



Pharmacotherapeutic Applications, Mechanisms, and Clinical Management of Neostigmine: Implications for Pharmacists, Pharmacy Technicians, and

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Abstract

Background: Neostigmine is a reversible acetylcholinesterase inhibitor widely used in clinical practice, primarily for reversing non-depolarizing neuromuscular blockade during anesthesia. Its pharmacologic actions, peripheral selectivity, and broad therapeutic relevance necessitate a clear understanding of its clinical applications, safety profile, and monitoring requirements.

Aim: This review aims to summarize the pharmacotherapeutic applications, mechanisms, pharmacokinetics, administration considerations, adverse effects, and clinical precautions associated with neostigmine to support informed decision-making among pharmacists and healthcare professionals.

Methods: The article synthesizes peer-reviewed evidence and guideline recommendations, emphasizing FDA-approved indications, off-label uses such as acute colonic pseudo-obstruction, pharmacokinetic characteristics, dosing strategies, and monitoring standards.

Results: Neostigmine effectively reverses neuromuscular blockade by increasing acetylcholine availability at the neuromuscular junction. It demonstrates predictable pharmacodynamics, though clearance varies significantly with renal function. Off-label use in acute colonic pseudo-obstruction is supported by gastrointestinal and surgical society guidelines. Adverse effects include bradyarrhythmias, bronchoconstriction, excessive secretions, and paradoxical muscle weakness; these risks necessitate co-administration with antimuscarinic agents and continuous monitoring. Drug interactions, contraindications, and patient-specific considerations (pregnancy, renal impairment, pediatrics, geriatrics) further inform individualized therapy.

Conclusion: Neostigmine remains an essential pharmacologic tool for perioperative care and neuromuscular management. Optimizing its use requires precise dosing, vigilant monitoring, awareness of patient-specific risks, and interprofessional collaboration to enhance outcomes and minimize complications.

Keywords: Neostigmine, acetylcholinesterase inhibitor, neuromuscular blockade reversal, pharmacokinetics, adverse effects, acute colonic pseudo-obstruction, monitoring.

Introduction

Neostigmine is a water-soluble, ionized compound that functions as a reversible inhibitor of acetylcholinesterase, thereby increasing acetylcholine levels at neuromuscular junctions. This pharmacologic action forms the basis for its primary therapeutic applications in clinical practice. The United States Food and Drug Administration (FDA) has approved neostigmine for the reversal of neuromuscular blockade induced by non-depolarizing neuromuscular blocking agents. These agents are frequently used during surgical procedures to induce controlled muscle relaxation, facilitating optimal surgical

conditions. Administration of neostigmine following surgery allows the accumulation of acetylcholine at postsynaptic receptors, overcoming the competitive inhibition caused by non-depolarizing blockers. Consequently, skeletal muscle contractility is restored, enabling the patient to achieve spontaneous respiration, adequate airway protection, and the ability to maintain sufficient muscular function after anesthesia. This effect is critical in preventing postoperative respiratory complications and ensuring safe recovery from anesthesia.[1][2][3] Beyond its FDA-approved indications, neostigmine has several off-label uses that leverage its cholinergic effects. One

prominent application is the management of acute colonic pseudo-obstruction (ACPO), also known as Ogilvie syndrome, a condition characterized by acute colonic dilation without a mechanical or anatomic obstruction. While not formally approved for this indication, neostigmine is frequently administered when conservative measures, such as bowel rest, decompression, and supportive care, fail to alleviate colonic distension. Use in this setting requires careful patient selection and cardiovascular monitoring due to the risk of bradyarrhythmias and other cholinergic side effects, particularly in individuals with underlying cardiac conduction abnormalities or those with pacemakers.[4][5] Guidelines from the American Society for Gastrointestinal Endoscopy recommend neostigmine for ACPO when conservative management is ineffective after 72 hours, when patients are at risk for perforation, or when conservative measures are contraindicated. A second dose may be administered if the initial response is inadequate, provided no contraindications are present.[6] Similarly, the American Society of Colon and Rectal Surgeons endorses neostigmine as a nonoperative therapeutic option in cases of persistent ACPO absent mechanical obstruction or perforation.[7]

