EDITORIAL

"NEOSTIGMINE-RESISTANT CURARIZATION"

The concept of "neostigmine-resistant curarization" was introduced by Hunter 1956[1]. However, Churchill-Davidson 1959 stated that before the concept of "neostigmine-resistant curarization" can be accepted, it is first necessary to prove that a neuromuscular block was in fact present, and second, that neostigmine failed to reverse the blockade[2].

Baraka has shown in–vitro using the isolated phrenic nerve-diaphragm preparation, as well as in the anesthetized human, that neostigmine can only reverse a blocking dose of tubocurarine. In contrast, an overdose cannot be readily reversed by neostigmine, confirming the statement that "neostigmine-resistant curarization" really exists[3-6]. Using the isolated phrenic nerve-diaphragm preparation of rats, the addition of neostigmine to the perfusion bath of a preparation just blocked by tubocurarine could reverse completely the neuromuscular block. However, if an overdose of tubocurarine is added to the perfusion bath, complete neuromuscular block occurred despite the presence of a reversal dose of neostigmine in the bath. Further additional dose of neostigmine could not reverse the block[6]. These results have been confirmed in man by showing that adequate reversal of neuromuscular block by neostigmine is only achieved against doses of tubocurarine that are not much greater than the blocking concentrations. Doubling the dose of tubocurarine was only partially reversed, while tripling the dose could not be reversed irrespective of using additional doses of neostigmine[3-6].

The reversal effect of neostigmine is secondary to its antiacetylcholinesterase activity. The accumulated acetylcholine does not reverse nondepolarizing neuromuscular block by displacing the relaxant molecules from the receptors (i.e. pharmacokinetic effect), but probably by its action on the free endplate cholinergic receptors (i.e. pharmacodynamic action). This has been shown by Waser 1967 in the mouse diaphragm autoradiographs by the use of labeled curarine; the minimum lethal dose of radiocurarine was mixed with the reversal dose of neostigmine; although neuromuscular transmission was restored, radioactivity in the endplate was not noticeably diminished[7].

In contrast with the pharmacodynamic reversal by neostigmine, the mechanism of reversal of aminosteroided NMBs such as rocuronium by the ∞-cyclodextrin sugammadex is a pharmacokinetic process secondary to encapsulation of the steroid relaxant molecule in the central compartment. This process will decrease the plasma level of the free (unbound) NMB concentration. Due to the binding of NMB, a concentration gradient develops that moves the relaxant molecules from the biophase towards the central compartment by diffusion. This causes liberation of the acetylcholine receptors to which acetylcholine can then bind[8,9].

In non-curarized muscles, the cholinergic endplate receptors are around 5,000,000, while the released acetylcholine needs to attach itself to only 500,000 receptors to result in muscle contraction. The rest of the receptors can be considered according to Paton and Waud as "safety margin". Thus, to achieve neuromuscular block by one ED95 of a nondepolarizing relaxant about 75%-90% of the receptors (i.e. the safety margin) need to be occupied, and only 10-25% of the receptors are free[10]. An overdose of curare will occupy the remaining 10-25% of the receptor sites, and hence the neuromuscular cannot be reversed, irrespective of the neostigmine dose used.

Normally, the ACh released is rapidly hydrolysed by the acetylcholinesterase enzyme in less than 1 millisecond. The addition of neostigmine which inhibits the enzyme will delay the hydrolysis of the released acetylcholine resulting in an increase of its concentration and its duration of action. Initially, it has been thought that reversal of nondepolarising block by neostigmine is due to displacement of the curare molecules from the endplate receptors by the accumulated acetylcholine. However, it has been shown by Waser using the radioactive curare that the concentration of curare at the receptors remains constant following reversal of the neuromuscular block by neostigmine[7]. This has been confirmed by Baraka in-vivo[3-5] who showed in man that the serum concentrations of tubocurarine were not different whether reversal could be achieved or not achieved. Thus, the results of Waser in animals, and by Baraka in man confirm that reversal of antidepolarizing neuromuscular block by neostigmine is a pharmacodynamic and not pharmacokinetic effect. It also confirms that overdose of relaxant which occupies the endplate receptors explains the so called "neostigmine-resistant curarization".

