



Factors that affect the onset of action of non-depolarizing neuromuscular blocking agents

Yong Byum Kim¹, Tae-Yun Sung², and Hong Seuk Yang³

Department of Anesthesiology and Pain Medicine, ¹Gil Medical Center, Gachon University College of Medicine, Incheon, ²Konyang University Hospital, Konyang University College of Medicine, Daejeon, ³Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Neuromuscular blockade plays an important role in the safe management of patient airways, surgical field improvement, and respiratory care. Rapid-sequence induction of anesthesia is indispensable to emergency surgery and obstetric anesthesia, and its purpose is to obtain a stable airway, adequate depth of anesthesia, and appropriate respiration within a short period of time without causing irritation or damage to the patient. There has been a continued search for new neuromuscular blocking drugs (NMBDs) with a rapid onset of action. Factors that affect the onset time include the potency of the NMBDs, the rate of NMBDs reaching the effect site, the onset time by dose control, metabolism and elimination of NMBDs, buffered diffusion to the effect site, nicotinic acetylcholine receptor subunit affinity, drugs that affect acetylcholine (ACh) production and release at the neuromuscular junction, drugs that inhibit plasma cholinesterase, presynaptic receptors responsible for ACh release at the neuromuscular junction, anesthetics or drugs that affect muscle contractility, site and methods for monitoring neuromuscular function, individual variability, and coexisting disease. NMBDs with rapid onset without major adverse events are expected in the next few years, and the development of lower potency NMBDs will continue. Anesthesiologists should be aware of the use of NMBDs in the management of anesthesia. The choice of NMBD and determination of the appropriate dosage to modulate neuromuscular blockade characteristics such as onset time and duration of neuromuscular blockade should be considered along with factors that affect the effects of the NMBDs. In this review, we discuss the factors that affect the onset time of NMBDs.

Key Words: Acetylcholine receptor, Anesthesia, Drug interactions, Neuromuscular junction, Neuromuscular monitoring, Non-depolarizing neuromuscular blocking agents, Onset time, Pharmacodynamics, Pharmacokinetics.

Introduction

Neuromuscular blockade in anesthetic management refers to the phenomenon in which non-depolarizing neuromuscular blocking drugs (NMBDs) block the binding of neurotransmitters to a subunit of the nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction of the motor neurons of skeletal muscle. Such a neuromuscular blockade plays an important role in the safe management and maintenance of patient airways, surgical field improvement, and respiratory management [1]. The ideal NMBD should have a rapid onset and short duration of action, no cardiovascular side effects, no accumulation in the body, no active metabolites, organ-dependent drug metabolism

Corresponding author: Hong Seuk Yang, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olymplic-ro 43-gil, Songpa-gu, Seoul, 05505 Korea
Tel: 82-2-3010-3865, Fax: 82-2-470-1363
Email: hsyang@amc.seoul.kr
ORCID: <https://orcid.org/0000-0003-2023-8705>

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and elimination, and an available and adequate antagonist [2].

The onset of NMBD action depends on the degree of twitch depression after administration [3]. Although succinylcholine has long been used in clinical trials, it has gradually been removed from clinical practice, except in emergencies, because of its adverse effects [4]. Several studies have been conducted to develop new NMBDs with an onset of action similar to that of succinylcholine [2,5].

The Clinical Importance of Rapid Onset of NMBD

The purpose of rapid-sequence induction of anesthesia and intensive care is to obtain a stable airway, adequate depth of anesthesia, and appropriate respiration within a short period of time without causing irritation or damage to the patient [6]. Laryngoscope manipulation and airway management must proceed with ease; if a stable depth of anesthesia and neuromuscular blockade is not maintained during induction of anesthesia, the time required for airway management is prolonged and excessive pressure may be applied to ensure adequate ventilation. The excess inhaled air causes expansion of the stomach, which can then lead to regurgitation and aspiration of stomach content into the lung. This in turn results in increased morbidity and mortality, with pulmonary complications such as airway obstruction, atelectasis, pneumonia, and hypoxia that cause damage to the major organs, such as the heart and brain [7]. Rapid-sequence induction of anesthesia is also indispensable for emergency surgery and obstetric anesthesia, for which preoperative fasting is unlikely.

