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Dose-response Curves for Edrophonium, Neostigmine, and Pyridostigmine after Pancuronium and D-tubocurarine

F. Donati, Ph.D., M.D., F.R.C.P.(C.), S. M. McCarroll, M.B., F.F.A.R.I.C.S.,† C. Antzaka, M.D.,† D. McCready,‡ D. R. Bevan, M.B., M.R.C.P., F.F.A.R.C.S.§*

To determine the potencies of neostigmine, pyridostigmine, and edrophonium in reversing pancuronium and d-tubocurarine blockade, dose-response curves were established for first twitch height recovery and train-of-four ratio. One hundred and twenty ASA physical status I or II patients scheduled for elective surgery received either 0.06 mg/kg pancuronium or 0.36 mg/kg d-tubocurarine during a thiopental-nitrous oxide-enflurane anesthetic. Train-of-four stimulation was applied every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When first twitch height had recovered spontaneously to 10% of its initial value, neostigmine (0.005, 0.01, 0.02 or 0.05 mg/kg), pyridostigmine (0.02, 0.04, 0.1, or 0.2 mg/kg), or edrophonium (0.1, 0.2, 0.4 or 1 mg/kg) was injected by random allocation. Recovery was measured 10 min after the injection of the antagonist. First twitch ED50's were 0.013, 0.085, and 0.17 mg/kg after pancuronium, and 0.017, 0.11, and 0.27 mg/kg after d-tubocurarine, for neostigmine, pyridostigmine, and edrophonium, respectively. The ED50 for pyridostigmine and edrophonium obtained after d-tubocurarine was significantly larger ($P < 0.05$) than that after pancuronium. The train-of-four dose-response curves were significantly flatter for edrophonium than for the other two agents, indicating a greater ability of edrophonium to antagonize fade at low doses. It is concluded that the potency of reversal agents may be different for different relaxants, and that potency ratios might depend upon the end-point chosen as full neuromuscular recovery. (Key words: Antagonists, neuromuscular relaxants: neostigmine; pyridostigmine; edrophonium. Monitoring: train-of-four. Neuromuscular relaxants: d-tubocurarine; pancuronium.)

EDROPHONIUM, NEOSTIGMINE, AND PYRIDOSTIGMINE are used clinically to reverse non-depolarizing neuromuscular blockade.[1,2] They differ in the mechanism of their interactions with acetylcholinesterase,[3] and their onset times.[1] In addition, they may have effects other than acetylcholinesterase inhibition.[4]

Dose-response curves have been obtained during constant infusions at 90% d-tubocurarine,[2] pancuronium,[5] and vecuronium[5] blockade, using single twitch stimulation. However, in the clinical setting, reversal agents are administered when neuromuscular function recovers spontaneously, and the potency of these drugs is not necessarily the same as during a constant infusion of relaxant. The relationship between train-of-four fade and first twitch depression depends on the relaxant[6] and the reversal agent used.[7,8] These observations suggest that the neuromuscular blocking drugs and their antagonists may have different mechanisms of action,[7,9] and that the potency of reversal agents might depend on the relaxant used. In addition, dose-response relationships for the reversal agents have not been made with train-of-four stimulation, which is a more sensitive index of neuromuscular recovery.[10,11]

Therefore, this study was designed to establish dose-response relationships for edrophonium, neostigmine, and pyridostigmine after neuromuscular blockade had been produced with either of d-tubocurarine or pancuronium. The reversal agent was given at the same level of spontaneous recovery of first twitch tension in all patients (10% of control). Recovery was assessed at a fixed, clinically relevant time (10 min) after injection of the reversal drug. Train-of-four monitoring was used, and dose-response relationships were established for recovery of both first twitch tension and train-of-four ratio.