Neostigmine reverses nondepolarising neuromuscular block by inactivating acetylcholinesterase. There is an optimal dose of neostigmine for reversal. Doses exceeding 0.05-0.07 mg.kg-1 are unlikely to achieve any additional effect and may decrease rather than improve neuromuscular transmission. Neostigmine may even cause neuromuscular transmission failure when given in overdose to patients who have already recovered from neuromuscular block. This can impair upper airway dilator volume, genioglossus muscle function and diaphragmatic function[11,12].

Incomplete recovery of neuromuscular transmission is an important contributing factor in the development of postoperative respiratory events. In a prospective blinded study, Berg et al[13] have shown that the incidence of postoperative pulmonary complication was <5% in patients receiving the intermediate-acting muscle relaxants such as atracurium and vecuronium, and in those patients who received pancuronium and had T-O-F ratios ≥0.7 at the end of surgery. However, pancuronium when associated with a T-O-F ratio <0.7 resulted in a threefold increase in the probability of respiratory complications. The authors concluded that residual curarization caused by a long-acting neuromuscular blocker is a significant risk factor for postoperative pulmonary complications.

Monitoring Of Postoperative Residual Curarizaiton (PORC)

For many years, a train-of-four T-O-F ratio 0.7 was considered sufficient to exclude PORC[14]. Clinically, this level of neuromuscular block is characterized by the ability to maintain 5 seconds head lift and hand grip, to protrude the tongue, as well as a return to normal eye-lid tone and jaw tone, and recovery to an adequate tidal volume, vital capacity and inspiratory force. However, in recent years, a T-O-F ratio of 0.7 does not guarantee sufficient neuromuscular recovery, and today's general consensus is that to exclude clinically significant PORC, the T-O-F ratio should be ≥0.9. Even at a T-O-F ratio of ≥0.9 or 1.0 measured at the adductor pollicis muscle, some subjects still have impaired pharyngeal or respiratory function[15].

Subjective monitoring of neuromuscular block by visual or tactile evaluation of the response to nerve stimulation may decrease but does not exclude the risk of PORC. Objective monitoring by actual quantification of the T-O-F ratio is ≥0.9. Good practice based on evidence dictates that objective monitoring should be the acceptable standard of care whenever neuromuscular block is used. T-O-F ratio ≤0.9 patients are more likely to develop postoperative hypoxemia and to experience symptoms of muscle fatigue than those whose T-O-F ratio equaled or exceeded this ratio.

Skeletal muscles such as masseter muscle[16] contract not as a single twitch response but as a tetanic response usually above 10-20 Hz, and not at 2 Hz which is the frequency of stimulation by the T-O-F. Thus, a T-O-F ratio of 0.7 or even 0.9 does not guarantee complete neuromuscular recovery. Therefore, it may be advisable, before recovery of patient from anesthesia, to check the recovery of neuromuscular transmission by the traditional tetanic fade and post-tetanic facilitation, using tetanic stimulation at high frequency of 50 Hz applied for 5 seconds. The muscular response is perceived as a sustained forceful contraction with no fade when neuromuscular recovery is achieved. In the presence of residual neuromuscular block, tetanic fade is observed. Double-burst stimulation may be a suitable alternative; it consists of two bursts of stimuli at 50 Hz with an interval of 750 ms. Each burst consists of 3 impulses. A fading of the second impulse series compared to the first correlates with an incomplete neuromuscular recovery[17]. The method is more sensitive for tactile evaluation of a residual blockade in comparison with a tactile evaluation of the fade using TOF stimulation[18].

In conclusion, "neostigmine-resistant curarization" does exist. An overdose of the antidepolarizing neuromuscular blockers, whether absolute or relative, is the most important contributing factor. Objective monitoring should be the acceptable standard whenever neuromuscular blockers are used during anesthesia. However, clinical evaluation should remain as the golden standard of care.

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