Neostigmine also has diagnostic utility, particularly in the assessment of neuromuscular disorders such as myasthenia gravis. The neostigmine test can aid in the diagnosis of myasthenia gravis, especially in seronegative patients or when electrodiagnostic studies are inconclusive. By temporarily improving neuromuscular transmission, neostigmine administration allows clinicians to evaluate muscle strength objectively, providing a functional assessment of neuromuscular junction integrity. This application is especially valuable in patients whose standard diagnostic studies fail to yield definitive results, serving as a reliable adjunctive tool in both diagnosis and clinical evaluation.[8][9] Overall, neostigmine's primary role in reversing non-depolarizing neuromuscular blockade remains central to perioperative management, while its off-label and diagnostic applications demonstrate its broader clinical utility. The drug's effects on cholinergic neurotransmission underpin both its therapeutic and diagnostic relevance, necessitating careful monitoring and individualized patient assessment to optimize safety and efficacy.

Mechanism of Action

Neostigmine exerts its pharmacologic effects through reversible inhibition of acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine at the neuromuscular junction. Acetylcholine, a primary neurotransmitter in somatic motor pathways, is synthesized, stored, and released from the terminals of motor neurons to transmit signals to skeletal muscle fibers. Under normal physiological conditions, acetylcholinesterase rapidly degrades acetylcholine into choline and acetic acid,

terminating synaptic transmission and allowing precise regulation of muscle contraction. As an acetylcholinesterase inhibitor, neostigmine binds to the active site of the enzyme, forming a covalent intermediate that prevents the hydrolysis of acetylcholine. Specifically, neostigmine interacts with the anionic and esteratic sites of acetylcholinesterase, creating a reversible blockade that allows acetylcholine to accumulate at the postsynaptic membrane. This increased concentration of acetylcholine enhances its availability to bind to nicotinic receptors on the muscle endplate, overcoming the competitive antagonism caused by nondepolarizing neuromuscular blocking agents administered during surgery. By promoting neuromuscular transmission, neostigmine accelerates the recovery of skeletal muscle function, facilitating spontaneous respiration, restoration of airway reflexes, and overall postoperative neuromuscular recovery.[10][11][12]

Neostigmine's pharmacokinetic properties are influenced by its quaternary ammonium structure, which renders it highly polar and prevents penetration of the blood-brain barrier. Consequently, its activity is largely restricted to the peripheral nervous system, minimizing central nervous system effects. This selective action ensures that neostigmine reverses neuromuscular blockade without significant neuropsychiatric or central autonomic effects. Overall, its mechanism involves targeted augmentation of acetylcholine at the neuromuscular junction, rapid reversal of pharmacologic paralysis, and restoration of functional muscle activity while maintaining a favorable safety profile in peripheral tissues [10][11][12].

Pharmacokinetics

Neostigmine demonstrates pharmacokinetic properties that are critical for its clinical application, particularly in the perioperative setting. The drug is most commonly administered via intravenous injection, which ensures complete bioavailability and rapid onset of action. This route bypasses the variable absorption associated with oral or intramuscular administration, providing predictable plasma concentrations necessary for timely reversal of neuromuscular blockade. Once in systemic circulation, neostigmine exhibits moderate protein binding, ranging from 15% to 25%, primarily to human serum albumin. Its volume of distribution (Vd) following intravenous administration ranges from 0.12 to 1.4 L/kg, indicating distribution largely within extracellular fluid with limited penetration into adipose tissue. This distribution profile supports its peripheral activity at neuromuscular junctions while minimizing central nervous system exposure due to its quaternary ammonium structure. Neostigmine undergoes metabolic transformation primarily through enzymatic hydrolysis by cholinesterases, with additional hepatic metabolism mediated by microsomal enzymes. These metabolic pathways

contribute to the drug's reversible action at acetylcholinesterase sites and its limited systemic accumulation. Elimination of neostigmine occurs predominantly via renal excretion. Its elimination of half-life varies with age, ranging from approximately 24 to 113 minutes, reflecting differences in renal function between neonates, pediatric patients, and adults. The dependence on renal clearance necessitates careful dosing in individuals with impaired renal function to avoid prolonged cholinergic effects. Overall, neostigmine's pharmacokinetic profile supports its rapid, targeted peripheral action, with predictable distribution and elimination that are integral to its safe and effective clinical use.[13]

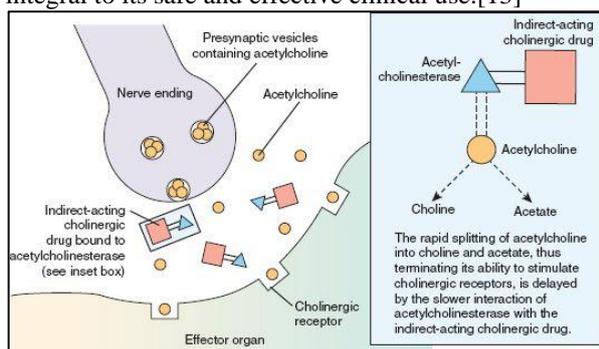


Fig. 1: Mechanism of Action.

