Pharmacologic Reversal of Neuromuscular Blocking Agent (Acetylcholinesterase inhibitors)

Acetylcholinesterase inhibitors can be used to inhibit the action of acetylcholine esterase, thereby increasing the concentration of acetylcholine available at the synaptic cleft to competitively antagonize nondepolarizing NMBA. There are a finite number of acetylcholinesterase molecules to block, and once they are fully blocked, no further increase in acetylcholine can occur. The ability to reverse a nondepolarizing block with acetylcholinesterase inhibitor depends on the relative ratio of available acetylcholine to NMBA at the NMJ. To assure this ratio is favorable and provide complete reversal, acetylcholinesterase inhibitor should not be given until there is spontaneous recovery with a TOF count of at least 2, and some authorities recommend a TOF count of 4. With deep or profound blocks (TOF count < 2), providers should wait for spontaneous recovery before giving acetylcholinesterase inhibitor for reversal of the block.

Acetylcholinesterase Inhibitors: Neostigmine and edrophonium are classic neuromuscular blockade reversal agents. They act indirectly through inhibition of the acetylcholinesterase (AChE) enzyme, which normally metabolizes acetylcholine (ACh) into choline and acetate. It is one of the most efficient enzymes known; a single molecule has the capacity to hydrolyze an estimated 300,000 molecules of ACh per minute. When the enzyme is inhibited, the concentration of ACh in the neuromuscular junctional cleft is increased, allowing ACh to compete for ACh receptor sites from which neuromuscular blocking agents (NMBAs) have dissociated).

The active center of the AChE molecule consists of a negatively charged subsite that attracts the quaternary group of choline through ionic forces as well as an esteratic subsite, where nucleophilic attack occurs. Neostigmine binds to the AChE enzyme through formation of a covalent bond of a carbamoyl-ester complex at the esteratic site of the enzyme. Edrophonium, another AChE inhibitor, has neither a carbamate nor an ester group; instead, it binds to the AChE molecule by virtue of its electrostatic attachment to the anionic site of the molecule, which is further strengthened by hydrogen bonding at the esteratic site. This ionic binding is much weaker than the covalent bonds, rendering edrophonium less potent than neostigmine. Both neostigmine and edrophonium are quaternary ammonium ions. They are poorly lipid soluble and do not

effectively penetrate lipid cell-membrane barriers, such as the gastrointestinal tract or the blood-brain barrier. They have very large volumes of distribution because of extensive tissue storage in organs such as the liver and kidneys. Renal excretion accounts for approximately 50% of the elimination of neostigmine and approximately 67% of the elimination of edrophonium. Neostigmine and edrophonium have similar elimination half-lives and duration of action, 76 and 66 minutes, respectively. The prolongation of their elimination half-lives by renal failure is similar to that affecting clearance of the NMBAs.

Although the nicotinic effects produced by the increased amounts of available ACh are desirable for reversing neuromuscular blockade, the muscarinic effects of the ACh on the gastrointestinal, pulmonary, and cardiovascular systems can be problematic. The predominant effect on the heart is bradycardia as a result of slowed conduction velocity of the cardiac impulse through the atrioventricular node. The prolongation of QTc interval in the ECG may induce ventricular arrhythmias. Hypotension may result from decreases in peripheral vascular resistance. Cholinesterase inhibitors enhance the secretion of gastric fluid and increase the motility of the entire gastrointestinal tract, probably caused by accumulated ACh at the ganglion cells of the Auerbach plexus and its effects on smooth muscle cells. However, a causal relationship between neostigmine administration and postoperative nausea and vomiting has not been confirmed. Bronchial, lacrimal, salivary, gastric, and sweat gland secretion is also increased. To counteract these muscarinic effects, anticholinergic drugs such as atropine or glycopyrrolate are coadministered. Because of its more rapid onset of action, atropine is usually combined with edrophonium, whereas neostigmine is usually coadministered with glycopyrrolate. These drugs also have side effects that need to be considered, especially atropine. Atropine is a tertiary amine, and it can cross the blood-brain barrier; in excessive doses, it can cause central anticholinergic toxicity, especially in the elderly. The typical signs include agitation, confusion, disorientation, and hallucinations as well as dry mouth; warm, dry skin; tachycardia, and visual disturbances. Because atropine is faster in onset and more likely to cause tachyarrhythmias, which can be disadvantageous in patients with coronary artery disease, many anesthesiologists consider glycopyrrolate, which has a more gradual onset of action, the better option for antagonizing the muscarinic side effects of anticholinesterases. To blunt the tachycardia associated with

coadministration of atropine with edrophonium, smaller, incremental doses are recommended, rather than a single, rapid bolus injection.

Anticholinesterase Side Effects

- Cardiac: bradycardia, hypotension
- Pulmonary: bronchospasm, hypoxia, increased secretions
- GI: increased GI motility and secretions, PONV (controversial)
- Eye: miosis, and decreased intraocular pressure
- NMJ: in high doses may lead to a SCh-like blockade and possibly direct inhibition of ACHr

Anticholinesterases in CRF

Neostigmine, pyridostigmine, and edrophonium are primary excreted via both glomerular filtration and active tubular secretion. Neostigmine is water-soluble and roughly 50% of it undergoes renal excretion compared to 75% of pyridostigmine and edrophonium. Clearance of these drugs is significantly reduced in patients with ESRD and dosing adjustments may need to be made accordingly. When dosing neostigmine a ceiling effect is noted around 0.035 – 0.05 mg/kg in healthy individuals. Recurarization is unlikely in ESRD patients because the reduction in plasma clearance of anticholinesterases exceeds that of neuromuscular blocking agents. When used in combination with cholinergic blocking drugs (atropine & glycopyrrolate) no dosing adjusted is needed as toxic side effects are unlikely when administered as a single dose during neuromuscular reversal.