Patients and Methods

After approval by the Hospital Ethics Committee, 120 patients, ASA physical status I or II, were studied during various elective surgical procedures of at least 90 min duration. Patients with hepatic, renal, or neuromuscular disease were excluded, as were those with electrolyte abnormality and those taking any medication known or suspected of interfering with neuromuscular function. The patients were randomized into 24 groups of five. They received either pancuronium or d-tubocurarine as a relaxant, and neostigmine, pyridostigmine, or edrophonium as an antagonist. For each agent, four doses were selected in the range which was expected to produce 20–90% recovery of single twitch tension.[2]

Premedication with atropine, 0.006–0.01 mg/kg, or glycopyrrolate, 0.003–0.005 mg/kg, and morphine, 0.1 mg/kg, or meperidine, 1 mg/kg, was given intramuscularly 1 h before the scheduled start of the surgical procedure. On arrival in the operating room, the patients' ECG and blood pressure were monitored. Anesthesia was

* Assistant Professor of Anaesthesiology, Departments of Anaesthesia, Royal Victoria Hospital & McGill University.

† Clinical Fellow, Departments of Anaesthesia, Royal Victoria Hospital & McGill University.

‡ Organon Pharmaceuticals.

§ Professor of Anaesthesiology and Chairman, Departments of Anaesthesia, Royal Victoria Hospital & McGill University.

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Address reprint requests to Dr. Donati: Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, H3A 1A1, Canada.

TABLE 1. Demographic Data

Group		Sex (M/F)	Age (yr) (Mean ± SEM)	Weight (kg) (Mean ± SEM)
Relaxant	Reversal			
Pancuronium	Neostigmine	9/11	45 ± 3	66 ± 3
Pancuronium	Pyridostigmine	10/10	44 ± 3	72 ± 3
Pancuronium	Edrophonium	8/12	46 ± 3	68 ± 3
d-Tubocurarine	Neostigmine	11/9	51 ± 4	71 ± 3
d-Tubocurarine	Pyridostigmine	8/12	47 ± 3	68 ± 2
d-Tubocurarine	Edrophonium	8/12	48 ± 3	69 ± 3

induced with thiopental, 3–5 mg/kg, and maintained with nitrous oxide (70%) and enflurane (.5–1.5% inspired) in oxygen. The ulnar nerve was stimulated supramaximally at the elbow with square pulses of 0.2 ms in duration, delivered at a frequency of 2 Hz for 2 s and repeated every 12 s. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis muscle was measured with a force-displacement transducer (Grass FT-10), and recorded on paper. A baseline was established after induction of anesthesia, while the patient was manually ventilated *via* a mask. Then, either pancuronium, 0.06 mg/kg, or d-tubocurarine, 0.36 mg/kg, was given intravenously as a single bolus. If this initial dose did not produce at least 95% reduction of the amplitude of the first twitch, increments of 0.5 mg pancuronium or 3 mg d-tubocurarine were given until development of at least 95% block. Endotracheal intubation was accomplished when maximum neuromuscular block was achieved, and the patients were ventilated using a Mapleson D circuit with fresh gas flow of 70 $ml \cdot kg^{-1} \cdot min^{-1}$, which maintained the measured end-tidal CO_2 partial pressure in the range of 30–40 mmHg. After tracheal intubation, the inspired concentration of enflurane was maintained constant.

