Title: MIXTURES OF NEOSTIGMINE AND EDROPHONIUM ARE NOT SYNERGISTIC

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The antagonism of non-depolarizing neuromuscular blockade can be achieved more rapidly with equipotent doses of edrophonium than neostigmine.[1] In addition, the pattern of train-of-four recovery is different after each drug[2] which suggests that their sites of action may also differ. The present study was designed to determine whether equipotent combinations of edrophonium and neostigmine would augment the antagonism of pancuronium compared with either agent alone.

Patients & Methods: The protocol was approved by the Hospital Ethics Committee. After informed consent, 54 adult patients, ASA class I or II, undergoing elective procedures were studied. Anesthesia was induced with thiopental, 3-5 mg/kg and maintained with 70% nitrous oxide and supplemented with halothane (0.5-1.5% inspired). Neuromuscular transmission was measured with train-of-four stimulation applied every 12 seconds to the ulnar nerve at the elbow. The force of contraction of the adductor pollicis was measured with a Grass FT 10 transducer and recorded on a pen and ink recorder.

After stabilization of the twitch recording, pancuronium (5 mg/70 kg) was given as a bolus which produced twitch depression greater than 90% in all patients. When the height of the first twitch in the train recovered to 10% of the control value the block was antagonized with either neostigmine (0.01, 0.02, and 0.04 mg/kg) or edrophonium (0.2, 0.6, and 1.0 mg/kg). Each dose was given to 6 patients.

Log-dose response curves were constructed from the % recoveries of neuromuscular activity 10 min after administration of the anticholinesterase and regression lines constructed by the least squares regression method. Combinations of edrophonium and neostigmine using half the dose of each which produced 50%, 70% and 90% recovery of neuromuscular function were given to three further groups, of 6 patients each, and log-dose response curves constructed.

Results: The calculated ED_{50} and ED_{90} for neostigmine and edrophonium and the relative potencies are shown in table 1. The log-dose response curves were parallel as demonstrated by the same potency ratio (16:1) at each dose. Combinations of antagonists had simple additive effects without potentiation (table 2).

Table 1
Dose-responses of edrophonium and neostigmine

	ED_{50}	ED_{90}
	μg/kg	
Neostigmine	10.5	51
Edrophonium	167	828
Potency Ratio	16:1	16:1

Table 2
Pancuronium antagonism after edrophonium-neostigmine mixtures

	Expected Antagonism %	Actual Antagonism %
Edrophonium-	50	50.9 ± 1.7
Neostigmine-	70	71.5 ± 3.7
Combination	90	80.6 ± 2.8

Discussion: These results demonstrate that neostigmine is 16 times more potent than edrophonium in the antagonism of neuromuscular block produced with bolus doses of pancuronium. These results are similar to the potency ratio of 12:1 found by Cronnelly et al[1] in the antagonism of neuromuscular block produced by a continuous infusion of d-tubocurarine.

The edrophonium-neostigmine combination did not potentiate the antagonism. This does not rule out the possibility of different sites of action for the two drugs, but demonstrates the absence of synergism if different sites exist. In clinical practice the mixture of edrophonium and neostigmine appears not to offer any advantage over either agent alone.

References:

1. Cronnelly R, Morris RB, Miller RD. Edrophonium: Duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 1982; 57:261-6.

2. Donati F, Ferguson A, Bevan DR. Twitch depression and train-of-four ratio after antagonism of pancuronium with edrophonium, neostigmine or pyridostigmine. Anesth Analg 1983,62:314.