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# *Comparative Antagonism of* d-*Tubocurarine-, Gallamine-, and Pancuronium-induced Neuromuscular Blockades by Neostigmine*

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The durations of neuromuscular blockades with various doses of *d*-tubocurarine (*d*Tc), gallamine, and pancuronium, without and with neostigmine reversal, were determined in 60 unpremedicated surgical patients anesthetized with nitrous oxide–halothane. Neostigmine, 0.25 mg, was administered intravenously every 3 minutes, beginning when twitch height showed 5 per cent recovery of the control twitch height. During spontaneous recovery from relaxant effects, times to achieve twitch heights which were 5 per cent of control twitch heights increased equally for *d*Tc, gallamine, and pancuronium to doses of 12, 80, and 2.4 mg/m$^2$, respectively. However, with gallamine, 120 mg/m$^2$, this time was 80 to 100 per cent longer than with *d*Tc, 18 mg/m$^2$, or pancuronium, 3.6 mg/m$^2$. Significantly more neostigmine (30 to 50 per cent) was needed to antagonize blockades produced by gallamine. These results suggest that the mechanism of action of gallamine may differ from those of *d*Tc and pancuronium. (Key words: Pancuronium; *d*-Tubocurarine; Gallamine; Neostigmine; Antagonism; Neuromuscular blockade.)

GALLAMINE was originally described as a nondepolarizing muscle relaxant, with a duration of action slightly shorter than that of *d*-tubocurarine (*d*Tc), and it was said to be readily antagonized by neostigmine.[1] However, occasional clinical reports have suggested that more neostigmine is needed to antagonize neuromuscular blockades produced by gallamine than is needed to antagonize those produced by either *d*Tc or pancuronium, even in the presence of normal renal function.[2-4] These reports prompted us to evaluate the ability of neostigmine to antagonize equivalent degrees of neuromuscular blockade produced by *d*Tc, gallamine, and pancuronium. We also compared dose–duration curves of these three relaxants, using larger doses than those studied by Lund and Stovner.[5] The results of this study confirm the observation that more neostigmine is needed to antagonize a neuromuscular blockade induced by gallamine than to antagonize blockades by either *d*Tc or pancuronium.

## Methods

Sixty unpremedicated surgical patients were studied intraoperatively. Their mean body surface area and mean age were 1.71 ± 0.17 (SD) m$^2$ and 55 ± 15 (SD) years. The operative procedures were total hip arthroplasty (29 patients), craniotomy (13), intra-abdominal operations (12), and upper-extremity operations (6). Anesthesia was induced and maintained with halothane and 60 per cent nitrous oxide and the trachea was intubated without the use of other drugs. End-tidal concentrations of halothane, determined by ultraviolet analysis, were held between 0.45 and 0.75 per cent. Anesthesia was maintained for at least 35 minutes before the first injection of a muscle relaxant was made. Controlled ven-

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tilation kept $Pa_{CO_2}$ at 36 ± 4 (SD) torr. Esophageal temperature was between 35.3 and 36.8 C. Neuromuscular transmission was studied by stimulation of the ulnar nerve at the wrist, and force of thumb adduction was measured with a force-displacement transducer.[6, 7] A voltage at least two times that necessary to evoke a maximal twitch response was used. A Grass S-44 stimulator was used to administer single stimuli of 0.1 msec duration.