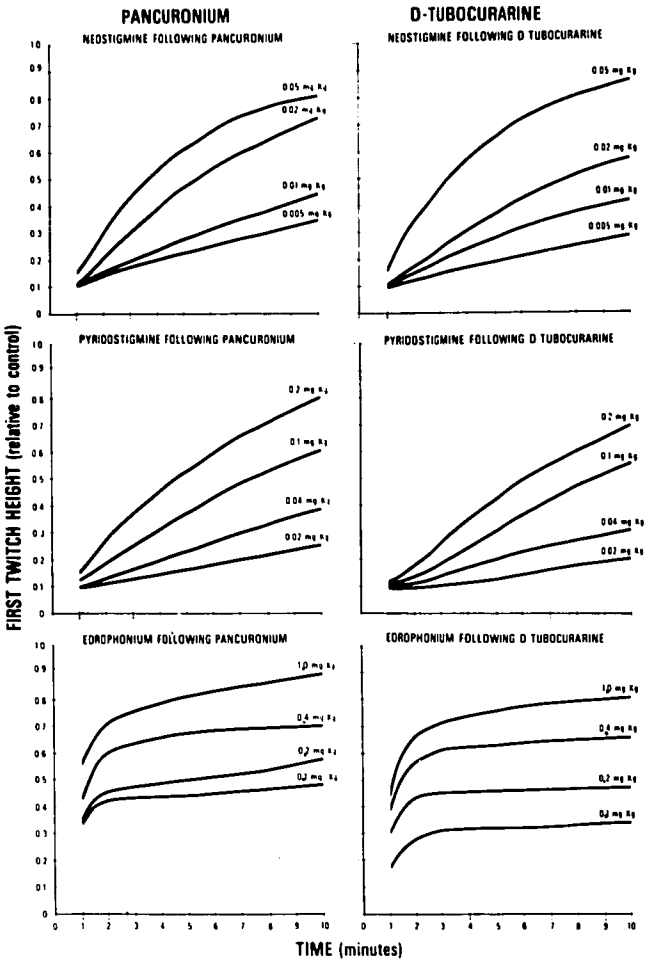

FIG. 1. Time course of first twitch height *versus* time after administration of reversal agent for all doses used, after pancuronium (left) and d-tubocurarine blockade (right). Mean values only are shown. Standard errors have been omitted for the sake of clarity.

When the amplitude of the first twitch had recovered to 10% of its initial value, one of the three reversal agents was given in one of the four doses chosen by random allocation, with atropine, 0.4–1.5 mg. These were neostigmine 0.005, 0.01, 0.02, or 0.05 mg/kg, pyridostigmine 0.02, 0.04, 0.1, or 0.2 mg/kg, or edrophonium 0.1, 0.2, 0.4, or 1 mg/kg. No further reversal agent was given for at least 10 min. Then, an additional dose was given to bring the train-of-four ratio to at least 0.7.

Dose-response curves were constructed using amplitude of the first twitch and train-of-four ratio measured 10 min after the antagonist was given. The logit transformation of recovery of the first twitch was plotted against the logarithm of the dose.[12] The effect of the reversal agent was estimated by subtracting from the total measured recovery the anticipated spontaneous recovery, which was obtained by extrapolating the twitch height linearly from the last 5 min before the reversal agent was given.

The relationship between train-of-four ratio and dose of reversal agent was plotted in the same way, except that no extrapolation was attempted because train-of-four ratio was zero in all cases when the reversal agent was given and was expected to remain at zero for the following 10 min. Linear regressions were made from the logit-log plot, and confidence intervals were obtained by evaluating the standard error of estimate.[13] Comparisons were made between the two relaxants using Student's *t* test. When comparing the three reversal drugs, analysis of variance was made, and if a statistically significant difference was found, the Bonferroni correction was applied.[14] Results were considered statistically significant when the *P* value was 0.05 or less.

Results

The patients' demographic data are presented in table 1. There were 54 males and 66 females. The mean age

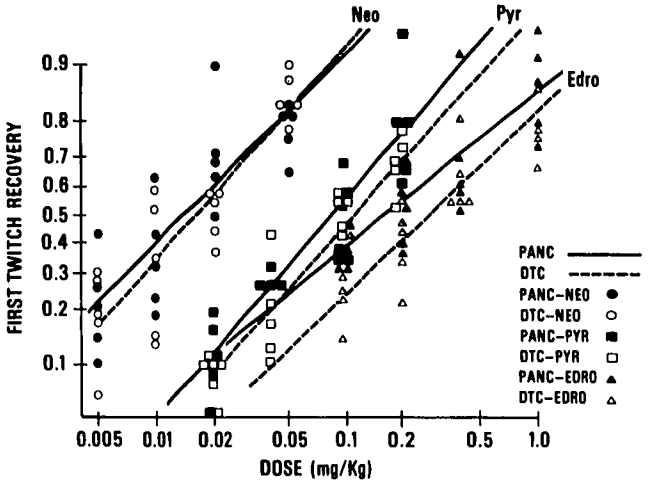

FIG. 2. Dose-response curves for first twitch height recovery, obtained 10 min after injection of the reversal agent.

