59

Nondepolarizing Neuromuscular Blocking Agents

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The introduction of nondepolarizing neuromuscular blocking agents (NMBAs) into clinical practice marked a significant advance in anesthesia and surgery. The past 20 years have seen a significant evolution in nondepolarizing NMBAs, with the appearance of new drugs, free from many of the undesirable side effects of their predecessors. The most dramatic change has been the recent introduction of a novel reversal agent, sugammadex, into clinical practice in the United States. Sugammadex rapidly reverses the action of aminosteroid class NMBAs, such as rocuronium, thus providing a viable alternative to succinylcholine for rapid-onset but short-acting muscle relaxation.

Mechanism of Action

By competing with acetylcholine (ACh) for binding to nicotinic receptor α subunits, nondepolarizing NMBAs cause receptor inhibition, thus resulting in skeletal muscle relaxation. The nondepolarizing NMBAs may also be capable of directly blocking the ion channel, stopping the flux of Na^+ through the ion pore. Some nondepolarizing NMBAs block Na^+ channels on prejunctional nicotinic ACh receptors, interfering with mobilization of ACh from sites of synthesis. Calcium-dependent release of ACh is not affected.

Characteristics of Neuromuscular Nondepolarizing Blockade

Muscle relaxation caused by nondepolarizing NMBAs is characterized clinically by a train-of-four T4/T1 ratio of less than 1 (with < 0.7 representing adequate surgical relaxation), tetanic "fade," posttetanic potentiation, absence of fasciculations, potentiation by other nondepolarizing NMBAs, and antagonism of the block by acetylcholinesterase inhibitors. Blockade by nondepolarizing NMBAs occurs more rapidly in the laryngeal adductors, diaphragm, and masseter than in the adductor pollicis. The ED_{95} is the dose needed to produce 95% suppression of a single-twitch response evoked by a peripheral nerve stimulator in the presence of NO_2-barbiturate-opioid anesthesia and is used as a measure of potency. Administration of one to three times the ED_{95} allows tracheal intubation. The speed of onset of blockade is inversely proportional to the potency of the NMBA.

Alterations in Sensitivity

Enhanced NMBA effects occur with administration of inhalation anesthetics, local anesthetics, diuretics, antiarrhythmics, aminoglycosides, magnesium, and lithium. Hypothermia, acidosis, and hypokalemia also increase the potency of nondepolarizing NMBAs. Patients with myasthenia gravis are very sensitive to the effects of nondepolarizing NMBAs. In contrast, patients with burn injuries are resistant to the effects owing to proliferation of nicotinic receptors (upregulation). Administration of 10% of the intubating dose of an NMBA 2 to 4 min before the full intubating dose is given is known as *priming*. Priming may accelerate the onset of muscle relaxation to approximately 60 s.

Chemical Structure and Pharmacokinetics

Currently used nondepolarizing NMBAs are benzylisoquinolinium and aminosteroid compounds, both of which have one or more positively charged quaternary ammonium groups (Tables 59.1 and 59.2). ACh has a single quaternary ammonium. The presence of a quaternary ammonium group on nondepolarizing NMBAs means that they are highly ionized water-soluble compounds at physiologic pH. Lipid solubility is limited, so nondepolarizing NMBAs do not easily cross lipid-membrane barriers such as the blood-brain barrier. After a single dose, the volume of distribution is similar to the extracellular

fluid volume; the volume of distribution, plasma clearance, and elimination may be affected by patient age or the presence of renal or hepatic dysfunction. Although many nondepolarizing NMBAs rely on hepatic or renal clearance, or both, some are eliminated in an unusual fashion (see later discussion).

TABLE 59.1

Nondepolarizing Neuromuscular Blocking Agents by Duration of Action

Structural Class	Short-Acting Agent	Intermediate-Acting Agent	Long-Acting Agent
Benzylisoquinolinium	Mivacurium*	Atracurium Cisatracurium	d-Tubocurarine* Metocurine* Doxacurium*
Aminosteroid	Rapacuronium*	Vecuronium Rocuronium	Pancuronium
Asymmetrical mixed-onium chlorofumarate	Gantacurium*	–	–

*Not available in the United States.