Succinylcholine has played an important role in clinical practice as a neuromuscular blocker with a rapid onset of action for the past 80 years. However, the use of succinylcholine results in myalgia; elevated gastric, intracranial, and intraocular pressure; as well as hyperkalemia, myoglobinemia, myoglobinuria, and malignant hyperthermia. Thus, there has been a continued search for new NMBDs that have a rapid onset of action but without adverse effects [4].

To obtain a rapid onset of action, the dosage of NMBDs can be increased, which also increases the duration of action. However, with the use of the new selective antagonist sugammadex and monitoring of neuromuscular function, neuromuscular block induced by aminosteroid NMBDs can be reversed safely [8,9].

Factors that Affect Onset Time

Onset time and potency

There is an inverse relationship between the onset time and

potency of NMBDs, and changes in the degree of binding of NMBDs to nAChR can also alter their onset time [10,11]. Thus, administering a large amount of an NMBD may accelerate the onset of action, making it comparable to succinylcholine [12,13]. NMBDs should bind to 70–90% or more of nAChRs to block neuromuscular function at the neuromuscular junction. If the drug potency is low, administering a large dose can lead to binding to nAChRs among a large number of molecules, which then also leads to a rapid onset of action [14].

In a comparison of potency and onset time, the order of decreasing potency was as follows: rocuronium > atracurium > vecuronium > cisatracurium > pancuronium [15,16]. If potency is high, the onset time is delayed and recovery is slow, because removal of the NMBD by buffered diffusion at the neuromuscular junction is slow [16].

Rate of NMBDs reaching the effect site

If blood flow to the muscle is considerable, the onset of action will be rapid, but if it is decreased, onset will be delayed. Compared to laryngeal muscle and the adductor pollicis, the onset time for laryngeal muscles is faster because of the shorter distance and greater blood flow from the heart [17]. In addition, the onset time for the orbicularis oculi is faster than that for the adductor pollicis, which is one of the muscles more suitable for monitoring neuromuscular function during tracheal intubation [18].

Administration rate

Factors associated with the route of drug administration can speed up the onset of action. Oral administration of sufficient fluid (1,500 ml) 2 h before surgery can prevent dehydration and thus prolong the onset of action [19]. In terms of intravenous administration, the onset is accelerated if the drug is injected into a central blood vessel, particularly the pulmonary artery, rather than a peripheral blood vessel [20]. In addition, the site of administration should be elevated above the heart or a catheter with a large inner diameter should be used to rapidly achieve a high target concentration of NMBD [21].

Onset time by dose control

Mass administration method

The dose of NMBDs administered is based on the amount of ED95 that can suppress twitch height by 95%. The dose required for intubation is 2–3 times the ED95 amount [22,23]. As the dose increases, depression of the twitch response is accelerated [22,24].

Mixed administration method

The purposes of this method are to reduce side effects, speed up the onset of action, and shorten the duration of action. For example, combined administration of mivacurium and rocuronium may result in reduced side effects and enhanced neuromuscular blocking effects [25]. However, it is not the preferred approach, because new NMBDs with a more rapid onset of action and short duration of action, as well as available selective antagonists, are available.

Precurarization (priming principle)

According to the margin of safety theory, more than 75–80% of nAChR should be combined with a neuromuscular blocking agent to cause muscle paralysis. Thus, 10% of the dose should be administered initially to bind with some nAChR [26–28]. The precurarization regimen varies depending on the type of NMBD used, the administration interval, the initial dose, and the total dose [29,30]. However, in the case of sensitive patients, visual disturbances, difficulty swallowing, lung aspiration, respiratory weakness, and complete paralysis (albeit rare) may occur before the onset of action [31,32].

Timing methods

Timing approaches can also be used to promote the onset time, but this is not preferred in clinical practice because of the possibility of creating discomfort during induction of anesthesia [33].

Combining drugs to increase cardiac output

Cardiotonic drugs increase the circulating blood volume by accelerating cardiac output and blood pressure.

- i. Ephedrine: Ephedrine increases cardiac output, which causes the neuromuscular blocker to reach the effect site quickly, leading to a rapid onset of action in proportion to its dose [34].
- ii. Esmolol: This selective beta blocker has negative inotropic and chronotropic effects. Combining this drug with NMBDs may delay the onset of action [35].

Type of muscle

Skeletal muscles are classified as type I (slow twitch, high oxidative) or type II (fast twitch, low oxidative) depending on their histology. Neonates and infants have more type II muscles than type I muscles and are more sensitive to NMBDs, showing a faster onset of action than adults [36,37].