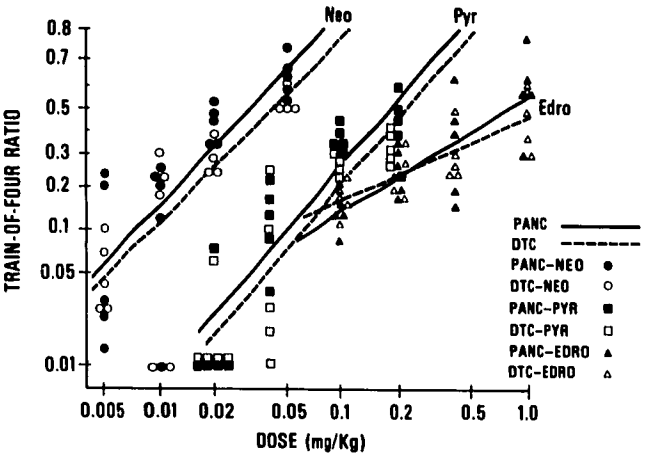

FIG. 3. Dose-response curves for train-of-four ratio, obtained 10 min after the injection of the reversal agent.

(±S.D.) was 47 (±13) yr and the mean weight was 69 (±12) kg. All groups were comparable.

Spontaneous recovery before the reversal agent was given was faster with pancuronium than d-tubocurarine. Mean time (±SEM) from 5% to 10% first twitch height recovery was 8.0 (±1.2) min for pancuronium and 13.0 (±1.9) min for d-tubocurarine ($P = 0.03$).

The effect of the reversal agents on first twitch height is shown in figure 1. At all doses, the effect of edrophonium was rapid and sustained, pyridostigmine had a slow onset, and the action of neostigmine was intermediate. Figure 2 shows dose-response curves for first twitch height 10 min after administration of the reversal agent. The curves did not deviate significantly from parallelism. Table 2 shows the doses required for 50% (ED50) and 80% (ED80) recovery. Neostigmine could not be shown to antagonize one relaxant better than the other, whereas pyridostigmine and edrophonium had a lower ED50 when used to antagonize pancuronium. Neostigmine was found to be 6.3 (±1.1) times as potent as pyridostigmine with pancuronium blockade and 6.7 (±0.9) times with d-tubocurarine blockade. It was 12.4 (±2.5) and 16.2 (±2.6) times as potent as edrophonium, with pancuronium and d-tubocurarine, respectively.

Figure 3 shows the dose-response relationships for the train-of-four ratio. Analysis of variance indicated that the slopes of these lines were statistically different both after d-tubocurarine ($P = 0.0003$) and pancuronium ($P = 0.005$) blockade. With both relaxants, the edrophonium curve was significantly flatter than that of the other agents. The dose required for a train-of-four ratio of 0.5 (ED50) of all reversal agents was larger with d-tubocurarine, but the difference was significant only in the case of edrophonium (table 3).

The potency ratios varied with the level of train-of-four recovery, because of the different slopes of the dose-response curves. At a train-of-four ratio of 0.5, neostigmine was 5.8 (±1.1) times as potent as pyridostigmine to antagonize pancuronium, and 5.4 (±1.1) times as potent to antagonize d-tubocurarine. Compared with edrophonium, neostigmine was 25 (±3) and 28 (±3) times as potent in antagonism of pancuronium and d-tubocurarine, respectively.

TABLE 2. Dose Required (mg/kg) for 50% (ED50) and 80% (ED80) Recovery of First Twitch Height 10 Min after Injection of Reversal Agent

	Pancuronium	d-Tubocurarine	P
Neostigmine			
ED50	0.013 ± 0.0015	0.017 ± 0.0012	NS
ED80	0.045 ± 0.0055	0.045 ± 0.0034	NS
Pyridostigmine			
ED50	0.085 ± 0.0054	0.11 ± 0.005	0.001
ED80	0.22 ± 0.015	0.30 ± 0.014	0.02
Edrophonium			
ED50	0.17 ± 0.024	0.27 ± 0.027	0.006
ED80	0.68 ± 0.102	0.88 ± 0.093	NS

Discussion

This study demonstrated that the effect of the reversal agents may depend on the relaxant used. Both pyrido-

TABLE 3. Dose Required (mg/kg) for 50% Recovery of Train-of-four Ratio 10 min after Injection of Reversal Agent

