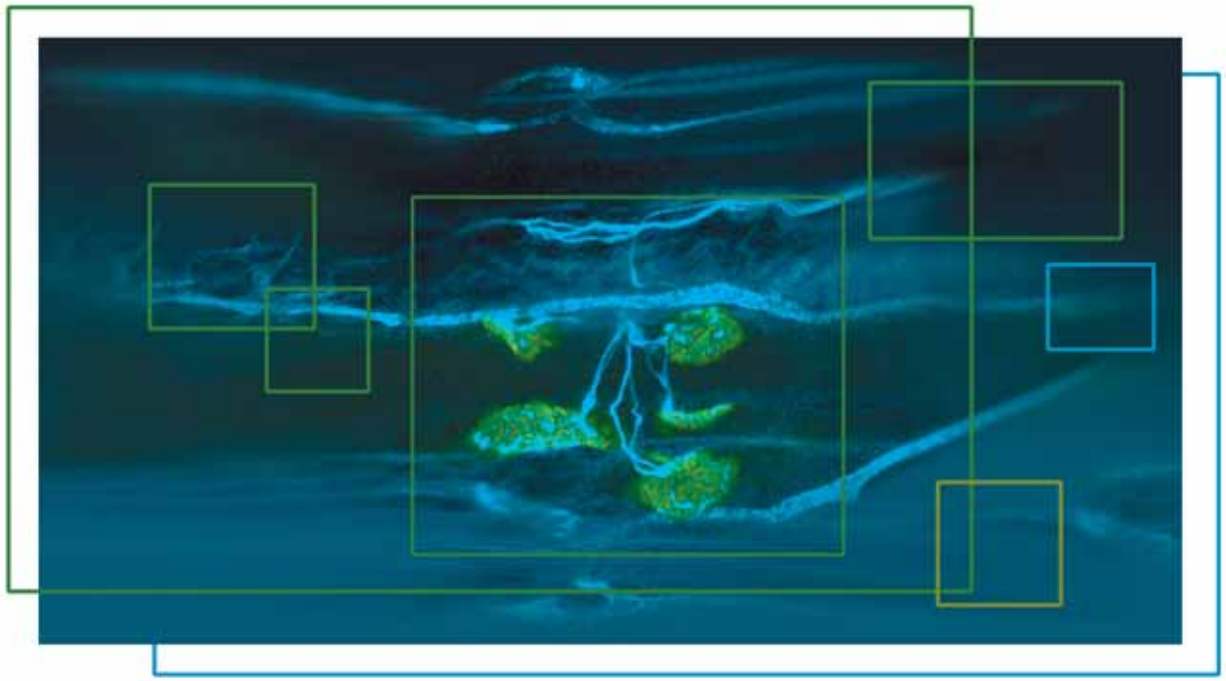

Guide to Neuromuscular Blocking Agents

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Since the introduction of tubocurarine as the first neuromuscular blocking (NMB) agent, numerous new drugs for the use of muscle relaxation have been developed. Initially marketed for muscle relaxation to ease endotracheal intubation and provide optimal operating conditions, the application of NMB agents has expanded to include critically ill patients in the intensive care unit and emergency department.

The authors have no conflict of interest relevant to this educational review.

Succinylcholine, which achieves intubating conditions quickly with a brief duration of action, can be contraindicated under certain circumstances. Nondepolarizing agents, such as atracurium and vecuronium developed in the 1980s, presently provide a more rapid onset of action with a shorter duration than previously available agents. The ideal target for future drug development is a newer generation of nondepolarizing NMB agents with properties similar to those of succinylcholine; however, current research is shifting toward administration of NMB agents in combination with newer, more potent reversal agents.

The most recent breakthrough is the development of sugammadex (Org 25969), the first selective relaxant binding agent (SRBA), which is presently in Phase III trials. Currently available anticholinesterase agents are not capable of reversing profound blockade, even in higher doses, without potential cardiac and autonomic side effects. Sugammadex is a modified γ-cyclodextrin that tightly encapsulates aminosteroid-based agents, in particular rocuronium and vecuronium, thereby rapidly decreasing NMB concentrations at the motor end plate. Preliminary clinical trials report reversal to train-of-four (TOF) ratios of 0.90 within 2 to 5 minutes after administration of doses ranging from 2 to 8 mg/kg.[1-3] Consequently, sugammadex may offer a fast-acting, safe alternative for NMB reversal.

The following tables provide information such as dosing recommendations, pharmacodynamic information, and drug–disease state interactions.[4-16] This information can be useful not only to anesthesiologists and other perioperative personnel but also to those who require NMB agents for the care of critically ill patients outside the operating room.