Each patient received an initial dose of *d*Tc chloride, 6, 12, or 18 mg/m²; or gallamine triethiodide 40, 80, or 120 mg/m²; or pancuronium bromide 1.2, 2.4, or 3.6 mg/m², intravenously (iv). Five patients were studied at each dose of muscle relaxant. During spontaneous recovery from relaxant effect, additional doses of *d*Tc, 3 mg/m², or gallamine, 20 mg/m², or pancuronium, 0.6 mg/m², were given when twitch height had recovered to 5 per cent of control twitch height. None of the patients studied had any history of renal disease. Urinary outputs of patients who received more than 120 mg/m² of gallamine were always more than 30 ml/hour. Each patient received only one relaxant. Five per cent recovery time was defined as that time from administration of relaxant to recovery of 5 per cent of the control twitch height. For example, if a control twitch height of 40 mm were completely abolished (100 per cent block), a 5 per cent recovery time would be that time from relaxant administration to appearance of a twitch height of 2 mm. If the control twitch height of 40 mm were partially abolished to 10 mm (75 per cent block), a 5 per cent recovery time would be that time from relaxant administration to appearance of a twitch height of 11.5 mm (10 mm plus 5 per cent of the depressed twitch height of 30 mm). When the end of the operative procedure was near and when twitch height had recovered to 5 per cent of control twitch height, neostigmine, 0.25 mg, and atropine, 0.1 mg, were administered iv every three minutes until adduction of the thumb was sustained in response to a tetanic stimulus of 50 Hz for 5 seconds (sustained tetanus). At this time, neuromuscular block was considered to be completely antagonized. Although more than 50 per cent of the receptors may be occupied in the presence of sustained tetanus at 50 Hz,[8] tetanic stimuli using greater frequency were not used because inhalation anesthetics themselves cause fade at higher frequencies.[6] The doses of neostigmine necessary for 20, 50, and 80 per cent recovery of control twitch height, sustained tetanus, and absence of posttetanic facilitation were determined. The maximally facilitated twitch arbitrarily must be two or more times greater than the pretetanus twitch for posttetanic facilitation to be considered present.[9]

The remaining 15 patients received *d*Tc, 12 mg/m², gallamine, 80 mg/m², or pancuronium, 2.4 mg/m², intravenously, and the neuromuscular blockades which ensued were not antagonized by neostigmine. Times from relaxant administration to 20, 50, and 80 per cent return of control twitch height, sustained tetanus, and absence of posttetanic facilitation were determined and the results compared with those obtained when the blocks from those doses of relaxants were antagonized by neostigmine.

Analysis of variance and the Studentized range test were used for part of the statistical analyses. Linear regression and correlation coefficient analysis were carried out for the remaining results.[10]

## Results

Complete abolition of twitch height occurred with all initial doses of relaxant administered except in two instances with gallamine, 40 mg/m² (68 and 85 per cent depression of twitch height), in one patient after *d*Tc, 6 mg/m² (92 per cent), and in one patient after pancuronium, 1.2 mg/m² (88 per cent). Time to 5 per cent recovery of control height was directly related to the initial dose of muscle relaxant administered. However, with larger doses, a gallamine-induced neuromuscular blockade lasts much longer than blockades induced by *d*Tc and pancuronium (fig. 1). Although times to 5 per cent recovery of control twitch height were about the same for *d*Tc, gallamine, and pancuronium at doses of 12, 80, and 2.4 mg/m², 1.5 times those doses produced a neuromuscular blockade with gallamine which lasted twice as long as those

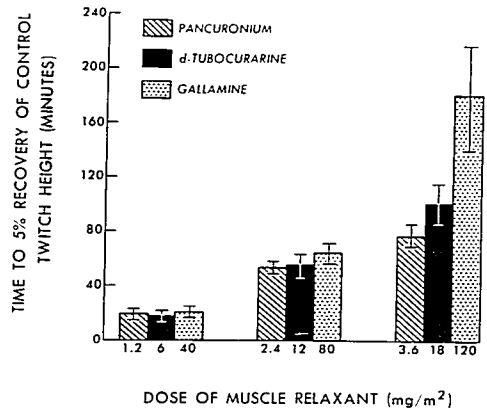


FIG. 1. Correlation between doses of relaxants and times to 5 per cent recovery of control twitch height. Brackets represent ±SD.

induced by either *d*Tc or pancuronium ($P < 0.01$).

Beginning at 5 per cent recovery of control twitch height, the dose of neostigmine needed to antagonize a *d*Tc-, gallamine-, or pancuronium-induced neuromuscular block was not dependent on the dose of relaxant administered ($r = 0$ to 0.25; $P > 0.1$) (figs. 2 and 3). For this reason, the dose of relaxant was not considered when comparing the amounts of neostigmine needed to antagonize the neuromuscular blockades produced by *d*Tc, gallamine, and pancuronium.