	Pancuronium	d-Tubocurarine	P
Neostigmine	0.031 ± 0.004	0.043 ± 0.006	NS
Pyridostigmine	0.18 ± 0.017	0.23 ± 0.023	NS
Edrophonium	0.77 ± 0.11	1.23 ± 0.16	0.025

stigmine and edrophonium were more effective against pancuronium than d-tubocurarine blockade. In addition, the edrophonium dose-train-of-four recovery relationship was flatter than with the other reversal agents, suggesting a different mechanism of action. Ten minutes was chosen as the end-point of reversal action because it is clinically acceptable. Also, it is close to the peak action of both neostigmine (7 min) and pyridostigmine (12 min), when these drugs are administered during a constant infusion of d-tubocurarine.[2] Peak action of edrophonium occurs much earlier (figure 1),[2] but the effect is sustained, such that dose-response relationships at 10 min are not different than at 2 min.

Enflurane potentiates d-tubocurarine and pancuronium neuromuscular blockade[15,16] and the inhalational agent most likely delayed the time to 10% spontaneous recovery in this study.[17] The effect of enflurane is time dependent,[18] but the decrease in twitch height at 1.3–1.4% end-tidal, is only 9% per hour, an effect which is unlikely to affect the action of reversal agents over a 10 min period. Using the same end-tidal concentrations of enflurane, Delisle and Bevan[17] found a slight impairment of recovery, especially at times longer than 10 min after the administration of neostigmine. In the current study, mean end-tidal enflurane concentrations were approximately 0.6%, because mean inspired values were about 1.0%, *i.e.*, much lower than in the preceding studies.[17,18] Thus, the effect of these small concentrations of enflurane on assisted recovery, once 10% spontaneous recovery is attained, is expected to be negligible. Indeed, the ED50 for recovery of first twitch obtained in this study for neostigmine and edrophonium were comparable with those reported in a similar study where halothane was the inhalational agent and pancuronium the relaxant.[19] The ED50's for neostigmine and edrophonium were 0.0105 and 0.167 mg/kg, respectively, compared with 0.013 and 0.17 mg/kg in this study. In spite of corrections made for spontaneous recovery, the reversal agents were expected to be more potent when given during the spontaneous recovery phase following a bolus dose than during a constant infusion of relaxant. This is because relaxant molecules displaced from the receptor by excess acetylcholine might move more easily away from the neuromuscular junction if plasma concentrations are declining.

When neostigmine was used to antagonize a constant 90% block produced by an infusion of d-tubocurarine, Cronnelly *et al.*[2] reported an ED50 of 0.022 mg/kg, slightly greater than the value of 0.017 mg/kg in this study. The same methodology was used for a pancuronium infusion, and the ED50 of neostigmine was 0.010 mg/kg,[7] which was less than the value of 0.013 mg/kg reported here. Nevertheless, the different estimates are comparable, considering the dispersion of results. This suggests that the ED50 of neostigmine obtained during a constant infusion of a relaxant is close to that found after a bolus dose of pancuronium or d-tubocurarine, probably because of the rather slow elimination of these relaxant drugs. On the other hand, following a bolus dose of a more rapidly eliminated relaxant, such as vecuronium or atracurium, neostigmine would be expected to be more potent. The dose of neostigmine required to reverse neuromuscular blockade was less after a bolus dose of vecuronium than pancuronium,[20] whereas it was the same when the relaxants were given as constant infusions.[5]

The ED50 of pyridostigmine for recovery of first twitch during a constant infusion of d-tubocurarine (0.098 mg/kg)[2] is similar to the value reported here (0.11 mg/kg). However, edrophonium appeared more potent during a d-tubocurarine infusion (ED50 = 0.125 mg/kg)[2] than after a bolus dose of the drug (ED50 = 0.27 mg/kg). The effect of edrophonium peaks in less than 2 min, so that the potency calculated 10 min after the injection of the drug may be an underestimate. However, there was very little change between 2–10 min with any of the doses used (fig. 1), and the ED50, if calculated on the basis of recovery at 2 min, was similar to that at 10 min. The dispersion of values, which tended to be greater with edrophonium than for neostigmine or pyridostigmine, might play an important role in the discrepancy, but a different behavior of edrophonium when used to antagonize a bolus dose of a relaxant cannot be excluded.