Table 1. Dosing Guidelines and Pharmacodynamic Parameters of NMB Agents*

					Long Surgical Procedures	
Class	**Drug (Trade Name, Manufacturer)**	**Intubation Dose,† mg/kg**	**Onset,‡ min**	**Duration,§ min**	**Repeat Bolus,† mg/kg**	**Average Infusion Rate†,‖ (range)**
Ultra–short-acting	**Succinylcholine** (various)	0.6 (0.3-1.1)	1	4-6	0.04-0.07	2.5-4.3 mg/min (0.5-10)
Intermediate-acting	**Atracurium** (various)	0.4-0.5	3-5	20-35	0.08-0.1	5-9 mcg/kg/min (2-15)
	Cisatracurium (Nimbex, GlaxoWellcome)	0.15-0.2	1.5-2	55-61	0.03	1-2 mcg/kg/min (1-3)
	Rocuronium (Zemuron, Organon)	0.6 (0.45-1.2)	1-3	22-67	0.1-0.2	10-12 mcg/kg/min (4-16)
	Vecuronium (various)	0.08-0.1 (up to 0.28)	2.5-3	25-30	0.01-0.015	1 mcg/kg/min (0.8-1.2)
Long-acting	**Pancuronium** (various)	0.06-0.1	2-4	60-100	0.01-0.06	—

* NMB agents should always be used in combination with sedative and/or anesthetic agents.

† Dosing information pertains only to adults and may vary based on the use of co-induction agents.

‡ The onset of time to maximum block or time to good/excellent intubation conditions is dose dependent.

§ Clinically effective duration of action.

‖ Infusion doses reflect initiation after early evidence of spontaneous recovery from the initial bolus dose.

Based on prescribing information/manufacturer's data and reference 4.

Table 2. Infusion Dosing Recommendations and Routes of Elimination for NMB Agents*

Structural Classification	Relaxant	ICU Bolus Dose,† mg/kg	ICU Continuous Infusion†,‡ (usual range)	Route of Elimination§	Metabolites
Depolarizing					
	Succinylcholine	—	—	Plasma cholinesterase	No clinically active metabolites
Nondepolarizing					
Amino-steroidal compounds	**Pancuronium**	0.06-0.1	1 mcg/kg/min (1-2)‖	Primarily renal, some biliary	3-hydroxy metabolite has 1/3 to 1/2 the activity of parent; may accumulate in renal/hepatic failure
	Rocuronium	0.6-1	10-12 mcg/kg/min (4-16)	Primarily biliary, some renal	No clinically active metabolites
	Vecuronium	0.08-0.1	1 mcg/kg/min (0.8-1.2)	Primarily biliary, some renal	3-desacetyl metabolite has 1/2 the activity of parent; may accumulate in renal/hepatic failure
Benzyliso-quinolinium compounds	**Atracurium**	0.4-0.5	4-12 mcg/kg/min (4.5-29.5)‖,¶	Ester hydrolysis and Hoffman elimination	Laudanosine metabolite has been associated with CNS excitation; may accumulate in renal/hepatic failure
	Cisatracurium	0.1-0.2	2.5-3 mcg/kg/min (0.5-10.2)	Ester hydrolysis and Hoffman elimination	Laudanosine metabolite has been associated with CNS excitation; may accumulate in renal/hepatic failure

* NMB agents should always be used in combination with sedative and/or analgesic agents.

† Dosing information pertains only to adults.

‡ Infusion should be titrated to achieve appropriate degree of neuromuscular blockade (as determined by clinical response and peripheral nerve stimulation).

§ Dose adjustments may be required in patients with organ dysfunction.

‖ Pancuronium is generally not recommended for continuous infusion; may be given in intermittent boluses of 0.04-0.1 mg/kg.

¶ Prolonged infusion of atracurium has been associated with tolerance, necessitating significant dose increases or conversion to other NMB agents.

CNS, central nervous system; **ICU,** intensive care unit

Based on prescribing information/manufacturer's data and reference 5.

Table 3. Dosing Guidelines for Rapid Sequence Intubation*

Drug	Priming Dose,†,‡ mg/kg	Intubating Dose,‡ mg/kg	Intubating Conditions Achieved, s	Clinical Duration,§ min
Depolarizing				
Succinylcholine	None	1	45-60	5-10
	Nondepolarizing pretreatment	1.5	45-60	5-10
Nondepolarizing				
Rocuronium	None	0.6-1.2	45-60	31-67
Vecuronium	None	0.3-0.4	90-120	90-130
	0.01	0.15-0.2	90-120	60-75

* NMB agents should always be used in combination with sedative and/or anesthetic agents.

† This dose should be administered when preoxygenation is begun with the intubating dose 2-4 min after the priming dose. Primary dose has potential adverse effects including respiratory depression and aspiration.

‡ Dosing information pertains only to adults.

§ Time from intubation dose administration to twitch recovery to 25% of control.

Based on prescribing information/manufacturer's data and references 6-12.

