Neostigmine Pharmacology

Neostigmine is a parasympathomimetic agent and a cholinesterase inhibitor that is indicated for the treatment of myasthenia gravis and to reverse the effects of muscle relaxants.

Pharmacology

Neostigmine is an oxy-diaphoretic inhibitor of the acetylcholinesterase enzyme, which is the enzyme that metabolizes acetylcholine into choline and acetic acid. This means that it binds and inhibits via acid-transferring (or binding to the anionic site of the enzyme creating a covalent bond) allowing acetylcholine to build up at the neuromuscular junction and overcome the competitive inhibition of nondepolarizing blocking drugs.

Pharmacodynamics

Neostigmine is a cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the effects of muscle relaxants such as gallamine and tubocurarine, rocuronium, etc.

Neostigmine is a quaternary ammonium compound that does not penetrate the blood-brain barrier unlike physostigmine

By inhibiting acetylcholinesterase, more acetylcholine is available in the synapse, therefore, more of it can bind to the fewer receptors present in myasthenia gravis and can better trigger muscular contraction.

Neostigmine is water-soluble, an ionized compound that reversibly inhibits the enzyme acetylcholinesterase. After administration of neostigmine, the concentration of acetylcholine is increased in the neuromuscular junction, which allows for muscles to contract with full strength, and patients can breathe spontaneously and protect their airways safely after the emergence stage from anesthesia.

Mechanism of action

Neostigmine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor.

The drug inhibits acetylcholinesterase which is responsible for the degradation of acetylcholine. So, with acetylcholinesterase inhibited, more acetylcholine is present By interfering with the breakdown of acetylcholine, neostigmine indirectly stimulates both nicotinic and muscarinic receptors which are involved in muscle contraction. It does not cross the blood-brain barrier.

Neostigmine is used to accelerate the reversal of nondepolarizing neuromuscular blockade of nicotinic receptors in the neuromuscular junction at the end of surgery.

It is administered intravenously as a bolus.

Intravenous (IV) dosage is **0.03 mg/kg to 0.07 mg/kg** (up to 5 mg), with the higher dose for first twitch responses that are close to but not substantially greater than 10%.

The peak effect (antagonism) occurs at approximately 7 to 10 minutes, and the duration of action is approximately 55 to 75 minutes.

The principal route of excretion is the **kidney**.

Neostigmine is typically administered along with an antimuscarinic agent like **glycopyrrolate or atropine** to attenuate the parasympathomimetic activity at other non-muscular acetylcholine receptor sites

Neostigmine is considered the drug of choice for routine practice in the reversal of neuromuscular blocking agents in the pediatric population. This is due to a greater final recovery from a blockade.

The elimination half-life of neostigmine is less in children, but distribution volumes are similar in infants, young children, and adults. As in adults, the speed of onset of antagonism is dependent on the degree of neuromuscular blockade at that time; however, the dose requirements are slightly less in children when compared to adults.

Adverse drug reactions

There are a number of adverse effects of neostigmine that can affect multiple organ systems, most of which are related to the cholinergic side effects of the drug.

Cardiac muscarinic effects that can be seen include bradyarrhythmias like junctional escape rhythms, complete heart block, and even asystole.

A potentially life-threatening adverse effect of neostigmine is **bronchoconstriction**.

Neostigmine can stimulate the muscarinic receptors in the airway smooth muscle, potentially leading to bronchospasm.

This adverse effect can be mostly attenuated with concurrent administration of an anticholinergic agent like glycopyrrolate.

Other adverse effects include increased secretions, miosis, nausea, and increased peristalsis.

In pregnancy, neostigmine can cross the placenta and cause fetal bradycardia, and concurrent administration of atropine, which also crosses the placenta, should be considered in this situation.

Another significant side effect of neostigmine and other anticholinesterase inhibitors is paradoxical anticholinesterase-associated muscle weakness.

Contraindications

Contraindications of neostigmine include hypersensitivity to neostigmine and peritonitis or mechanical obstruction of the intestinal or urinary tract.

Neostigmine should also not be administered if zero twitches are observed on a peripheral nerve stimulator after the administration of a nondepolarizing neuromuscular blocking drug.

Neostigmine should be used with caution in patients with coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome, and myasthenia gravis.

It is important to consider the relative duration of action of neuromuscular blocking agents when administering neostigmine as a reversal agent.

Administering neostigmine after a relative degree of spontaneous recovery of neuromuscular function is important to prevent "recurarization," which can manifest as increased weakness in the post-operative recovery unit due to the lasting effect of the neuromuscular blocking drug.

The duration of action of neostigmine is increased in patients with renal failure as it is excreted by the kidneys.

Ways to use acetylcholinesterase reversal agents to reduce the risk of residual neuromuscular blockade:

Train-of-four counts less than one or no response. Do not use neostigmine for reversal of neuromuscular blockade. Wait until the train-of-four count is greater than one.

Train-of-four count of two or three. Administer the proper dose of Neostigmine (or another acetylcholinesterase inhibitor) and extubate when the adductor pollicis train-of-four ratio is 0.9 or greater.

Train-of-four count is greater than 0.4. Administer a moderate dose of neostigmine and extubate when the adductor pollicis train-of-four ratio is 0.9 or greater.

Train-of-four count is greater than 0.7. Avoid using neostigmine as the risk of anticholinesterase-induced muscle weakness is greater.

Toxicity

Overdosage of Neostigmine can cause a cholinergic crisis, which is characterized by increasing muscle weakness, and through the involvement of the muscles of respiration, may result in death.