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Mini Review

Neostigmine in the Sugammadex Era: Why the Older Reversal Agent Still Belongs in the Pharmacy

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Abstract

Neostigmine has reversed nondepolarizing neuromuscular blockade since the 1930s, and for most of that time, it was the only pharmacological reversal agent available to clinicians. Sugammadex changed the neuromuscular block reversal routine. Sugammadex reverses Rocuronium- and Vecuronium-induced blockade faster than Neostigmine and can reverse deeper levels of blockade when administered at an appropriate dose. Current American and European guidelines favor Sugammadex in several clinical settings. Thus, a growing number of clinicians may now complete training with limited experience administering Neostigmine. That shift is genuine but partial. Sugammadex binds only the aminosteroid neuromuscular relaxants Rocuronium and Vecuronium and does nothing for Cisatracurium or Atracurium, which means that when pharmacological reversal of benzylisoquinolinium blockade is required, an anticholinesterase remains necessary. Many hospitals and resource-limited settings continue to rely on Neostigmine because of availability and cost. Neostigmine also carries clinical applications outside anesthesia that Sugammadex cannot cover. This mini review makes the case that Neostigmine is not obsolete, that the reasons to keep it are structural rather than sentimental, and that clinicians with limited exposure to it still need to understand how it works and where it fails.

Introduction

Draw up the Neostigmine and the Glycopyrrolate, administer both, wait a few minutes, then extubate. For decades, that sequence defined neuromuscular block reversal, and most clinicians stopped thinking about the drug behind it. Neostigmine was synthesized in 1931 as a stable, water-soluble analogue of Physostigmine. Once curare reached the operating room, Neostigmine became the routine pharmacological answer to a paralyzed patient at the end of a case [1]. Sugammadex rewrote the neuromuscular block reversal routine. Sugammadex encapsulates Rocuronium and Vecuronium molecules in the plasma, reducing their availability at the neuromuscular junction and allowing reversal of even deep neuromuscular blockade within minutes when appropriately dosed [2]. The 2023 practice guidelines from the American Society of Anesthesiologists (ASA) recommend Sugammadex over Neostigmine in several situations involving Rocuronium- or Vecuronium-induced blockade, and the European Society of Anaesthesiology and Intensive Care guideline

similarly recognizes its advantages [3,4]. In hospitals that stock Sugammadex freely, an entire cohort of clinicians may finish training having administered Neostigmine rarely, if at all. It would be easy to write Neostigmine off. The move away from Neostigmine is real in well-funded operating rooms, but it is neither universal nor complete. The clinicians with limited experience using Neostigmine may be the ones who most need to understand it when it is the reversal agent available on the shelf. The reasons for keeping Neostigmine are built into chemistry, availability, and clinical practice.

Discussion

Sugammadex binds only half the neuromuscular relaxants

Sugammadex has a defined spectrum and does not widen. Sugammadex binds to the aminosteroid neuromuscular relaxants Rocuronium and Vecuronium and has no clinically useful affinity for the benzylisoquinolinium drugs [5]. A patient who received Cisatracurium or Atracurium will not achieve pharmacological reversal from a vial of Sugammadex. When pharmacological reversal is required following benzylisoquinolinium neuromuscular blockade, Neostigmine remains the conventional option. Cisatracurium remains useful in selected patients, including those with significant renal or hepatic dysfunction, where its organ-independent elimination is an important advantage. Neostigmine, in contrast, can antagonize nondepolarizing neuromuscular blockade by increasing acetylcholine at the neuromuscular junction rather than binding to one particular drug class. This broader pharmacological spectrum remains one advantage Neostigmine will not give up. No generic version of Sugammadex will change that.

One drug on the shelf

Price and availability have kept Sugammadex off many formularies. In some critical access hospitals, rural centers, and resource-limited health systems, Neostigmine may remain the only pharmacological reversal agent routinely available. There, Neostigmine is not the second choice. It is the available choice. Neostigmine's own price history shows how little drug cost has to do with pharmacology. After the FDA's Unapproved Drugs Initiative pushed Neostigmine through formal approval, the average noncontract price of a vial of Neostigmine reportedly climbed from about $28 to $175, a jump of more than 500%, while nothing about the molecule itself changed [6]. Generic Sugammadex is now beginning to enter the market. A generic product was reported to have received FDA approval in the United States in 2026, a development that may reduce the price gap between Sugammadex and Neostigmine [7]. Whether that change will alter formularies everywhere remains to be seen. A cheaper Sugammadex still does not reverse Cisatracurium or Atracurium.