TABLE 59.2

Characteristics of Commonly Used Neuromuscular Blocking Agents

Agent	Intubating Dose (mg/kg)	Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Onset (s)*	Duration of Action	Vagolysis	Histamine Release	Elimination	Comments
Succinylcholine	1.5	NA	30–90	Very short	Variable	Slight	Butyrylcholinesterase	Depolarizing muscle relaxant
Mivacurium	0.15	3–12	90–150	Short	No	Yes	Butyrylcholinesterase	No longer available in U.S.
Rapacuronium	1.5	NA	45–90	Short	Yes	Yes	Kidney, ester hydrolysis	No longer available
Rocuronium	0.9–1.2	9–12	60–90	Intermediate	Yes	No	Liver, kidney	–
Cisatracurium	0.15–0.2	1–3	90–120	Intermediate	No	No	Hofmann degradation	–
Atracurium	0.5	3–12	90–150	Intermediate	No	Yes	Hofmann degradation, ester hydrolysis	–
Vecuronium	0.08–0.12	1–2	90–150	Intermediate	No	No	Liver, kidney	–
Pancuronium	0.08–0.12	NA	Slow	Long	Yes	No	Kidney, liver	–
Gantacurium	0.4–0.6	NA	90–120	Very short	No	Yes	Cysteine adduction, ester hydrolysis	Still investigational

*Time to intubation.

NA, Not applicable.

Nonrelaxant Side Effects

Nonrelaxant side effects of nondepolarizing NMBAs include histamine release and cardiovascular and autonomic effects (see Chapter 60).

Commonly Used Nondepolarizing Neuromuscular Blocking Agents

Rocuronium

Rocuronium is a monoquaternary aminosteroid NMBA. When administered at three times ED_{95}, rocuronium has an onset of action similar to that of succinylcholine, although the laryngeal muscles are relatively more resistant to the effects of rocuronium. Therefore rocuronium is often used as an alternative relaxant for rapid-sequence induction when the depolarizing NMBA succinylcholine is contraindicated. Doses used for rapid tracheal intubation (0.9–1.2 mg/kg) are roughly twice that of the common intubating dose (0.6 mg/kg). These larger doses typically cause neuromuscular blockade that may last for an hour or more if not antagonized by sugammadex.

Vecuronium

Vecuronium is a monoquaternary aminosteroid NMBA with a structure similar to that of rocuronium. At an ED_{95} of 0.05 mg/kg, its onset of action is 3 to 5 min and its duration of action is 20 to 35 min. The drug is supplied in powder form because it is unstable in solution. Vecuronium is metabolized by the liver and cleared by the kidney. Biliary excretion also plays a role in its elimination. Repeated dosing of vecuronium causes a cumulative effect that is less than that of pancuronium but greater than that of atracurium. Vecuronium has minimal, if any, cardiovascular effects. As an aminosteroid, the action of vecuronium can be reversed by sugammadex.

Atracurium

Atracurium is an intermediate-acting NMBA that is a mixture of 10 stereoisomers. At an ED_{95} dose of 0.2 mg/kg, its onset and duration of action are 3 to 5 min and 20 to 35 min, respectively. Atracurium is metabolized and eliminated independent of the liver and kidney. It undergoes spontaneous nonenzymatic in vivo degradation (Hofmann elimination) at normal body pH and temperature. The drug also undergoes hydrolysis by nonspecific plasma esterases, unrelated to butyrylcholinesterase. One third of administered atracurium is degraded by Hofmann elimination and two thirds by ester hydrolysis. Both pathways produce laudanosine, which, although not active as an NMBA, may cause central nervous system excitation at high doses in animals. At doses of atracurium used clinically in humans,

Gantacurium

Gantacurium, an NMBA under investigation in Phase 3 trials, represents a new class of nondepolarizing NMBAs known as *asymmetrical mixed-onium chlorofumarates.* It is degraded by two nonenzymatic chemical reactions, cysteine adduction and ester hydrolysis. Gantacurium has a pharmacodynamic profile similar to that of succinylcholine.

Sugammadex

Perhaps the most novel drug to come to the forefront is not itself a nondepolarizing NDMA, but rather a reversal agent. Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant binding agent to gain market approval. It is capable of reversing any depth of neuromuscular blockade induced by rocuronium and, to a lesser extent, vecuronium and pancuronium. The introduction of sugammadex to clinical practice has changed rocuronium from an intermediate-acting nondepolarizing NMBA to a potentially very short-acting agent. Typical dosing is based on total body weight and depends on the response to train-of-four stimulation. If spontaneous recovery of paralysis reveals two twitches on train-of-four testing, a dose of 2 mg/kg is recommended. If there is no spontaneous recovery, but there is posttetanic twitch, a dose of 4 mg/kg is recommended. To rapidly reverse paralysis, a dose of 16 mg/kg can be administered 3 min after a rapid-sequence induction dose of rocuronium. Its use in the United States was delayed for several years because of safety concerns, specifically, hypersensitivity reactions. Unlike neostigmine, sugammadex has no intrinsic anticholinergic properties, eliminating the need for concomitant administration of an antimuscarinic agent. The side effects of this drug are detailed in Chapter 60.

Suggested Readings

Abrishami A, Ho J, Wong J, et al. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database Syst Rev*. 2009;(4) [CD007362].

Carron M, Zarantonello F, Tellaroli P, Ori C. Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromuscular blockade: a meta-analysis of randomized controlled trials. *J Clin Anesth.* 2016;35:1–12.