would be the one with no cardiovascular effects and having a quick onset. Further, having a predictable duration of action is desirable if the expectancy is to have the patient extubated and spontaneous ventilation ensuring postoperatively. It seems that the two perfect options would be rocuronium and/or cis-atracurium. To make these medicines maximally efficient, the appropriate dose and sufficient anesthesia must be delivered. Hopefully, a nondepolarizing equivalent to succinylcholine will shortly be available.

Neuromuscular blocking drugs used in pediatric anesthesia.

There are differences between pediatric and adults in the response to neuromuscular blockers. The results of modern studies of neuromuscular blockers in pediatric patients are generally consistent with previous studies regarding age-related differences. Continuous assessment of these drugs in pediatric patients will supply the best information regarding the changes of the effects of neuromuscular blockers in healthy and sick infants and children [64-65].

Adverse effects of neuromuscular blockade and their antagonists.

Between all the drugs used for general anesthesia, neuromuscular blockers appear to play an outstanding part in the occurrence of severe adverse reactions. It now appears likely that most severe adverse drug reactions that occur during anesthesia are immunologic in type. Hesitantly the life-threatening anaphylaxis reactions occur during anesthesia at rates of between one in 1000 and one in 25,000 anesthesia procedures, with the neuromuscular blockers participating in 80% of statuses. The mortality from this dangerous interaction ranges between 3.4 to 6%. Suxamethonium chloride (succinylcholine) was found to be the most dangerous agent [66]. Drug-special immunoglobulin E antibodies to suxamethonium chloride and other neuromuscular blockers have been shown. This sensitivity to neuromuscular blockers seems to be a long-lasting phenomenon. During anesthesia, the clinical

manifestations of an allergy reaction are often disguised. Increase in heart rate and circulatory collapse may be the only signs of an allergy reaction and they are readily misdiagnosed. Bronchospasm is reported to be existent in around 40% of cases [67]. Successful treatment of these patients involves stabilization during the acute interaction and avoidance of future reactions. The last is based on the identification of the causative drug and potentially cross-reactive components. The use of suxamethonium chloride is related with many other side effects, like fasciculations, myalgia, potassium release, changes in the heart, increases in intragastric pressure and intraocular pressure, and malignant hyperthermia [68]. Because of the risks of hyperkalemia and cardiac arrest, suxamethonium chloride administration in babies with an unknown muscle atrophy has been changed now and is avoided to reduce its use in children [69]. Although neuromuscular blockers are designed specifically to prevent nicotinic cholinergic receptors at the neuromuscular junction, many of muscarinic cholinergic receptors bind on ganglia and smooth muscle, while changing para sympathetic fibers related to tones also affect cardiac rate and airway [26]. Most benzylisoquinoline muscle relaxants can stimulate histamine release, especially when they are administered rapidly, which can lead to disorders of cardiovascular function [70]. In addition, nondepolarizing neuromuscular blockers have been implicated in causing generalized weakness after their long term administration to patients in the intensive care unit [71]. The problem with these adverse drug interactions is their unpredictable nature. Therefore, prompt recognition with appropriate therapy can help to improve the outcome.

Conclusion

The muscle relaxant plays an important role in adequate muscle relaxation, which allows efficient and safe surgery, requiring automated ventilatory control.

