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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Neostigmine

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Last Update: September 2, 2020.

Continuing Education Activity

Neostigmine is water-soluble, an ionized compound that reversibly inhibits the enzyme acetylcholinesterase. Its FDA indication is for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery. The use of neostigmine is primarily found in the context of the reversal of neuromuscular blockade during the administration of anesthesia to patients undergoing surgery that require muscle relaxation. This activity outlines the indications, mechanism of action, methods of administration, important adverse effects, contraindications, monitoring, and toxicity of neostigmine so that providers can direct patient therapy to optimal outcomes in anesthesia reversal.

Objectives:

- Identify the mechanism of action of neostigmine.
- Summarize the indications where neostigmine use is beneficial.
- Describe the adverse effects and contraindications of neostigmine.
- Summarize the importance of improving care coordination among the interprofessional team to enhance the delivery of care for patients who can benefit from therapy with neostigmine.

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Indications

Neostigmine is water-soluble, an ionized compound that reversibly inhibits the enzyme acetylcholinesterase. Its FDA indication is for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery. The use of neostigmine is primarily found in the context of the reversal of neuromuscular blockade during the administration of anesthesia to patients undergoing surgery that require muscle relaxation. 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 emergence from anesthesia.[1][2][3]

Mechanism of Action

Acetylcholine is the neurotransmitter in the body that is made, stored, and released by the end of motor nerve terminals. Acetylcholine is metabolized by an enzyme called acetylcholinesterase that hydrolyzes acetylcholine in the neuromuscular junction. Neostigmine one of the drugs in the class of acetylcholinesterase inhibitors. Neostigmine is an oxy-diaphoretic inhibitor of the acetylcholinesterase enzyme, which means that it binds and inhibits via acid-transferring (or binding to the anionic site of the enzyme creating a covalent bond). Neostigmine inhibits acetylcholinesterase, which is the enzyme that metabolizes acetylcholine into choline and acetic acid. This allows acetylcholine to build up at the neuromuscular junction and overcome the competitive inhibition of nondepolarizing blocking drugs. It is used to accelerate the reversal of nondepolarizing neuromuscular blockade of nicotinic receptors in the neuromuscular junction at the end of surgery. Neostigmine is a quaternary ammonium compound that does not penetrate the blood-brain barrier.[4][5][6]

Administration

Peripheral nerve stimulator should be utilized to determine when neostigmine dosage should be initiated and for the administration of subsequent doses. Neostigmine should be administered when the first twitch response of a peripheral nerve stimulator is substantially greater than 10% of baseline, or when a second twitch is present. The drug is administered intravenously as a bolus. The drug 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.[7][8]

Pediatric administration: 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 in comparison to edrophonium. 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. If the pediatric patient has a train-of-four response with fade, a dose of 20 micrograms per kilogram of neostigmine, followed by 10 micrograms to 20 micrograms per kilogram of atropine or 5 micrograms to 10 micrograms per kilogram of glycopyrrolate is sufficient to achieve reversal of neuromuscular blockade and return of adequate muscle strength.

Adverse Effects

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 potential life-threatening adverse effect of neostigmine is bronchoconstriction. Neostigmine, along with other anticholinesterase inhibitors, can stimulate the muscarinic receptors in the airway smooth muscle which can lead 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. The majority of these effects can be minimized by concurrent dosing of an anticholinergic drug with a similar onset time, typically glycopyrrolate. 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. The clinical manifestation of muscle weakness include decreases in upper airway dilator muscle tone, impairment of respiratory muscles like the diaphragm, and reductions in minute volume which is the tidal volume multiplied by the respiratory rate.

Contraindications

Absolute contraindications of neostigmine include a 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 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.

Monitoring

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 itself as increased weakness in the post-operative recovery unit due to the lasting effect of the neuromuscular blocking drug. Of note, up to 70% of acetylcholine receptors may still be blocked with an apparently normal train of four from the peripheral nerve stimulator. 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:

1. Train-of-four counts less than one or no response. Do not use neostigmine for reversal of neuromuscular blockade. Wait until train-of-four count is greater than one.
2. Train-of-four count of two or three. Administer the proper dose of Neostigmine (or another acetylcholinesterase inhibitor) and extubate when adductor pollicis train-of-four ratio is 0.9 or greater.
3. Train-of-four count is greater than 0.4. Administer a moderate dose of neostigmine and extubate when adductor pollicis train-of-four ratio is 0.9 or greater.
4. Train-of-four count 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 described as increased muscle weakness and may result in death due to the involvement of respiratory muscles. If this occurs, the immediate use of atropine should be administered.

Enhancing Healthcare Team Outcomes

Neostigmine is primarily used by the anesthesiologist, anesthesia nurse, emergency department physician, and the intensivist. The patient must be monitored after administration of neostigmine as it can induce cholinergic side effects that can affect many organ systems. Besides bradycardia, a potentially life-threatening adverse effect of neostigmine is bronchoconstriction. ICU nurses and anesthesiologists should regularly monitor vital signs after neostigmine has been administered. When given to patients with myasthenia gravis, the lowest dose should be used and gradually titrated upwards depending on the response.

Continuing Education / Review Questions

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Bookshelf ID: NBK470596 PMID: 29261883