The total doses of neostigmine necessary to produce 20, 50, and 80 per cent recovery of control twitch, absence of posttetanic facilitation, and sustained tetanus were greater for gallamine than for either *d*Tc or pancuronium ($P < 0.01$) (fig. 4). Although more neostigmine was needed to antagonize *d*Tc-induced than pancuronium-induced neuromuscular blockades, these differences were not statistically significant, with one exception. More neostigmine was necessary for absence of posttetanic facilitation with *d*Tc-induced neuromuscular blockade than with pancuronium-induced blockade ($P < 0.05$) (fig. 4).

The times from 20 per cent recovery of control twitch height to sustained tetanus were 48, 69, and 59 minutes longer when neostigmine had not been given for *d*Tc, 12 mg/m², gallamine, 80 mg/m², and pancuronium, 2.4 mg/m² ($P < 0.01$) (table 1).

## Discussion

This study demonstrates that significantly more neostigmine is needed to antagonize a neuromuscular blockade produced by gallamine than to antagonize a blockade produced by *d*Tc or pancuronium. Also, we found that when we initiated antagonism of the nondepolarizing neuromuscular blockade at a constant level of 5 per cent recovery of control twitch height, the amount of neostigmine needed was not related to dose of relaxant administered (figs. 2 and 3). We suspect that initiating reversal at any constant level of recovery of control twitch height would have the same result. For example, we could have initiated reversal at 30 per cent recovery of control twitch height rather than 5 per cent and still found that the amount of neostigmine needed was not related to dose of relaxant administered. In other words, the point in recovery from a neuromuscular block at which reversal is initiated is a far more important determinant of neostigmine requirement than dose of relaxant administered.[11] Perhaps the same number of receptors is occupied with relaxant when the twitch has returned to 5

per cent of control twitch height irrespective of the dose of relaxant administered.[8] If so, the comparison of neostigmine requirements for antagonism of the neuromuscular blockades produced by these three relaxants is valid even if the doses of relaxant administered are not equipotent.

Our results allow only speculation concerning the mechanism by which more neostigmine is necessary to antagonize gallamine than either *d*Tc or pancuronium. Perhaps gallamine has a greater affinity for the cholinergic receptors at the postjunctional membrane. Although very attractive, this theory is not borne out by the binding constants determined for gallamine and *d*Tc, but not yet determined for pancuronium. The dissociation constant ($K_i$), which is the reciprocal of affinity, for gallamine is $3.0 \times 10^{-7}$ M; for *d*Tc it is $1.6 \times 10^{-7}$ M.[12] The $K_i$ is defined as the concentration of antagonist (*d*Tc or gallamine) which requires doubling the concentration of agonist (carbamylcholine or decamethonium) to restore the same responses produced by the agonist in the absence of antagonist.[13] The $K_i$ values suggest that *d*Tc has a greater affinity for the cholinergic receptor than gallamine. On this basis, one might predict that *d*Tc-induced neuromuscular blockade would be more neostigmine-resistant than gallamine-induced blockade; the exact opposite of what we found!

The $K_i$'s were determined without regard to potency of the muscle relaxant. The ratio of $ED_{50}$ (dose of muscle relaxant which causes a 50 per cent reduction in twitch height) to $K_i$ is about 5 for gallamine and 3 for *d*Tc in the guinea-pig diaphragm preparation.[13] The discrepancy between ratios suggests different mechanisms of action. Recent work of Gissen and Karis suggests that gallamine depresses the motor nerve terminal in the frog sartorius muscle preparation *in vitro*,[14] which may result in a decreased output of acetylcholine vesicles from a presynaptic impulse. This depression was not observed with *d*Tc or pancuronium. With a decreased output of acetylcholine from the motor nerve terminal, more neostigmine may be necessary to inhibit acetylcholinesterase for build-up of enough acetylcholine to antagonize gallamine. In the same *in-vitro* preparation, Gissen and Karis observed that neostigmine antagonism of gallamine was slower and less effective than was observed with either *d*Tc or pancuronium.[14]

Although its effect is relatively weak, gallamine has been shown to be a more potent inhibitor of acetylcholinesterase than *d*Tc.[15] Classically, gallamine and *d*Tc block neuromuscular transmission by competing with acetylcholine at the postjunctional membrane. If gallamine also inhibits acetylcholinesterase, then more acetylcholine will be present at the synaptic cleft, requiring more gallamine to compete for the receptor for a neuromuscular blockade. Does gallamine inhibition of acetylcholinesterase limit the ability of the added neostigmine to reduce acetylcholinesterase further?