Metabolism and Elimination of NMBDs

The metabolism and elimination of NMBDs play an impor-

tant role in maintaining adequate blood levels for the appropriate onset time. Time-course changes in plasma concentration after the administration of neuromuscular blockers differ according to characteristics of each NMBD. Increased the concentration and/or reached the maximum concentration at the effect site is dependent on the time course of the muscle relaxant in the plasma, the blood flow to the muscle, and the volume of interstitial space in the muscle because NMBDs are water soluble and pharmacologically active in the extracellular space. Reductions in blood levels are affected by redistribution, excretion, and metabolism and vary for each NMBD [36].

Metabolism

Metabolites of the ideal neuromuscular blocker should not have neuromuscular blocking effects per se but may differ depending on the nature of the NMBD. Only about 1% of rocuronium is metabolized, but most NMBDs are broken down extensively so that their action of duration is shortened [12,37]. Mivacurium is hydrolyzed rapidly by plasma cholinesterase, whereas atracurium and cisatracurium are metabolized by Hofmann elimination and ester hydrolysis. If NMBDs are eliminated rapidly because of their fast metabolism, administering large doses of NMBDs can accelerate the onset time [12,38,39].

Clearance

NMBDs with rapid plasma clearance are associated with a rapid onset of action. If the metabolism and redistribution of the drug progresses rapidly, its concentration in the blood will decline rapidly to the point of balance between the plasma concentration and the effect site fraction. Thus, higher doses of NMBDs will be required because the concentration of NMBDs at the effect site is reduced rapidly [40]. Atracurium and vecuronium, which have an intermediate duration of action, decrease their concentration in the blood more rapidly than do other NMBDs. However, their maximum effect occurs more rapidly than their concentration in the blood decreases, there is less of an effect on onset timing [11]. The mechanism of action of mivacurium and succinylcholine can be explained by this. For example, the onset of succinylcholine is delayed in patients with atypical plasma cholinesterase [11,40].

Buffered Diffusion to the Effect Site

Buffered diffusion refers to the process by which NMBDs spread to the neuromuscular junction from the blood. Factors that may affect buffered diffusion include the nerve–muscle contact area, the degree of muscle membrane folding, quantal content, the distribution of the contact area and the transverse

width of individual nerve–muscle contacts, the type of muscle, and temperature [41,42].

The onset of action at the neuromuscular junction depends on the degree of lipophilicity, binding to proteins, the rate at which the drug reaches the neuromuscular junction, the potency of the drug, its metabolism, and its excretion [43]. NMBDs reach their maximum plasma concentration immediately after intravenous administration; however, the maximal blocking effect may be delayed for most NMBDs. This delayed response is due to the efficacy fraction of the drug (its effect in proportion to its concentration), which is influenced by separation of the neuromuscular junction from the plasma or central compartment. Reaching the efficient fraction from the central fraction in the plasma is affected by the rate constant (Keo); the higher the Keo value, the faster the onset of action. Keo of rapacuronium is 2.4 times that of rocuronium and 3.4 times that of vecuronium in the adductor pollicis; it is 2.4 times that of rocuronium and 3.5 times that of vecuronium in the laryngeal adductors [41,42].

Affinity of the nAChR Subunit

An increase in the number of free molecules of NMBD that bind to the nAChR subunit at the neuromuscular synaptic cleft accelerates the onset of action. This affinity depends on the structure of the nAChR subunit [44,45]. The nAChR to which NMBDs bind consists of five subunits, *i.e.*, $\alpha_2\beta\delta\epsilon$ in the adult type and $\alpha_2\beta\delta\gamma$ in the fetal type. The strength of binding of the two alpha subunits to acetylcholine (ACh) or NMBDs also differs about 100-fold between the two alpha subunits because the different affinities of the gamma and epsilon subunits [46,47]. In nerve damage caused by burns and immobilization, the nAChR is composed of five $\alpha 7$ subunits and is resistant to NMBDs, because there are five sites to which the NMBD can bind [44,45]. In this way, changes in the nAChR type among various neuromuscular diseases or conditions, such as burns, immobilization, or myasthenia gravis, with increased or decreased numbers of nAChRs also change the onset time of NMBDs [48].