Administration

Neostigmine is available in multiple dosage forms suitable for precise clinical use. Intravenous solutions include concentrations of 5 mg/10 mL and 10 mg/10 mL, while prefilled syringes are provided in 3 mg/3 mL and 5 mg/5 mL strengths. The primary clinical application of neostigmine is the reversal of nondepolarizing neuromuscular blockade following surgical procedures, typically administered via slow intravenous injection. Additionally, neostigmine can be used in the management of myasthenia gravis through intramuscular or subcutaneous routes, allowing flexibility depending on patient needs and clinical context. For adult patients undergoing reversal of neuromuscular blockade, a peripheral nerve stimulator is recommended to guide the timing and dosing of neostigmine. Therapy is initiated when the first twitch response exceeds 10% of the baseline measurement or when a second twitch is observable. The drug is delivered as an intravenous bolus, with a typical dosage range between 0.03 mg/kg and 0.07 mg/kg, not exceeding 5 mg. Higher doses are reserved for situations in which the first twitch response is near the 10% threshold but has not significantly surpassed it. Peak antagonistic effects are generally achieved within 7 to 10 minutes, and the duration of action extends approximately 55 to 75 minutes. To mitigate the parasympathomimetic effects that occur at muscarinic receptors outside the neuromuscular junction, neostigmine is routinely co-administered with an antimuscarinic agent, such as glycopyrrolate or atropine. This combination reduces adverse effects including bradycardia, salivation, and gastrointestinal

motility changes, while maintaining effective restoration of skeletal muscle function. Careful monitoring during administration ensures both efficacy and safety, allowing clinicians to optimize neuromuscular recovery and facilitate safe extubation and postoperative care.[14][15]

Specific Patient Populations

Neostigmine requires careful consideration in specific patient populations due to variations in pharmacokinetics, pharmacodynamics, and potential risks. In patients with hepatic impairment, the metabolism of neostigmine may be altered, as the drug undergoes biotransformation primarily through liver microsomal enzymes. Although formal pharmacokinetic studies in this population are lacking, clinicians are advised to exercise caution, as impaired hepatic function could lead to elevated plasma concentrations, prolonged effects, or increased risk of cholinergic adverse events. Close monitoring of clinical response and titration to effect are recommended in such cases. Renal impairment significantly affects neostigmine clearance. The elimination half-life is notably prolonged in patients with compromised kidney function. For example, transplant recipients have an average half-life of 104.7 minutes, whereas anephric patients may exhibit a half-life of up to 181 minutes. This prolongation increases the risk of excessive cholinergic stimulation, particularly with repeated dosing, and mandates careful adjustment and monitoring to avoid adverse outcomes.

Regarding pregnancy, no adequate, well-controlled studies have been conducted to establish the safety profile of neostigmine. Data remain limited, and the potential for fetal harm is unknown. Administration near term may cause uterine irritability and increase the risk of premature labor. Therefore, neostigmine should be used in pregnant patients only when clearly indicated, with benefits outweighing potential risks. During breastfeeding, neostigmine appears generally safe for short-term use, such as perioperative reversal of neuromuscular blockade. Clinical experience in treating myasthenia gravis suggests that single doses are unlikely to produce significant effects in breastfed infants due to the drug's short half-life. However, abdominal cramps in the neonate have been reported, and infants should be monitored if repeated doses are administered. Pyridostigmine is usually preferred for chronic management due to its more favorable safety profile. In pediatric patients, neostigmine is the preferred agent for reversing nondepolarizing neuromuscular blockade, demonstrating superior recovery compared with alternatives such as edrophonium. Although elimination half-life is shorter in children, distribution volumes are comparable to those in adults. Dose requirements are slightly lower in children, and reversal is guided by "train-of-four" monitoring. A dose of 20 µg/kg neostigmine, combined with 10–20

