Title: COMPARISON OF REVERSAL EFFECTS OF ANTICHOLINESTERASE DRUGS ALONE AND IN COMBINATION

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Introduction. The site of action and the latency period differs for each anticholinesterase drug. For example, edrophonium acts predominately on presynaptic receptors, pyridostigmine acts at postsynaptic receptors and neostigmine acts at pre and post synaptic regions. Edrophonium is known to have a more rapid onset of action than pyridostigmine, and neostigmine acts faster than pyridostigmine. This study sought to determine the effect of these drugs individually and in combination for reversing a nondepolarizing neuromuscular blockade.

Method. Eighteen mongrel dogs (8-10 kg) were used. Anesthesia was induced and maintained using pentobarbital. After tracheal intubation, ventilation of the lungs was controlled using a volume ventilator. The right hind limb was fixed to a rigid framework with a nail driven through the distal end of the femur. The gastrocnemius tendon was isolated, cut distally and attached to a force displacement transducer. Isometric tension in the muscle was recorded using a 50 gm preload. The sciatic nerve was stimulated (rectangular supramaximal pulse of 1 millisecond duration with a 0.1 Hz(frequency) using bipolar electrodes. Blood pressure, ECG and esophageal temperatures were continuously monitored. The experimental animals were divided into three groups of six dogs each. The 50% degree of twitch depression was maintained constant for at least 5 minutes before intravenous administration of anticholinesterase drugs. The anticholinesterase drugs were given in the following dosage schedule:pyridostigmine 0.1 mg/kg, edrophonium 1 mg.kg, neostigmine 0.015 mg/kg. Individual drug dose was halved with any combination of drugs. Each animal was subjected to three sets of experiments (two individual drugs and a combination) with an interval of 2 hours between each experiment. The order of administration and sequence of administration was randomized. Twitch height and the time to reach the peak twitch height were measured. Data were analyzed with F test and two way analysis of variance and Student's t-test.

Results. The effects of anticholinesterase drugs on twitch height are summarized in Table 1. The combination of pyridostigmine and neostigmine produced a greater increase in twitch height (30%) than pyridostigmine alone but this was not statistically significant. This combination however produced a greater increase in twitch height(87%, P 0.001) than neostigmine alone. The combination of pyridostigmine and edrophonium produced an increase in twitch height that was 32% less than pyridostigmine alone and 17% less than edrophonium alone. The combination of neostigmine and edrophonium provided the poorest reversal among three combinations.(see the ratio in Table I). As shown in Table II the time to reach the peak height was 3 minutes with edrophonium, 13 minutes with neostigmine, and 18 minutes with pyridostigmine (Table II) The time to reach peak height with combinations of edrophonium and pyridostigmine or neostigmine was similar to edrophonium alone. Combinations of pyridostigmine and neostigmine produced a time to peak height similar to that of each drug alone (14 minutes).

Discussion.Any combination with edrophonium produced poorer reversal than that of the drug alone. Also the time to reach peak height in combination with edrophonium is always the same as edrophonium alone. This suggests that the combination of two drugs which have different time courses for producing effects at the neuromuscular junction do not additive effects but rather antagonize each other. The direct effect of edrophonium at presynaptic sites is to evoke the release of acetylcholine, which is an all or none phenomenon. Therefore, the second drug which has a slower time course to effect can not provide additional effects at the presynaptic sites. The effect of combining neostigmine and pyrodostigmine is synergestic compared to neostigmine alone. This may have clinical significance. When additional anticholinesterase is required after neostigmine administration, pyridostigmine may provide synergestic effects beyond that provided by additional neostigmine.

Conclusions. Administration of combinations of drugs with similar effects can produce synergistic effect was seen only with the combination of pyridostigmine and neostigmine. The other two combinations produced less reversal than the same drug alone. When additional neostigmine is required for complete reversal after the first neostigmine administration, pyrodostigmine may be a better choice than neostigmine.

TABLE I

Increased muscle twitch height (in mm)
after the administration of anticholinesterase(s)

	E	P	E+P	E	N	E+N	P	N	P+N
Anticholinesterase muscle twitch height mm	20.6	23.2	17.6	26	15	14.1	26.2	18.2	34.1
Standard Deviation of error	2.3	3.7	2.8	2.6	0.8	0.7	2.6	1.1	3.2
The ratio between the single and the combination	E: E+P = 1: 0.85			E: E+N = 1:0.54			P: P+N = 1:1.30		
	P: E+P = 1: 0.75			N: E+N = 1:0.94			N: P+N = 1:1.87		
T-Test	E: E+P P< 0.001			E: E+N P<0.001			P: P+N P<0.001		
	P: E+P N.S.			E: E+N N.S.			P: P+N N.S.		

E - Edrophonium N - Neostigmine P - Pancuronium N.S. - not significant

TABLE II

Time to reach peak height (in min)
after administration of anticholinesterase(s)

Anticholinesterase	E	P	E+P	E	N	E+N	P	N	P+N
Mean (min)	3.1	17.1	3.4	3.0	13.9	2.5	19.0	12.8	14.1
Standard Deviation of error	0.2	1.9	0.4	0.4	0.6	0.4	1.4	1.1	0.9