Drugs That Affect ACh Production and Release at the Neuromuscular Junction

The amount of ACh at the neuromuscular junction and drugs that move to the nerve endings to enhance release or to increase or decrease the synthesis of ACh by reabsorbing the choline degraded after release also affect the onset of action. Corticosteroids are used commonly in clinical practice. Corticosteroids have a direct mechanism of action on motor nerve axons, increasing ACh synthesis and spontaneous as well as stimulated release of ACh, thereby improving muscle performance but also preventing neuromuscular block. The recovery

of neuromuscular block was accelerated when 8 mg dexamethasone was administered 2–3 h before surgery [49]. Long-term exposure to both corticosteroids and NMBDs decreases nAChR at the neuromuscular junction and increases resistance to NMBDs. There is a slight difference between aminosteroids and benzylisoquinolinium types of NMBDs in response to long-term corticosteroid administration [50,51]. Long-term (> 4 weeks) administration of prednisolone in patients with chronic inflammatory bowel disease slowed the onset of action of rocuronium by 35% and reduced its duration of action by 25–30%, whereas there were no differences in the onset time of atracurium, although its duration of action was reduced by 20% [50–52].

Drugs That Inhibit Plasma Cholinesterase

Plasma cholinesterase is an enzyme that degrades ACh, which is released from the synaptic cleft of the neuromuscular junction. The enzyme may be defective because of congenital or acquired conditions. If plasma cholinesterase activity is abnormal, the metabolism of drugs such as mivacurium and succinylcholine is affected. There is no effect on ACh synthesis at the neuromuscular junction, but its degradation is slow, and the concentration of ACh is increased, so neuromuscular blockade may be altered [53,54]. Drugs that are metabolized by plasma cholinesterase, such as ester-type local anesthetics (e.g., procaine) and steroid-type induction agents (e.g., propanidid), substantially reduce the amount of available plasma cholinesterase and thus affect the activity of NMBDs [44,54]. This can potentiate the onset time of mivacurium.

NMBDs also inhibit plasma and erythrocyte cholinesterases. These inhibitory actions are partly competitive, partly noncompetitive, and reversible, decreasing as the concentration of ACh increases [55]. This cholinesterase inhibitory effect is not related to the expression of NMBDs, except that mivacurium is degraded by plasma cholinesterase. Thus, in cases in which plasma cholinesterase levels may be affected, dose control and monitoring of neuromuscular function are required [56,57].

Presynaptic Receptors Responsible for the Release of ACh at the Neuromuscular Junction

Several types of receptors are found at neuromuscular presynaptic sites. Some of these receptors interact to control the release of ACh during rest or stimulation [58,59]. For example, muscarinic ACh receptors (AChRs), neuronal nicotinic cholinergic receptors, and purinergic receptors interact in the presynaptic neuronal region. Muscarinic AChRs primarily affect muscle tension in smooth muscle, but they also have modulating effects at the neuromuscular junction of striated muscle. Although some types of muscarinic receptors have stabilizing

or structural functions in nerve endings, M1 and M2 receptors, respectively, facilitate and inhibit ACh release. When M1 receptors are blocked by specific antagonists, the evoked release of ACh and spontaneous miniature endplate potential (mEPP) frequency are reduced, but the evoked release of ACh is increased when M2 receptors rather than M1 receptors are blocked [60]. Atropine acts as a nonspecific muscarinic blocker to modulate ACh release by inhibiting both M1 and M2 receptors, which decreases the spontaneous mEPP frequency and increases the evoked release of ACh [59,61]. In addition, presynaptic purinergic A1 and A2A receptors also modulate the spontaneous and evoked release of ACh. During spontaneous or evoked release of ACh from the presynaptic terminal, the concentration of the endogenous purinergic agonist adenosine is increased at the neuromuscular junction, controlling ACh release through a feedback mechanism [62].

Factors that Affect Muscle Contractility

Muscle weakness, nerve conduction, and muscle contractility also affect neuromuscular blockade [63].

Local anesthetics

Local anesthetics may reduce muscle contractility by blocking nerve conduction and impairing the sensitivity of nAChR [11]. Intravenous lidocaine accelerates the action of rocuronium as well as facilitates intubation [64,65].

Antibiotics

Antibiotics such as aminoglycoside antibiotics and tetracycline, polymyxin B, and lincomycin may enhance the action of NMBDs or may have a neuromuscular blocking effect [63]. These antibiotics lead to a leftward shift in the dose–response curve and a rapid onset time of NMBDs [66,67].