The dose-response curves obtained after d-tubocurarine and pancuronium were different, especially for pyridostigmine and edrophonium. The reason for this differential effect on first twitch height is unclear. The pre-synaptic effects of d-tubocurarine, as estimated by the relationship between train-of-four fade and first twitch depression, are probably greater than those of pancuronium,[8,11] but this should have a minimal influence on recovery of first twitch height. The preferential binding of pancuronium to one alpha subunit of the acetylcholine receptor as opposed to the other[21,22] might play a role. Acetylcholine needs to bind to both alpha subunits of the receptor to activate it. Pancuronium seems to have a preference for one of these subunits,[21] and it is likely that the reversal of a block which implies displacement of one molecule, instead of two, from the receptor would be easier to accomplish. In addition, the reversal agents have properties other than acetylcholinesterase inhibition,[4] and may interact with different relaxants in different ways. Whatever the mechanism, the dose-response curve for a reversal drug might depend on which relaxant was used to produce the block. This is reflected in the longer time required for neostigmine to antagonize gallamine compared with d-tubocurarine or pancuronium.[23]

Dose-response relationships obtained after train-of-four

stimulation may be more important than after single twitch stimulation, because the former is a more sensitive indicator of neuromuscular blockade.[10,11] With edrophonium, train-of-four recovery was greater after reversal of pancuronium than d-tubocurarine. This was expected, because d-tubocurarine exhibits more fade than pancuronium.[6] Compared with neostigmine, the potency ratios of pyridostigmine and edrophonium obtained with pancuronium or d-tubocurarine were similar. Whereas pyridostigmine's potency ratio was approximately the same for train-of-four as for first twitch recovery (about 6), edrophonium was less capable of reversing fade (potency ratio of 25–28) than first twitch (potency ratio of 12–16). This seems to contradict the prediction made from train-of-four analysis in a previous study, where it was observed that edrophonium had a greater ability to reverse fade.[7] In fact, the fade-reversing effect of edrophonium has been observed only when reversal was incomplete, corresponding to train-of-four ratios of 0.1–0.3,[7] and in the antagonism of mild block.[8] The results of the current investigation explain the previous findings by demonstrating a flatter dose-response curve for edrophonium (fig. 3). Thus, the fade-reversing properties of edrophonium are observed at low doses, but this comparative advantage is lost at higher doses.

The data obtained in this study suggest that adequate reversal (100% first twitch recovery and 70% or more train-of-four ratio) might be achieved by using doses greater than used clinically or by waiting longer than 10 min. For example, if given during pancuronium blockade at 10% first twitch height recovery, the usual clinical dose of neostigmine, 0.04 mg/kg, would be expected to produce 80% first twitch height recovery and 57% train-of-four ratio after 10 min. With d-tubocurarine, the corresponding figures are 79% first twitch height and 47% train-of-four ratio. Similarly, with pyridostigmine, 0.2 mg/kg, one would be expected to achieve first twitch height recoveries of 79% and 71%, and train-of-four ratios of 45% and 37% after pancuronium and d-tubocurarine, respectively. Under the same conditions, edrophonium, 1.0 mg/kg, would produce 78% and 72% first twitch height recovery and 42% and 37% train-of-four ratio, respectively. Thus, if usual doses of either reversal agent are used following pancuronium or d-tubocurarine blockade, neuromuscular recovery should be expected to be incomplete after 10 min.

However, several factors favor a much more complete reversal in clinical practice. First, if two or more twitches are visible following train-of-four stimulation, then first twitch height is greater than 10% as used in this study. Time to full recovery would be expected to be shorter, because it is inversely related to the degree of spontaneous recovery.[24] Second, other muscles, such as the diaphragm, are much less sensitive to relaxants than the adductor pollicis.[25,26] Third, the reversal agent is normally given when alveolar concentrations of inhalational agent decrease, whereas they were kept constant in the current study. Finally, if atracurium or vecuronium is used, reversal might be more rapid. Thus, the potency of reversal agents should be considered relaxant-dependent and their effects should be assessed with train-of-four monitoring as well as observation of the patient's ability to breathe, cough, and maintain a patent airway.

