Title: DOSE-RESPONSE: ONSET AND DURATION OF EDROPHONIUM-PYRIDOSTIGMINE MIXTURES

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Introduction: If muscle relaxant antagnoists share a similar mechanism, additive effects (1+1=2) should result from their mixture. However, edrophonium may have a predominant presynaptic mechanism compared to neostigmine or pyridostigmine. (1,2)Therefore, mixtures of edrophonium with neostigmine or pyridostigmine may demonstrate inhibitory (1+1=1) or potentiating (1+1=3) effects during reversal of neuromuscular blockade. To examine this we determined the dose-response, onset and duration of antagonism induced by edrophonium-pyridostigmine mixtures in anesthetized patients. Results are compared with data reported for edrophonium, neostigmine and pyridostigmine given alone. (2,3)

Methods: After obtaining informed consent approved by the Committee on Human Research, 12 adult surgical patients were anesthetized with Thiopental (2-4mg/kg), nitrous oxide (60%), and Halothane (0.6-0.7% end-tidal as measured by mass spectrometry). Force of thumb adduction in response to supramaximal ulnar nerve stimulation (0.15 Hz at 0.15ms) was measured and recorded. d-Tubocurarine was administered by continuous infusion at a rate sufficient to maintain a 90% depression of muscle twitch tension Following at least 20-30 minutes of stable twitch tension, glycopyrrolate (0.1-0.2mg) was administered followed within 3-4 min. by a mixture of edrophonium and pyridostigmine. The mixtures contained edrophonium, 0.02mg/kg, plus pyridostigmine, 0.035mg/kg (n=4), edrophonium, 0.032mg/kg, plus pyridostigmine, 0.05mg/kg (n=4), edrophonium, 0.08mg/kg, plus pyridostigmine, 0.08mg/kg (n=4). These doses represent combinations of the ED_{10} (that dose producing 10% antagonism) $+ED_{10}$, the $ED_{20}+ED_{20}$, and the $ED_{40}+ED_{40}$ for each agent. These doses were calculated from previous dose response data and responses were confirmed.(2) The d-Tubocurarine infusion was continued until a stable 90% depression of muscle twitch height was re-established. Time for twitch tension to increase to peak antagonism (onset of action); and to decrease to 50%, and then 30% of peak effect (duration of action); were recorded, as was the magnitude of antagonism. Data were analyzed by analysis of variance, with differences considered significant at P=0.05.

Results: The time from administration of the mixtures until peak antagonism was very slow, ranging from 12.2 ± 1.6 min (mean-standard error) to 19.3 ± 1.9 min (Table I). The magnitude of antagonism was not different from that predicted on the basis of additive responses (Table I). The duration of antagonism was not significantly different from that seen with pyridostigmine alone. (Table I)

Conclusion: Mixtures of edrophonium and pyridostigmine did not result in antagonism of rapid onset and prolonged duration of action. Because of the discrepancy in onset times for the components of the mixture, onset time was essentially that of pyridostigmine alone.(3) Dose-response data indicated simple addition of effect from these two compounds and therefore does not support the concept of different mechanisms or sites of action. The duration of antagonism produced by the mixture was not different than that observed with pyridostigmine alone.(3) Combination of a long acting drug with one of shorter duration might be expected to produce a duration of action not different from that of the longer acting component. This is in fact what was observed. We conclude that mixture of edrophonium and pyridostigmine were additive and provide no clinical advantage.

TABLE I

Onset, Magnitude and Duration of Antagonism (mean ± SE)

Dose	Onset (min)	Magnitude %*	Duration (min) 50**	30**
$ED_{10}+ED_{10}$	19.3 ± 1.9	22 ± 2.8	62 ± 7.8	74 ± 9
$ED_{20}+ED_{20}$	17.6 ± 0.9	39 ± 6.2	70 ± 13.4	91 ± 9.6
$ED_{40}+ED_{40}$	12.6 ± 1.7	71 ± 9.2	110 ± 5	137 ± 7
Edrophonium ED_{80}	1.2 ± 0.2	80 ± 5.6	43 ± 5	66 ± 7
Pyridostigmine ED_{80}	12.2 ± 1.6	80 ± 4.8	83 ± 7.1	130 ± 7.0

*% of dTC depressed twitch antagonized.
**% of peak antagonism during wanning of effect.

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