References

1. Bösenberg AT. Pediatric anesthesia in developing countries. Curr Opin Anesthesiol. 2007; 20(3):204-10.
2. Cherian M, Merry A, Wilson I. The World Health Organization and Anaesthesia. Anaesthesia. 2007; 62(s1):65-6.
3. Tonner P. Balanced anaesthesia today. Best Practice & Research Clinical Anaesthesiology. 2005; 19(3):475-84.
4. Bufler J, Wilhelm R, Parnas H, Franke C, Dudel J. Open channel and competitive block of the embryonic form of the nicotinic receptor of mouse myotubes by (+)-tubocurarine. J Physiol 1996; 495(1):83-95.
5. Buzello W, Diefenbach C, Nigrovic V. Muscle relaxants: a clinical update. Acta Anaesthesiol Scand Supplementum. 1995; 109:165-7.
6. Lee C. Structure, conformation, and action of neuromuscular blocking drugs. Br J Anaesth. 2001; 87(5):755-69.
7. Waser P. Chemistry and pharmacology of natural curare compounds. Neuromuscular Blocking and Stimulating Agents. Int Enc Pharmacol Ther. 1972; 14(1):205-39.
8. Hill SA, Scott RP, Savarese JJ. Structure-activity relationships: from tubocurarine to the present day. Baillière's Clinical Anaesthesiology. 1994; 8(2):317-48.
9. Gandiha A, Marshall I, PAUL D, SINGH H. Neuromuscular and other blocking actions of a new series of mono and bisquaternary aza steroids. Journal Pharmacy and Pharmacology. 1974; 26(11):871-7.
10. Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonists. Miller's anesthesia. 2005; 7:859-911.
11. Appiah-Ankam J, Hunter JM. Pharmacology of neuromuscular blocking drugs. Continuing Education in Anaesthesia Critical Care & Pain. 2004; 4(1):2-7.
12. Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonists.Miller anesthesia.2005; 859-911.
13. Fodale V, Santamaria L. Laudanosine, an atracurium and cisatracurium metabolite. Eur J Anaesthesiol. 2002; 19(7):466-73.
14. Basta SJ, Savarese JJ, Ali HH, Embree PB, Schwartz AF, Rudd GD, et al. Clinical pharmacology of doxacurium chloride. A new long-acting nondepolarizing muscle relaxant. Anesthesiology. 1988; 69(4):478-86.
15. Bevan DR. Newer neuromuscular blocking agents. Basic & Clinical Pharmacology & Toxicology. 1994; 74(1):3-9.
16. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott R, Sunder N, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology. 1988; 68(5):723-32.
17. Maddineni V, Mirakhur R, McCoy E, Fee J, Clarke R. Neuromuscular effects and intubating conditions following mivacurium: a comparison with suxamethonium. Anaesthesia. 1993; 48(11):940-5.
18. Buckett W, Hewett C, Savage D. Pancuronium bromide and other steroidal neuromuscular blocking agents containing acetylcholine fragments. J Medicinal Chemistry. 1973; 16(10):1116-24.
19. Bowman WC. Pharmacology of neuromuscular function: Butterworth-Heinemann; 2013.
20. durant nn, marshall ig, savage ds, nelson dj, sleigh t, carlyle ic. The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45, and other pancuronium analogues, in the cat. Journal Pharmacy and Pharmacology. 1979; 31(1):831-6.
21. McCoy EP, Maddineni VR, Elliott P, Mirakhur RK, Carson IW, Cooper RA. Haemodynamic effects of rocuronium during fentanyl anaesthesia: comparison with vecuronium. Can J Anesth. 1993; 40(8):703-8.
22. Goudsouzian NG, Martyn JJ, Liu LM, Gionfriddo M. Safety and efficacy of vecuronium in adolescents and children. Anesth Analg. 1983; 62(12):1083-8.
23. Mertes PM, Laxenaire M-C, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. Journal American Society of Anesthesiologists. 2003; 99(3):536-45.
24. Bhananker SM, O'Donnell JT, Salemi JR, Bishop MJ. The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: an analysis of food and drug administration reporting of adverse events. Anesth Analg. 2005; 101(3):819-22.
25. Bevan DR. Neuromuscular Blocking Agents François Donati.
26. Keegan RD. Muscle Relaxants and Neuromuscular. Veterinary Anesthesia and Analgesia. 2015:260-76.
27. Moore E, Hunter J. The new neuromuscular blocking agents: do they offer any advantages? Br J Anaesth. 2001; 87(6):912-25.
28. Naguib M, Samarkandi A, Bakhamees H, Magboul M, El-Bakry A. Comparative potency of steroidal neuromuscular blocking drugs and isobolographic analysis of the interaction between rocuronium and other aminosteroids. Br J Anaesth. 1995; 75(1):37-42.
29. Proost J, Eriksson L, Mirakhur R, Roest G, Wierda J. Urinary, biliary and faecal excretion of rocuronium in humans. Br J Anaesth. 2000; 85(5):717-23.
30. Naguib M. How serious is the bronchospasm induced by rapacuronium? Anesthesiology: Journal American Society of Anesthesiologists. 2001; 94(5):924-5.
31. Kron SS. Severe bronchospasm and desaturation in a child associated with rapacuronium. Journal American Society of Anesthesiologists. 2001; 94(5):923-4.
32. Meakin GH, Pronske EH, Lerman J, Orr R, Joffe D, Savaree AM, et al. Bronchospasm after rapacuronium in infants and children. Journal American Society of Anesthesiologists. 2001; 94(5):926-7.
33. Goudsouzian NG. Rapacuronium and bronchospasm. Anesthesiology. 2001; 94(5):727-8.
34. Sparr H, Mellinghoff H, Blobner M, Nöldge-Schomburg G. Comparison of intubating conditions after rapacuronium (Org 9487) and succinylcholine following rapid sequence induction in adult patients. Br J Anaesth. 1999; 82(4):537-41.
35. Miller cn. Implementation of medicinal leech preparation to investigate the connection between the motor neuron and muscle fiber via sharp electrode electrophysiology. 2011; (5):18-20.
36. Zaimis E, Head S. Depolarising neuromuscular blocking drugs. Neuromuscular junction: Springer; 1976. p. 365-419.
37. Cisterna BA, Cardozo C, Sáez JC. Neuronal involvement in muscular atrophy. Front Cell Neurosci. 2014; 8: 405.