Table 4. Antagonism of Nondepolarizing NMB Agents

Reversal Agent (Trade Name, Manufacturer)	Usual Single Dose*	Maximum Recommended Dose*	Onset,† min	Duration,‡ min	Mechanism of Action
Edrophonium (various)	10 mg	40 mg	0.5-1	10	Acetylcholinesterase inhibitor
Edrophonium plus atropine (Ohmeda)	0.05-0.1 mL/kg (0.5-1 mg/kg edrophonium, 0.007-0.014 mg/kg atropine)	1 mg/kg edrophonium	0.8-2	70	Acetylcholinesterase inhibitor with anticholinergic
Neostigmine (various)§	0.5-2 mg	5 mg	20‖	60	Reversible acetylcholinesterase inhibitor
Pyridostigmine (various)§	10 mg	20 mg	12-20	120-180	Reversible acetylcholinesterase inhibitor

* Dosing information pertains only to adults.

† A return of train-of-four ratio to 0.9.

‡ Maintenance of a train-of-four ratio >0.9.

§ Atropine 0.6-1.2 mg I.V. bolus recommended just before NMB agent to minimize cholinergic effects.

‖ Onset of neostigmine is dose dependent.

Based on prescribing information/manufacturer's data and reference 5.

Table 5. Significant Drug Interactions With NMB Agents

Drug/Class	Clinical Effect	Dep	Non-dep	Management
Antiarrhythmic agents (eg, quinidine, procainamide, lidocaine)	Enhanced NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.
Antibiotics (eg, aminoglycosides, tetracyclines, polymyxins, clindamycin, piperacillin)	Potential for prolonged respiratory depression, excessive blockade	+	+	Observation for residual effects following NMB agent administration.
Antiepileptics (eg, carbamazepine, fosphenytoin, phenytoin)	More rapid recovery time following NMB administration		+	Monitor patients for clinical response; may need higher/more frequent doses of NMB agent.
Aprotinin (Trasylol, Bayer)	Prolonged NMB activity	+		Response should be monitored using lowest dose possible to achieve adequate blockade.
Azathioprine	Enhanced NMB activity (Dep) Reversal of NMB activity (Nondep)	+	+	Monitor effects of NMB agent and adjust dose as needed.
Calcium-channel blockers (eg, nicardipine, verapamil)	Enhanced NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.

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Table 5. Significant Drug Interactions With NMB Agents *(continued)*

Drug/Class	Clinical Effect	Dep	Non-dep	Management
Corticosteroids	Muscle weakness		+	Minimize duration of coadministration if possible; if prolonged concomitant use is necessary, allow patient to have NMB-free periods to reduce total dose administered.
	Prolonged NMB activity (Dep) Decreased NMB activity (Nondep)	+	+	Response should be monitored to achieve adequate blockade.
Cyclophosphamide	Enhanced or prolonged succinylcholine-induced apnea has been reported.	+		Response should be monitored using lowest dose possible to achieve adequate blockade.
Digoxin	Risk of cardiac arrhythmias	+	+	Noted specifically with succinylcholine; cardiac monitoring should be performed if used concomitantly.
Inhalation anesthetics (eg, enflurane, isoflurane)	Enhanced NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.
Lithium	Prolonged NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.
Magnesium salts	Enhanced NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.
Metoclopramide	Prolonged NMB activity	+	+	Noted specifically with mivacurium. Response should be monitored using lowest dose possible to achieve adequate blockade.
Oral contraceptives (when taken chronically)	Prolonged NMB activity	+	+	Noted specifically with succinylcholine because it is metabolized via plasma cholinesterase. Response should be monitored using lowest dose possible to achieve adequate blockade.
Oxytocin	Enhanced NMB activity	+	+	Response should be monitored using lowest dose possible to achieve adequate blockade.
Tacrine	Prolonged NMB activity	+		Response should be monitored using lowest dose possible to achieve adequate blockade.
Terbutaline	Enhanced NMB activity	+		Response should be monitored using lowest dose possible to achieve adequate blockade.
Tricyclic antidepressants	Risk of ventricular arrhythmias		+	Documented in patients receiving chronic TCAs who are anesthetized with halothane and administered pancuronium.

Dep, depolarizing agent; **NMB,** neuromuscular blocking; **Nondep,** nondepolarizing agent; **TCAs,** tricyclic antidepressants; **+** indicates presence of interaction.

Based on references 5, 13-15.

Table 6. Significant Disease State Interactions

Potential Clinical Effect	Disease State/Medical Conditions
Potentiation of neuromuscular blockade	**Neuromuscular diseases:** myasthenia gravis, Eaton-Lambert syndrome **Electrolyte disturbances:** hypermagnesemia, hyponatremia, hypokalemia, hypocalcemia **Acidosis (conditions that prolong metabolism):** atypical plasma cholinesterase, renal disease, hepatic disease
Antagonism of neuromuscular blockade	**Neuromuscular diseases:** hemiparesis or paraparesis, demyelinating lesions, peripheral neuropathies **Other:** hypercalcemia, alkalosis, burn injury
Increased risk for cardiac arrhythmias or cardiac arrest with succinylcholine	**Acute phase of injury following:** major burns, multiple trauma, spinal cord injury, extensive denervation of skeletal muscle, upper motor neuron injury **Other:** hyperkalemia, digitalis toxicity

Based on references 5, 13-16.

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