A working life outside the operating room

Neostigmine does jobs Sugammadex was never designed for. The best evidence comes from acute colonic pseudo-obstruction, or Ogilvie syndrome, where a 2-milligram (mg) intravenous dose relieved colonic distension in 10 of 11 patients in a randomized trial, whereas none in the placebo group responded [8]. Neostigmine also has clinical applications outside the operating room, including selected situations involving myasthenia gravis and gastrointestinal dysmotility. The evidence and indications vary according to the clinical setting, but Sugammadex has no role in these conditions. A hospital pharmacist may therefore encounter a Neostigmine question from the medical floor or intensive care unit as readily as from the operating room.

What the Sugammadex generation never learned

Learning reversal as a single, dependable injection comes at a cost because Neostigmine is neither simple nor forgiving. Neostigmine has a ceiling effect. Once sufficient acetylcholinesterase inhibition has been achieved, additional Neostigmine may provide little further improvement in neuromuscular recovery while increasing the risk of muscarinic adverse effects [9]. The weak patient who appears to need more Neostigmine may be in a block too deep for an anticholinesterase to reverse effectively. In that situation, simply giving additional Neostigmine may not produce meaningful reversal and may instead increase adverse effects such as bradycardia and increased secretions. If the neuromuscular relaxant was Rocuronium or Vecuronium, Sugammadex may be the appropriate reversal strategy depending on the depth of blockade and the clinical circumstances. Otherwise, continued ventilation, monitoring, and time may be required. Neostigmine can also produce unwanted effects when administered after substantial spontaneous recovery from neuromuscular blockade. Neostigmine, given after recovery from blockade, has been shown to increase upper airway collapsibility and reduce handgrip strength in some experimental settings [10,11]. How much this weakness affects clinically meaningful recovery remains debated, and at least one randomized trial found no meaningful weakness after full spontaneous recovery [12]. Neostigmine is never a free injection. A patient who has already achieved adequate recovery,

confirmed with quantitative neuromuscular monitoring, may not benefit from additional Neostigmine. Because Neostigmine increases acetylcholine at muscarinic as well as nicotinic receptors, it is generally administered with an antimuscarinic agent, usually Glycopyrrolate and sometimes Atropine. The clinician who has trained mainly with Sugammadex may have limited experience with the pairing of Glycopyrrolate and Neostigmine, the risk of bradycardia and increased secretions, the slower onset and peak effect of Neostigmine, its effects on plasma cholinesterase, and its potential to prolong the action of a subsequent dose of Succinylcholine. These are not reasons to avoid learning Neostigmine. They are reasons to understand it.

Conclusion

Sugammadex is notably faster, reaches depths Neostigmine cannot reliably reverse, and may become increasingly affordable as generic products enter the market. Sugammadex gives clinicians a strong argument for using it when the clinical situation and neuromuscular blocking agent allow. That is not the same as an argument for forgetting Neostigmine. Neostigmine remains the conventional pharmacological reversal option for benzylisoquinolinium neuromuscular relaxants when reversal is required. It continues to be widely relevant where Sugammadex is unavailable or not routinely stocked, and it has clinical roles outside anesthesia that Sugammadex does not share. The decision to reach for Sugammadex or Neostigmine should not be made in isolation from the patient or the block. The decision should be based on the neuromuscular blocking agent used, the depth of the neuromuscular block, the patient's clinical condition, and the availability of quantitative monitoring. The literature is clear on one point: residual neuromuscular blockade remains a risk when recovery is not adequately assessed before extubation. Both the ASA and European Society of Anaesthesiology and Intensive Care guidelines emphasize the importance of quantitative neuromuscular monitoring and confirmation of adequate recovery before extubation.3,4 The choice of reversal agent matters, but so does knowing the block that needs to be reversed. Measure the neuromuscular block level, confirm adequate recovery before extubation, and let the number help decide. A clinician who truly understands Neostigmine already knows why.

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