38. Follansbee WP. The cardiovascular manifestations of systemic sclerosis (scleroderma). Current Problems In Cardiology. 1986; 11(5):244-98.
39. Brull SJ, Naguib M. Selective reversal of muscle relaxation in general anesthesia: focus on sugammadex. Drug Design, Development and Therapy. 2009;3: 119-21.
40. Bowman W. Neuromuscular block. Br J Pharmacol. 2006; 147(S1).
41. Brunton LL, Lazo JS, Parker KL. Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 2006.
42. Lee C. Goodbye suxamethonium! Anaesthesia. 2009; 64(s1):73-81.
43. Lee C, Jones T. Molecular conformation–activity relationship of decamethonium congeners. Br J Anaesth. 2002; 88(5):692-9.
44. Tranquilli WJ, Thurmon JC, Grimm KA. Lumb and Jones' veterinary anesthesia and analgesia: John Wiley & Sons; 2013.
45. Ganzberg SI. Emergency Management. Oral Sedation for Dental Procedures in Children: Springer; 2015. p. 195-209.
46. Savarese JJ, Kitz RJ, Ginsburg S. Neuromuscular blocking agents. Google Patents; 1980.
47. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, et al. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology: Journal American Society of Anesthesiologists. 1995; 82(5):1139-45.
48. Bowman W, Rodger I, Houston J, Marshall R, McIndewar I. Structure: action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat. Anesthesiology. 1988; 69(1):57-62.
49. Booij L, Crul J. A comparison of vecuronium with the hypothetical ideal neuromuscular blocking drug. Clinical experiences with Norcuron (Org NC 45, vecuronium bromide) Amsterdam: Excerpta Medica. 1983:3-8.
50. Robertson EN, Booij L, Fragen R, Crul J. Intradermal histamine release by 3 muscle relaxants. Acta Anaesthesiologica Scandinavica. 1983; 27(3):203-5.
51. Florvaag E, Johansson S, Öman H, Harboe T, Nopp A. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. Allergy. 2006; 61(1):49-55.
52. Harboe T, Johansson S, Florvaag E, Öman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. Allergy. 2007; 62(12):1445-50.
53. Godoy DA, Piñero GR. Intensive Care in Neurology and Neurosurgery: Pathophysiological Basis for the Management of Acute Cerebral Injury: SEEd; 2013:1305-1327.
54. Berg H, Viby-Mogensen J, Roed J, Mortensen C, EngbÊk J, Skovgaard LT, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. Acta Anaesthesiologica Scandinavica. 1998(41):1-9.
55. Eriksson LI. The effects of residual neuromuscular blockade and volatile anesthetics on the control of ventilation. Anesth Analg. 1999; 89(1):243-51.
56. Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, et al. Impact of anesthesia management characteristics on severe morbidity and mortality. Anesthesiology: Journal American Society of Anesthesiologists. 2005; 102(2):257-68.
57. Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. Anesth Analg. 2005; 100(6):1840-5.
58. Baurain M, Hoton F, d'Hollander A, Cantraine F. Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium? Br J Anaesth. 1996; 77(4):496-9.
59. Kim KS, Lew SH, Cho HY, Cheong MA. Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. Anesth Analg. 2002; 95(6):1656-60.
60. Keys TE. Anaesthesia: essays on its history: Springer Science & Business Media; 2012.
61. Eriksson LI. Miller's Anesthesia: 1: Elsevier Health Sciences; 2009:859-912p.
62. Euliano TY, Gravenstein JS, Gravenstein N, Gravenstein D. Essential anesthesia: from science to practice: Cambridge University Press; 2011.
63. Hopkin DB. Hazards and errors in anaesthesia: Springer Science & Business Media. 2012; (2):89-95.
64. Hemmerling TM, Donati F. Neuromuscular blockade at the larynx, the diaphragm and the corrugator supercilii muscle: a review. Canadian Journal of Anesthesia. 2003; 50(8):779-94.
65. Fisher D. Neuromuscular blocking agents in paediatric anaesthesia. Br J Anaesth. 1999;83(1):58-64.
66. Mertes P-M, Laxenaire MC. Adverse reactions to neuromuscular blocking agents. Current Allergy and Asthma Reports. 2004; 4(1):7-16.
67. Mertes P, Aimone-Gastin I, Gueant-Rodriguez R, Mouton-Faivre C, Audibert G, O'Brien J, et al. Hypersensitivity reactions to neuromuscular blocking agents. Current Pharmaceutical Design. 2008; 14(27):2809-25.
68. Nagelhout JJ. Neuromuscular Blocking Agents, Monitoring. Nurse Anesthesia-E-Book. 2013:158.
69. Martyn JAJ, Richtsfeld M. Succinylcholine-induced Hyperkalemia in Acquired Pathologic StatesEtiologic Factors and Molecular Mechanisms. Anesthesiology: Journal American Society of Anesthesiologists. 2006; 104(1):158-69.
70. Claudius C, Garvey L, Viby-Mogensen J. The undesirable effects of neuromuscular blocking drugs. Anaesthesia. 2009; 64(s1):10-21.
71. Barohn RJ, Jackson CE, Rogers SJ, Ridings LW, McVey AL. Prolonged paralysis due to nondepolarizing neuromuscular blocking agents and corticosteroids. Muscle & Nerve. 1994; 17(6):647-54.