NEOSTIGMINE VERSUS SUGAMMADEX FOR REVERSAL OF NEUROMUSCULAR BLOCK

Neostigmine is the classic acetylcholinesterase antagonist, which is widely used for reversal of neuromuscular block of all nondepolarising relaxants. This is a pharmacodynamic effect secondary to inhibition of the acetylcholine esterase at the neuromuscular endplate, resulting in a subsequent increased and prolonged effect of acetylcholine on the free endplate receptors. That is why, an overdose of nondepolarising muscle relaxant, blocking the entire endplate receptors’ pool cannot be antagonized by neostigmine resulting in the so-called “neostigmine-resistant curarization”.

“Neostigmine-resistant curarization” has been described by Hunter 1956. However, Churchill-Davidson (1959) stressed the fact that there are many causes of prolonged cessation of respiration, and before the term “neostigmine-resistant-curarization” can be accepted, it is first necessary to prove that a neuromuscular block is in fact present, and secondly that neostigmine fails to reverse the block.

Using the isolated phrenic nerve diaphragm preparation, immersed in Krebs solution. Baraka (1964) demonstrated that there is a ceiling to the maximum reversal capacity of neostigmine. Neostigmine could not reverse neuromuscular block of an overdose of tubocurarine which was added to the perfusion bath. This in-vitro-observation was confirmed in vivo by Baraka (1967) who showed in man that reversal of neuromuscular block by neostigmine depended on the degree of neuromuscular block and the plasma level of tubocurarine at the time of reversal. Neostigmine could not reverse the doses of tubocurarine that are much greater than the blocking dose. In addition, the report showed that the plasma level of tubocurarine following reversal by neostigmine is not significantly different from that observed without neostigmine reversal, suggesting the fact that reversal of nondepolarising block by neostigmine is a pharmacodynamic, and not a pharmacokinetic effect. This finding has been confirmed by Waser who showed that the radioactive curare concentration in the diaphragm remains the same before and after reversal of neuromuscular block by neostigmine. That is why, reversal of curare by neostigmine cannot be achieved if the whole endplate receptor pool is occupied by the neuromuscular blocker.

The degree of reversal of nondepolarising neuromuscular block by neostigmine can be monitored by the train-of-four fade (Hassan Ali et al, 1975). T-O-F fade ratio <0.7-0.9 is associated with upper airway obstruction, inadequate recovery of pulmonary function, reduced pharyngeal muscle coordination, increased risk of aspiration, and impaired hypoxic ventilation response.

Because of the possible limitations, and muscarinic side-effects of the pharmacodynamic reversal of neuromuscular block by neostigmine, the possibility of pharmacokinetic reversal by
sugammadex (a modified gamma cyclodextrin) has been recently introduced into clinical anesthesiology practice. As mentioned by Miller, and Naguib, the introduction of sugammadex is another milestone in clinical neuromuscular pharmacology, which provides an opportunity to change the practice of anesthesiology.

Sugammadex offers a new approach for reversal of nondepolarising neuromuscular block; it exerts its reversal effect by forming very tight combination in a 1:1 ratio with the steroidal neuromuscular blocking agents (rocuronium > vecuronium > pancuronium) (Bom et al. 2002). Intravenous administration of sugammadex during rocuronium-induced neuromuscular blockade results in a guest-host complex in equilibrium with a very high association rate and very low dissociation rate resulting in rapid removal of free rocuronium from the plasma. This creates a concentration gradient favoring movement of rocuronium from the neuromuscular junction into plasma where it is encapsulated by the free sugammadex molecules. Therefore, the neuromuscular blockade of rocuronium is terminated rapidly by the diffusion of rocuronium away from the neuromuscular junction into the plasma.

In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%), and to a lesser extent degree by renal excretion (10%-25%). However, because of the soluble nature of the rocuronium-cyclodextrin complex, urinary excretion becomes the major route of elimination. One of the features that makes sugammadex so different from anticholinesterases is that it takes effect more quickly and reliably than neostigmine, even when an overdose of the nondepolarising relaxants is occupying the entire endplate receptor pool.

In conclusion, reversal of nondepolarising neuromuscular block by neostigmine is a pharmacodynamic effect secondary to inhibition of the acetylcholine-esterase. The accumulated acetylcholine will act on the free endplate receptors. Thus, an overdose of nondepolarising relaxants blocking the whole receptors’ pool cannot be reversed by neostigmine resulting in the so-called “Neostigmine-resistant curarization”. The advantage of reversal of nondepolarising block by neostigmine is its low cost, and its broad spectrum reversal of all nondepolarising relaxants.

The advantage of sugammadex for reversal of nondepolarising neuromuscular block is the absence of the muscarinic side-effects of neostigmine. Also, it can reverse the neuromuscular, even in the presence of an overdose blocking the whole receptors’ pool. However, the reversal effect of sugammadex is limited to the steroidal neuromuscular blockers such as rocuronium. Also, its cost is much higher than that of neostigmine.

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References
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³ Train-of-four
² Post-tetanic count
† Second twitch


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