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Nonrelaxant Side Effects of Nondepolarizing Neuromuscular Blocking Agents

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In addition to their action on the neuromuscular junction, nondepolarizing neuromuscular blocking agents (NMBAs) produce a variety of nonrelaxant effects. Many of these "side effects" may be unwanted and are potentially harmful. Nondepolarizing NMBAs are commonly implicated in medication-related adverse perioperative events. Some nonrelaxant effects may be used to the advantage of the patient and the practitioner.

Interference With Autonomic Function

Nondepolarizing NMBAs may interact with nicotinic and muscarinic cholinergic receptors in the sympathetic and parasympathetic nervous systems. The length of the carbon chain separating the two positively charged ammonium groups influences the specificity of a nondepolarizing NMBA for nicotinic receptors at autonomic ganglia (vs. nicotinic receptors at the neuromuscular junction). The so-called *autonomic margin* reflects the difference between the dose of a nondepolarizing NMBA that causes neuromuscular blockade and the dose that leads to circulatory effects. For example, blockade of autonomic ganglia leading to hypotension occurs with *d*-tubocurarine, an older nondepolarizing NMBA, at doses slightly higher than those required for blockade of the neuromuscular junction. However, the ED95 doses for neuromuscular blockade with the use of cisatracurium, vecuronium, and rocuronium are significantly lower than the doses that cause autonomic effects, so these drugs have a wide autonomic margin.

The effects of nondepolarizing NMBAs on the parasympathetic muscarinic receptors in the heart may be clinically significant. Pancuronium, for example, produces a vagolytic action on nodal cells mediated through muscarinic receptors. This action occurs at doses used clinically for neuromuscular blockade, leading to an increase in heart rate.

The sympathetic nervous system contains at least three sets of muscarinic receptors. Blockade of these receptors on dopaminergic interneurons decreases modulation of ganglionic traffic (disinhibition), and blockade of adrenergic neurons results in removal of a negative feedback system for catecholamine release. Muscarinic blockade at sympathetic adrenergic neurons, leading to inhibition of norepinephrine uptake, represents the mechanism behind the exaggerated response that is sometimes seen with pancuronium during light anesthesia. The drug may cause norepinephrine release independent of muscarinic blockade. Thus pancuronium may cause tachycardia and a predisposition to arrhythmias because of vagal block with a shift toward adrenergic tone, indirect sympathomimetic activation, and atrioventricular nodal blockade (greater than sinoatrial nodal blockade).

Histamine Release

The benzylisoquinolinium compounds cause nonimmunologic release of histamine and possibly other mediators from mast cells. Histamine release is a function of dose and the rate of administration. The physiologic effects of histamine include positive chronotropy (H2 receptors), positive inotropy (H2 receptors), positive dromotropy (H1 receptors), coronary artery effects (H1 receptors, vasoconstriction; H2 receptors, vasodilation), and peripheral vasodilation. Erythema of the face, neck, and torso may occur. Bronchospasm is rare, but may be severe, and it has been a limiting factor in the use of some nondepolarizing NMBAs. Rapid administration of atracurium in doses greater than 0.4 mg/kg and mivacurium at doses greater than 0.15 mg/kg has been associated with histamine-related hypotension. In general, however, histamine release causes minimal effects in healthy patients. If clinical manifestations occur, they are usually of short duration (lasting 1–5 min), and the response undergoes rapid tachyphylaxis, so subsequent doses of nondepolarizing NMBAs cause little, if any, effect. Vecuronium, at doses of 0.1 to 0.2 mg/kg, may

rarely cause severe bronchospasm, probably because of competitive inhibition of histamine-*N*-methyltransferase, thus inhibiting the degradation of histamine. Table 60.1 shows the approximate autonomic margins of safety of nondepolarizing NMBAs, and Table 60.2 illustrates the clinical autonomic effects of nondepolarizing NMBAs and the effects on histamine.

TABLE 60.1

Approximate Autonomic Margins of Safety of Nondepolarizing Neuromuscular Blocking Agents*

Drug	Vagus†	Sympathetic Ganglia‡	Histamine Release‖
BENZYLISOQUINOLINIUM COMPOUNDS			
Mivacurium	> 50	> 100	3.0
Atracurium	16	40	2.5
Cisatracurium	> 50	> 50	None
d-Tubocurarine§	0.6	2	0.6
AMINOSTEROID COMPOUNDS			
Vecuronium	20	> 250	None
Rocuronium	3–5	> 10	None
Pancuronium	3	> 250	None

†Number of multiples of the ED95 for neuromuscular blockade required to produce the autonomic side effect (ED50).

‡In the cat.

‖In human subjects.

§No longer available.

ED, Effective dose.

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TABLE 60.2

Clinical Autonomic Effects of Nondepolarizing Neuromuscular Blocking Agents

Drug	Autonomic Ganglia	Cardiac Muscarinic Receptors	Histamine Release
BENZYLISOQUINOLINIUM COMPOUNDS			
Mivacurium	None	None	Slight
Atracurium	None	None	Slight
Cisatracurium	None	None	None
d-Tubocurarine*	Blocks	None	Moderate
AMINOSTEROIDAL COMPOUNDS			
Vecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Pancuronium	None	Blocks moderately	None

*No longer available.