µg/kg atropine or 5–10 µg/kg glycopyrrolate, typically achieves effective restoration of muscle strength. Older adults may experience prolonged drug effects due to age-related reductions in renal function. Extended monitoring is necessary to ensure complete reversal of neuromuscular blockade and to prevent complications associated with residual paralysis. Overall, individualized dosing, careful monitoring, and awareness of organ function are essential when administering neostigmine across these vulnerable patient populations.[12]

Adverse Effects

Neostigmine is associated with a broad spectrum of adverse effects, many of which result from its cholinergic activity at muscarinic and nicotinic receptors throughout the body. Cardiac effects are among the most clinically significant, as neostigmine can induce bradyarrhythmias, including junctional escape rhythms, complete heart block, and in severe cases, asystole. These cardiovascular manifestations are mediated by stimulation of muscarinic receptors in the heart, which enhances parasympathetic activity and reduces heart rate. In vulnerable patients, such as those with preexisting conduction abnormalities, these effects can be life-threatening and necessitate close hemodynamic monitoring during and after administration.[16] Respiratory adverse effects are also critical, particularly bronchoconstriction. Neostigmine can activate muscarinic receptors in airway smooth muscle, potentially provoking bronchospasm, increased airway secretions, and difficulty with ventilation. To mitigate these risks, anticholinergic agents such as glycopyrrolate are coadministered. These agents have a similar onset of action and reduce bronchospasm, excessive salivation, and other parasympathetic-mediated effects. In pregnant patients, neostigmine crosses the placenta and can cause fetal bradycardia. Co-administration of atropine is often recommended to offset fetal and maternal parasympathetic stimulation, given its ability to traverse the placental barrier.[16] Another clinically relevant adverse effect is paradoxical muscle weakness, which may occur when excessive acetylcholine leads to overstimulation at the neuromuscular junction. This effect can manifest as reduced upper airway dilator muscle tone, diaphragmatic weakness, and decreased minute ventilation. Such complications increase the risk of postoperative respiratory compromise, especially if residual neuromuscular blockade is present or inadequately reversed. Comparative studies have highlighted the relative risks of neostigmine versus other reversal agents. For example, a meta-analysis evaluating neostigmine and sugammadex in patients undergoing bariatric surgery found that neostigmine is associated with a higher incidence of adverse outcomes, including postoperative residual curarization, nausea and vomiting, and cardiovascular complications. These findings underscore the

necessity for vigilant monitoring of hemodynamic status, respiratory function, and neuromuscular recovery to minimize perioperative morbidity. Overall, while neostigmine remains effective for reversing neuromuscular blockade, its adverse effect profile demands careful dose titration, coadministration of anticholinergic agents, and ongoing patient monitoring.[16][17]

Drug-Drug Interactions

Neostigmine interacts with several classes of drugs, primarily due to its effects on neuromuscular transmission. It should not be used to reverse the effects of depolarizing muscle relaxants, such as succinylcholine. In these cases, neostigmine can exacerbate or prolong the phase-1 neuromuscular block, leading to sustained paralysis and respiratory compromise. This occurs because acetylcholinesterase inhibition increases acetylcholine at the neuromuscular junction, which paradoxically maintains depolarization rather than reversing it. Aminoglycoside antibiotics, including streptomycin, neomycin, and kanamycin, also interact with neostigmine. These agents have inherent nondepolarizing neuromuscular blocking activity, reducing acetylcholine release and impairing neuromuscular transmission. When administered concurrently with neostigmine, their additive or synergistic effects can enhance muscle weakness or delay recovery from neuromuscular blockade. Clinicians must exercise caution, carefully adjust dosages, and closely monitor neuromuscular function to prevent respiratory complications and ensure effective reversal of blockade. These interactions highlight the importance of vigilance in perioperative medication management [17].