Magnesium and calcium

Magnesium reduces muscle contraction in proportion to its concentration in the blood and accelerates the effects of NMBDs [68,69]. In contrast, calcium increases ACh release while maintaining action potential at the neuromuscular junction [70].

Anticonvulsants

Short-term exposure to anticonvulsants such as phenytoin increases susceptibility to NMBDs, but resistance develops with long-term exposure [71].

Intravenous anesthetics

Intravenous anesthetics have no direct interaction with neuromuscular blockers, but etomidate (which has fewer cardiovascular effects) and ketamine (which acts on GABA receptors) may have indirect effects [72,73]. A single bolus dose of intravenous anesthetic (e.g., propofol) can decrease blood pressure and cardiac output, delaying the onset of action of NMBDs, but it also decreases muscle tone, which can accelerate the onset of action [74].

Inhalation anesthetics

Inhalation anesthetics improve the action of NMBDs by inhibiting muscle contraction, but there are few differences between anesthetics, because they do not saturate the body sufficiently during induction of anesthesia [63,75].

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors inhibit the action of NMBDs. Theophylline-related drugs (such as caffeine and aminophylline), nonselective phosphodiesterase inhibitors, and phosphodiesterase III inhibitors (such as milrinone) increase the contractility of cardiac muscle and skeletal muscle in patients with heart failure. This antagonizes the effects of NMBDs, resulting in delayed onset time and shortening of the duration of action [76,77].

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors)

Statins decrease the risk of cardiovascular disease by decreasing low-density lipoprotein cholesterol (LDL-C) levels. However, statins increase muscle creatine kinase (CK) with muscle toxicity. With long-term administration, the onset time of NMBDs is delayed and the duration of action is reduced [78,79].

Toxins

Botulinum and tetanus toxins block the release of ACh at the nerve terminal of the neuromuscular junction, resulting in muscle weakness or paralysis [45,80,81]. This may promote the onset of action of NMBDs.

Antiemetics

5-Hydroxytryptamine (5-HT₃) receptor antagonists, which assemble pseudosymmetrically in pentameric structures with muscle nAChR, potentiate the blocking effects of neuromus-

cular transmission in proportion to their dose [82,83]. 5-HT₃ receptor antagonists are more potent with the fetal-type gamma subunit than with the adult-type epsilon subunit. The interaction of 5-HT₃ receptor antagonists with NMBDs in adult nAChR is proportional to the antiemetic potency (hydrodolasetron >> granisetron > dolasetron > ondansetron) [84]. Metoclopramide inhibits the secretion of acetylcholine at the neuromuscular junction and potentiates the effects of NMBDs [85].

Site and Methods for Monitoring of Neuromuscular Function

Mechanomyography is the gold standard for monitoring neuromuscular function, but electromyography, acceleromyography, kinemyography, and phonomyography are also used in clinical practice; acceleromyography in particular is easy to use [86]. Acceleromyography may differ in dose and response from the time of maximal onset of action to the time of complete neuromuscular blockade (the absence of any twitch response). Thus, to minimize the effect, 50 s of tetanic stimulation is recommended for calibration [22]. The method can involve double-burst stimulation along with single twitch and train-of-four (TOF) stimulation. TOF stimulation can be analyzed faster than a single twitch [87,88]. Depending on the location of the muscle used to monitor neuromuscular function, muscle blood flow may differ, affecting the onset time. For example, the diaphragm and laryngeal muscle are more resistant to the NMBDs than the adductor pollicis. However, the onset of block in the diaphragm is earlier than at the adductor pollicis muscle [89,90].

Individual Variability

Individual differences in terms of age, sex, smoking, living environment, race, circadian variation, nutrition, obesity, and body temperature can affect the onset time of neuromuscular blockers. If there is resistance to NMBDs, the onset of action will be delayed, whereas sensitivity to NMBDs will shorten the onset of action [11].

Age and sex

The onset time of NMBDs is faster in young adults than in the elderly and in women than in men. In the elderly, the onset of action is delayed in proportion to aging from over 60 years to over 80 years of age [90-92].

Smoking

Cessation of smoking for 10 h before the administration of anesthesia delays the onset time and decreases the maintenance

dose of NMBDs compared to what is seen in smokers or non-smokers [93].

Geographic location

Individuals differ in their response to NMBDs depending on altitude. For example, people who live in high-altitude areas such as Tibet experience a slower onset than people who live in lower plains regions [94]. That is, regional differences affect the mechanism of action and dose of NMBDs required.

