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Editorial

Reversal of Nondepolarizing Neuromuscular Block by Neostigmine

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Editorial

"Neostigmine-resistant curarization" has been described by Hunter [1]. However, Churchill-Davidson [2] 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 that neostigmine failed to reverse the blockade.

Paton and Waud [3] showed that in order to achieve neuromuscular block by curare, it is necessary to have a minimum of 70% of the endplate receptor sites occupied by curare; complete neuromuscular block was seen when about 90% occupancy of the receptor sites is achieved. An overdose of tubocurarine will result in 100% occupancy.

Adequate reversal of nondepolarising neuromuscular block by neostigmine is only achieved against doses of tubocurarine that are not much higher than the blocking dose. A blocking dose of nondepolarising blocker could be reversed adequately with neostigmine. Doubling the dose necessitates a much higher concentration of neostigmine for reversal, while a triple dose could not be reversed irrespective of the dose of neostigmine used, resulting in the so-called "Neostigmine-resistant curarization".

The phenomenon of "neostigmine-resistant curarization" has been confirmed by Baraka using in-vitro experiments, and in-vivo clinical investigations. Using the isolated phrenic nerve-diaphragm preparation of rat immersed in krebs solution, Baraka [4] observed that neostigmine cannot reverse an overdose of tubocurarine added to the perfusion bath. This has been confirmed clinically in man by Baraka [5,6] who showed that the maximum antagonism of nondepolarising neuromuscular block with neostigmine is only achieved against levels of tubocurarine that are not much greater than the blocking concentration. Complete nondepolarising neuromuscular block is achieved when 75-90% of the endplate receptors is occupied. Thus, a higher concentration of tubocurarine can occupy the remaining free receptors of the endplate receptors pool, and hence the accumulated acetylcholine on the free following neostigmine administration is either partially or completely ineffective.

Normally, about 500,000 of the 5 million available endplate receptors are activated by acetylcholine released by a single nerve impulse. Thus, a large number of receptors are in "reserve", and could be occupied by an agonist. The antagonist action of acetylcholine esterase inhibitors such as neostigmine has been attributed to delayed hydrolysis of acetylcholine with consequent prolongation of its action, and increased concentration. Thus, the reversal effect of neostigmine may be attributed to potentiation of the action of acetylcholine on the free endplate receptor (i.e. a pharmacodynamic effect), and/or to displacement of the curare molecules from the endplate receptors (i.e. a pharmacokinetic effect). However, using radioisotopes, Waser [7] has shown that reversal of nondepolarising neuromuscular block by anticholinesterases is not secondary to displacement of the curare molecules from the endplate receptors. This has been confirmed by Baraka [5,6] in man who showed that reversal of tubocurarine neuromuscular block by neostigmine does not change the plasma levels of tubocurarine.

The experimental work of Waser, and the clinical findings of Baraka suggest that the reversal of nondepolarising neuromuscular block by neostigmine is not a pharmacokinetic process, but is a pharmacodynamic process enforcing the action of acetylcholine on the free endplate receptors unoccupied by curare. That is why, an overdose of nondepolarising relaxants which block the whole endplate receptor pool cannot be reversed by neostigmine, resulting in the so-called "neostigmine-resistant curarization".

In conclusion, an antagonism of nondepolarising neuromuscular block by neostigmine is a pharmacodynamic effect secondary to its anticholinesterase action which increases the concentration and duration of action of the chemical transmitter acetylcholine in the free endplate receptors unoccupied by curare. That is why an overdose of curare which blocks the whole receptor pool can result in the so-called "neostigmine-resistant curarization".

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