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Respiratory Effects

In addition to the effects of histamine on the respiratory system, nondepolarizing NMBAs may directly affect autonomic receptors in the lungs. At least three types of muscarinic receptors are found in the airways, as shown in Fig. 60.1. Nondepolarizing NMBAs have different antagonistic activities at both the M2 and M3 receptors. Blockade of M2 receptors on airway smooth muscle causes an increased release of acetylcholine, which will act on M3 receptors and cause bronchoconstriction. Blockade of M3 receptors causes bronchodilation by inhibiting vagally mediated bronchoconstriction. Rapacuronium, a nondepolarizing NMBA, blocks M2 receptors to a much greater extent than it blocks M3 receptors. Because this causes an unacceptably high incidence of bronchospasm, rapacuronium was withdrawn from the market.

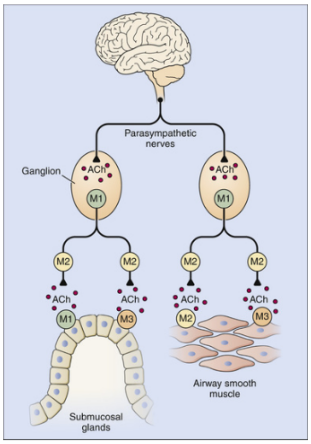

FIG. 60.1 The muscarinic M3 receptors are located postsynaptically on airway smooth muscle. Acetylcholine (ACh) stimulates M3 receptors to cause contraction. M2 muscarinic receptors are located presynaptically at the postganglionic parasympathetic nerve endings, and they function in a negative feedback mechanism to limit the release of ACh. (From Naguib M, Lien CA, Meistelman C. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, Eriksson LI, Fleisher LA, et al., eds. *Miller's Anesthesia.* 8th ed. Philadelphia; Churchill Livingstone; 2015:958–994. Fig. 34.8.)

Allergic Reactions

Although the development of anaphylaxis during anesthesia is rare, NMBAs are frequently implicated in such reactions. If a patient has reacted to one nondepolarizing NMBA, there is a significant risk of cross-reactivity to other NMBAs. The reactions are mediated through IgE. NMBAs were the most common causative agents in reports from Europe and Australia. The quaternary ammonium ions found in nondepolarizing NMBAs may cross-react with other medications and other environmental factors (e.g., food, cosmetics). Interestingly, pholcodine, a morphine analog commonly used as an antitussive in several European countries and Australia, sensitizes patients to develop IgE–mediated allergic reactions to NMBAs. The availability of pholcodine (it is not approved in the United States or Canada) likely explains the geographical variation in reported rates of anaphylaxis to NMBAs. Countries that have since banned the use of pholcodine have seen a decrease in rates of NMBA-related anaphylaxis.

Other Nonrelaxant Side Effects of Nondepolarizing Neuromuscular Blocking Agents

Teratogenicity and Carcinogenicity

NMBAs are highly ionized, but they and their metabolites are able to cross the placenta in small amounts. Nonetheless, at clinically relevant doses, human teratogenic effects—if they exist—are unproved. There are no data in the literature on carcinogenic effects of NMBAs.

Critical Illness Polymyoneuropathy

Medium-term and long-term administration of infusions of nondepolarizing NMBAs—especially those that are steroid based—in critically ill patients can lead to profound weakness, requiring prolonged periods of rehabilitation. Such weakness can occur in patients with multiorgan failure, even in the absence of NMBA use, but weakness is more likely to occur when continuous infusions of nondepolarizing NMBAs are used.

Toxic Metabolites

Laudanosine is a metabolite of atracurium that causes central nervous system stimulation and possibly seizures in high concentrations. Typically administered doses of atracurium and cisatracurium, however, do not cause such problems.

Drug Interactions

Pancuronium inhibits butyrylcholinesterase and leads to extremely prolonged action of mivacurium.

Sugammadex

Sugammadex initially met resistance in the marketplace because of concerns for hypersensitivity reactions. Subsequent studies in healthy volunteers have demonstrated the incidence of anaphylaxis only at high doses (i.e., 16 mg/kg), with a frequency of less than 1%. Allergic reactions ranging from isolated urticarial rash to anaphylaxis have been reported in patients without prior sensitization to cyclodextrins, suggesting a nonimmune phenomenon or a cross-reaction with immunoglobulins associated with unrelated chemical compounds. The most common adverse events associated with sugammadex are nausea, vomiting, pain, hypotension, and headache. In healthy volunteers, aPTT and INR were increased by up to 25% after administration of 16 mg/kg sugammadex; however, there appears to be no clinical evidence of significant coagulopathy. Because of its steroid-binding capabilities, nonhormonal contraception should be used for 7 days after administration of sugammadex because of the potential reduction of free circulating hormonal contraception.

Suggested Readings

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.

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