References

1. Ferguson A, Egerszegi P, Bevan DR: Neostigmine, pyridostigmine, and edrophonium and antagonists of pancuronium. ANESTHESIOLOGY 53:390–394, 1980
2. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. ANESTHESIOLOGY 57:261–266, 1982
3. Wood M: Cholinergic and parasympatomimetic drugs. Cholinesterases and anticholinesterases, Drugs and Anaesthesia. Edited by Wood M, Wood AJJ. Baltimore, Williams and Wilkins, 1982, pp 111–140
4. Miyamoto MD: The actions of cholinergic drugs on motor nerve terminals. Pharmacol Rev 29:221–247, 1978
5. Gencarelli PJ, Miller RD: Antagonism of ORG NC45 (vecuronium) and pancuronium neuromuscular blockade by neostigmine. Br J Anaesth 54:53–56, 1982
6. Williams NE, Webb SN, Calvey TN: Differential effects of myoneural blocking drugs on neuromuscular transmission. Br J Anaesth 52:1111–1115, 1980
7. Donati F, Ferguson A, Bevan DR: Twitch depression and train-of-four ratio after antagonism of pancuronium with edrophonium, neostigmine, or pyridostigmine. Anesth Analg 62: 314–316, 1983
8. Jones RM, Pearce C, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453–457, 1984
9. Bowman WC: Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 59:935–943, 1980
10. Waud BE, Waud DR: The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. ANESTHESIOLOGY 37:314–422, 1972
11. Ali HH, Utting JE, Gray C: Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 42:967–978, 1970
12. Norman J: Drug receptor reaction, Pharmacokinetics of Anaesthesia. Edited by Prys-Roberts C, Hug CC Jr. Oxford, Blackwell Scientific Publications, 1984, pp 25–37
13. Dixon WJ, Massey FJ Jr: Introduction to Statistical Analysis, 3rd edition. New York, McGraw-Hill, 1969, p 195
14. Wallenstein S, Zucker LL, Fleiss JL: Some statistical methods useful in circulation research. Circ Res 47:1–9, 1980
15. Gencarelli PJ, Miller RD, Eger EEII, Newfield P: Decreasing enflurane concentrations and d-tubocurarine neuromuscular blockade. ANESTHESIOLOGY 56:192–194, 1982
16. Fogdall RP, Miller RD: Neuromuscular effects of enflurane, alone and in combination with d-tubocurarine, pancuronium and succinylcholine, in man. ANESTHESIOLOGY 42:173–178, 1976
17. Delisle S, Bevan DR: Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. Br J Anaesth 54:441–445, 1982

18. Stanski DR, Ham J, Miller RD, Sheiner LB: Time-dependent increase in sensitivity to d-tubocurarine during enflurane anesthesia in humans. ANESTHESIOLOGY 52:483–487, 1980
19. Breen PJ, Doherty WG, Donati F, Bevan DR: The potencies of edrophonium and neostigmine as antagonists of pancuronium. Anaesthesia 40:844–847, 1985
20. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R: Clinical pharmacology of ORG NC 45 (Norcuron). ANESTHESIOLOGY 55:6–11, 1981
21. Sine SM, Taylor P: Relationship between reversible antagonist occupancy and the functional capacity of the acetylcholine receptor. J Biol Chem 256:6692–6699, 1981
22. Waud BE, Waud DR: Interaction among agents that block endplate depolarization competitively. ANESTHESIOLOGY 63:4–15, 1985
23. Miller RD, Larson CP, Way WL: Comparative antagonism of d-tubocurarine, gallamine, and pancuronium-induced neuromuscular blockade by neostigmine. ANESTHESIOLOGY 37:503–509, 1972
24. Rupp SM, McChristian JW, Miller RD, Toboada JA, Cronnelly R: Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium or vecuronium. ANESTHESIOLOGY 64:711–717, 1986
25. Wymore ML, Eisele JH: Differential effects of d-tubocurarine on inspiratory muscles and two peripheral muscle groups in anesthetized man. ANESTHESIOLOGY 48:360–362, 1978
26. Donati F, Antzaka C, Bevan DR: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. ANESTHESIOLOGY 65:1–5, 1986