Contraindications

Neostigmine has several absolute contraindications that must be carefully considered before administration. Hypersensitivity to neostigmine is a primary contraindication, as exposure can precipitate severe allergic reactions, including anaphylaxis. The presence of peritonitis is another absolute contraindication, given the risk of exacerbating bowel dysfunction and increasing morbidity. Mechanical obstruction of the intestinal or urinary tract also precludes the use of neostigmine, as enhanced cholinergic activity may precipitate severe complications such as perforation or increased intraluminal pressure. Additionally, neostigmine should not be administered when absent twitch responses are observed on a peripheral nerve stimulator following nondepolarizing neuromuscular blockade, as this indicates a deep block that is unlikely to respond to acetylcholinesterase inhibition and may increase the risk of paradoxical muscle weakness.[18]

Warnings and Precautions

Neostigmine requires vigilance in patients with cardiovascular disease. Administration can induce bradyarrhythmias, hypotension, syncope, or even cardiac arrest, particularly in individuals with

preexisting coronary artery disease or recent acute coronary events. Anticholinergic agents such as atropine or glycopyrrolate should be readily available to mitigate these effects.[19] Cardiac arrhythmias are a recognized risk, with bradycardia being the most common manifestation. Clinicians must monitor cardiac function closely during administration. Hypersensitivity reactions, including severe anaphylaxis, have been reported. Immediate access to resuscitation equipment and emergency medications is essential when administering neostigmine, especially in high-risk settings.[20] Large doses of neostigmine can precipitate neuromuscular dysfunction, particularly if the depth of blockade is minimal. Adjusting the dose according to peripheral nerve stimulator readings reduces this risk and ensures effective reversal without excessive cholinergic stimulation. Overdose can lead to a cholinergic crisis, which clinically resembles a myasthenic crisis with profound muscle weakness, respiratory compromise, and potential airway obstruction. Distinguishing between the two is critical, as management differs. Cholinergic crisis requires immediate discontinuation of anticholinesterase agents and administration of atropine to counteract excessive muscarinic effects. Careful dose titration, adherence to monitoring protocols, and readiness to manage adverse reactions are essential for the safe use of neostigmine in clinical practice.

Monitoring

Effective monitoring is critical when administering neostigmine as a reversal agent for neuromuscular blockade. The timing of administration is a key determinant of efficacy and safety. Neostigmine should only be administered after a relative degree of spontaneous recovery of neuromuscular function has occurred. Administering the drug too early may result in "recurarization," a condition in which residual neuromuscular blockade persists or reappears in the postoperative recovery unit. This can manifest as unexpected postoperative weakness, respiratory compromise, or delayed recovery, despite apparent recovery indicated by a peripheral nerve stimulator. Studies indicate that up to 70% of acetylcholine receptors may remain blocked even when a "train-of-four" (TOF) count appears normal, highlighting the need for careful neuromuscular assessment before neostigmine administration. In patients with renal impairment, the duration of neostigmine's effect is prolonged due to reduced renal clearance, further emphasizing the importance of individualized monitoring and dosing adjustments. Quantitative neuromuscular monitoring, as recommended by the American Society of Anesthesiologists (ASA), is essential for guiding neostigmine use. Monitoring the adductor pollicis muscle ensures accurate assessment of the train-of-four ratio, which should reach 0.9 or higher before extubation. A TOF ratio below this threshold increases

the risk of residual blockade, whereas ratios above 0.7 may predispose to paradoxical muscle weakness if neostigmine is administered. Guidelines suggest specific dosing strategies based on the TOF count or ratio: when the count is 1 or absent, neostigmine should not be administered, and recovery should be awaited; when the count is 2 or 3, appropriate dosing is recommended, with extubation contingent on achieving a TOF ratio of at least 0.9; for ratios greater than 0.4, a moderate dose can be administered, while ratios above 0.7 indicate avoidance of neostigmine due to heightened risk of anticholinesterase-induced weakness. Although sugammadex is preferred for reversing deep, moderate, or shallow neuromuscular blockades induced by rocuronium or vecuronium, neostigmine remains a reasonable alternative for minimal blockade. Its use, however, requires careful titration, close observation for cholinergic effects, and continuous neuromuscular monitoring. Proper monitoring reduces the risk of postoperative residual curarization, prevents respiratory compromise, and ensures timely restoration of muscle strength, ultimately enhancing patient safety and improving postoperative outcomes.[21]