Body temperature

Hypothermia increases susceptibility to NMBDs, enhancing the duration of action and delaying the onset of action [16,95]. When an individual's core temperature decreases, the adductor pollicis does not affect the twitch height, even if the muscles are warmed regionally, because the influence of the core temperature is greater than that of the local muscle temperature. When the core temperature is reduced by 2.5°C, neuromuscular blockade can be enhanced by 45–50%. Thus, the core temperature should be maintained at 35°C, and the temperature at the peripheral site should be maintained at 32°C or higher [95-97].

Nutrition

In obese individuals, administration of NMBDs based on actual body weight results in a rapid onset of action and a long duration of action; thus, the dose is determined on the basis of ideal body weight rather than actual body weight [98,99]. In patients with poor nutritional status, depressed plasma protein levels, decreased muscle mass, and reduced water content in the muscles may delay the onset of action of NMBDs and shorten the duration of action but not the recovery time [99].

Circadian variation

When rocuronium (0.6 mg/kg) was administered based on lean body mass, the mean duration of action was 50 min at 08:00–11:00 and 29 min at 14:00–17:00. If these variations are fully determined, it will be possible to accelerate onset time while prolonging the duration of action [100].

Coexisting Disease

Diseases that cause changes in the nAChR subunit

Depending on the comorbid disease, up- and downregulation of the nAChR subunit may result in faster or slower expression of NMBDs [48]. A disease that results in a decreased number of

nAChRs, such as myasthenia gravis, shows an accelerated onset time. In cases of neuronal injury, burns, or immobilization, the number of neuronal nAChRs consisting of five $\alpha 7$ subunits is upregulated; these receptors are resistant to NMBDs. These changes in nAChRs reach a peak 2–3 weeks after the injury and then gradually return to normal [45,48]. In particular, in burn patients, the expression of action is delayed regardless of the plasma cholinesterase activity, postburn days, or size of the injury. This is because of a decreased affinity of nAChR, which is presumed to be due to the upregulation of nAChR, but the delayed recovery is presumably due to decreased activity of ACh-esterase [30,48].

Electrolyte and acid–base balance

In the case of electrolyte imbalances, such as hypocalcemia, hypokalemia, hypermagnesemia, and respiratory acidosis, the action of aminosteroid-type NMBDs may be enhanced, whereas the effects of the benzylisoquinolinium derivative cisatracurium are unclear, given that it is prone to Hoffman degradation and ester hydrolysis [101].

Hemodilution

To reduce the amount of blood transfused before surgery, dilution of the blood according to a patient's condition may lead to a decrease in plasma protein concentrations, a change in the concentration of electrolytes such as potassium and calcium, a change in the volume of distribution, and a change in Keo. In a previous study, acute isovolemic hemodilution accelerated the onset time and prolonged the duration of action of NMBDs [102].

Sepsis

Although there is no difference in the onset of action of NMBDs in sepsis, recovery may be delayed because ACh-esterase activity is reduced at the neuromuscular junction, the acid–base balance is disturbed, and hemodynamic impairments are

present [103].

Liver and kidney function

Liver disease prolongs the duration of action of rocuronium but has less of an effect on its onset of action. In patients with impaired renal function, there is no effect on the onset time, and the duration of action is prolonged [104,105].

Pregnancy

Physiological and pathological changes occur during pregnancy, leading to pharmacological changes [106]. However, there were no differences in the onset times of non-depolarizing neuromuscular blocking agents in a comparison of women who were not pregnant and women immediately after giving birth [107].

Cardiac disease

Myocardial infarction and cardiac failure are associated with decreased cardiovascular function and delayed onset of action. Patients with congenital heart disease (e.g., ventricular septal defect, atrial septal defect) often have a left-to-right or right-to-left shunt that affects the onset of action as a result of pharmacokinetic and pharmacodynamic changes of NMBDs [108].

Conclusions

NMBDs with a rapid onset of action are expected to be introduced in the next few years, and NMBDs with a lower potency will continue to be developed, even if the ED₉₅ of the new drugs is similar to or greater than that of rocuronium. Anesthesiologists should be aware of the use of NMBDs in the management of anesthesia as well as the patient's condition. The choice of NMBD and determination of the appropriate dosage to modulate neuromuscular blockade characteristics, such as the onset time and duration of neuromuscular blockade, should be considered.

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