Toxicity

Neostigmine toxicity occurs when excessive inhibition of acetylcholinesterase leads to overstimulation of muscarinic and nicotinic receptors, producing a spectrum of adverse effects. Early signs of overdose typically involve muscarinic symptoms, including nausea, vomiting, diarrhea, excessive salivation, increased bronchial secretions, sweating, and bradycardia. These manifestations result from heightened parasympathetic activity at non-muscular acetylcholine receptor sites. Severe overdose can progress to a full cholinergic crisis, characterized by profound skeletal muscle weakness, generalized fatigue, and paralysis. In critical cases, respiratory muscles, including the diaphragm and intercostal muscles, may be compromised, leading to respiratory failure and potentially death if prompt intervention is not provided. Distinguishing a cholinergic crisis from a myasthenic crisis is essential, as their treatments are diametrically opposed: cholinergic crises require discontinuation of anticholinesterase agents, whereas myasthenic crises necessitate increasing anticholinesterase therapy to restore muscle strength.[10][22] Management of neostigmine overdose begins with immediate administration of atropine to counteract muscarinic effects such as bradycardia, bronchospasm, and excessive secretions. Close monitoring of cardiac function, airway patency, and respiratory status is required, and artificial ventilation should be initiated if respiratory compromise is observed. Muscle strength and neuromuscular function should be continuously assessed, preferably using a peripheral nerve stimulator. In the case of a cholinergic crisis, all anticholinesterase medications must be discontinued

immediately, and ventilatory support should be provided as needed. In contrast, a myasthenic crisis demands careful escalation of anticholinesterase therapy alongside symptomatic management of muscarinic side effects with atropine. Proper dosing, careful monitoring of neuromuscular recovery, and awareness of early signs of toxicity are critical for preventing severe complications and ensuring patient safety when using neostigmine in clinical practice.[23]

Enhancing Healthcare Team Outcomes

Optimizing patient outcomes with neostigmine requires a coordinated, interprofessional approach. The drug is primarily utilized by anesthesiologists, nurse anesthetists, emergency medicine physicians, and intensivists to reverse neuromuscular blockade or manage conditions such as myasthenia gravis. Because neostigmine can induce significant cholinergic effects, including bradycardia, excessive secretions, and potentially life-threatening bronchoconstriction, continuous monitoring of vital signs and neuromuscular function is essential. ICU nurses play a critical role in this monitoring, ensuring early detection of adverse effects and prompt intervention. Pharmacists contribute by advising the clinical team on proper dosing, monitoring for drug-drug interactions, and recommending dose adjustments for patients with renal or hepatic impairment. Their input is particularly important when patients have comorbid conditions that may alter the pharmacokinetics or pharmacodynamics of neostigmine. Pharmacists also guide the safe use of adjunct medications, such as anticholinergic agents, to mitigate muscarinic side effects. When managing patients with myasthenia gravis, neurologists and critical care physicians should be actively involved. The lowest effective dose should be administered and titrated based on patient response, while the team monitors for signs of cholinergic crisis. Effective communication among all members of the healthcare team—physicians, pharmacists, nurses, and specialists—is essential for ensuring coordinated care, reducing the risk of complications, and promoting patient safety. Structured interprofessional collaboration facilitates timely decision-making, appropriate titration of therapy, and rapid response to adverse events. It also ensures consistent education for patients and caregivers regarding the potential side effects, monitoring requirements, and follow-up care. By integrating expertise from multiple disciplines, healthcare teams can optimize the efficacy of neostigmine, minimize risks, and achieve improved short- and long-term patient outcomes [23].

Conclusion:

Neostigmine continues to play a central role in modern anesthetic and perioperative practice due to its proven efficacy in reversing non-depolarizing neuromuscular blockade and its broader diagnostic and therapeutic applications. Its mechanism—reversible inhibition of acetylcholinesterase—provides rapid restoration of neuromuscular function

when administered at appropriate stages of recovery. However, its narrow therapeutic margin underscores the importance of individualized dosing and careful clinical assessment. Patients with renal impairment, cardiovascular disease, or unique physiologic conditions such as pregnancy require heightened vigilance because altered pharmacokinetics may increase the risk of cholinergic toxicity. Adverse effects, particularly bradyarrhythmias, bronchoconstriction, excessive secretions, and paradoxical muscle weakness, necessitate co-administration with antimuscarinic agents and continuous monitoring to ensure safety. Quantitative neuromuscular monitoring remains essential to guide timing, prevent incomplete reversal, and avoid complications such as recurarization. Interprofessional collaboration—integrating physicians, pharmacists, nurses, and specialists—enhances therapeutic outcomes by ensuring appropriate dosing, minimizing interactions, and promoting rapid recognition of adverse effects. Overall, neostigmine is a highly effective agent when used within evidence-based parameters. Its safe and optimal use depends on clinical expertise, adherence to monitoring standards, and patient-specific considerations, ensuring improved postoperative recovery and patient safety.

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