The common idea that gallamine is a shorter-acting muscle relaxant is questionable. To compare the durations of action of several muscle relaxants requires knowledge of equipotency. Determination of equipotency for these relaxants is impossible, since the dose–response and dose–duration curves are not parallel.[5] In fact, our results suggest that gallamine given in doses which are arithmetic multiples produces a neuromuscular blockade which lasts much longer than those produced by equal multiples of *d*Tc and pancuronium (fig. 1). Lack of knowledge of this concept may result in administration of subsequent doses of gallamine sooner than necessary for adequate muscle relaxation.[16] Every patient who received 120 mg/m$^2$ or more of gallamine had normal renal function and urine formation, thereby excluding impaired excretion as an explanation for the longer durations of neuromuscular blockade with the larger doses of gallamine.

Although few have studied the large doses of relaxants used in this study, several investigators have studied smaller doses. With few exceptions, the durations of neuromuscular blockade observed in this study are not very different from those of other studies.[6, 11, 17, 18] However, Norman *et al.*[19] observed a 50 per cent recovery time of 37 minutes from 0.05 mg/kg of pancuronium. Using a slightly smaller dose, Foldes *et al.*[20] observed a 70 per cent recovery time of 60 minutes. In contrast, we found 50 and 80 per cent recovery times of 119 and 128 minutes, respectively (table 1). Foldes administered nitrous oxide–narcotic–

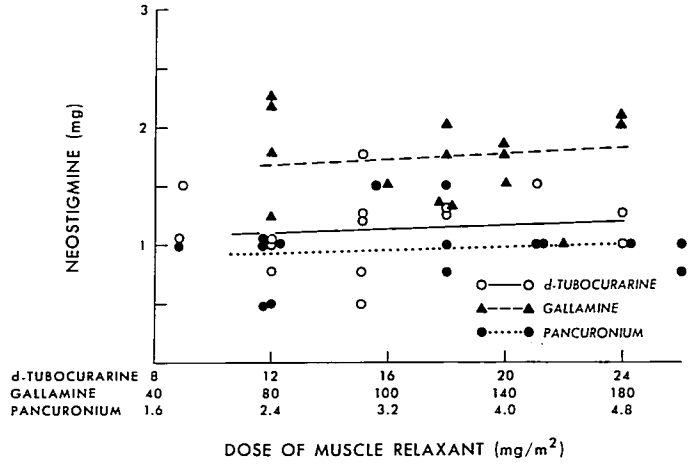


FIG. 2. Correlation between doses of relaxants and doses of neostigmine needed for recovery to 50 per cent of control twitch height. The lines represent analysis of linear regression.

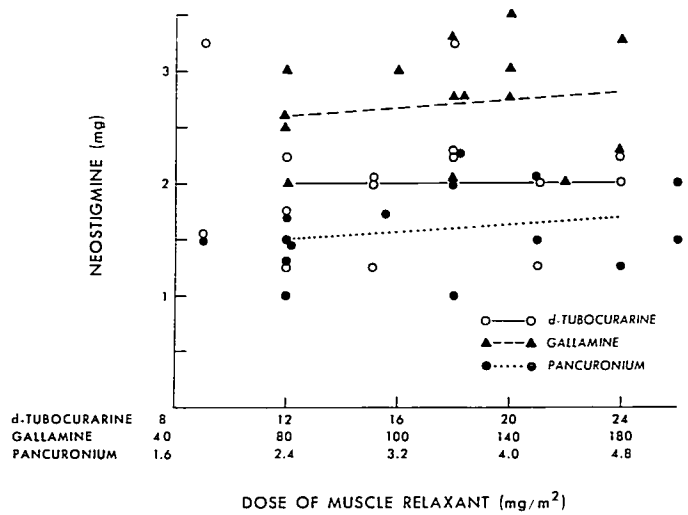


FIG. 3. Correlation between doses of relaxants and doses of neostigmine needed for tetanus to be sustained at 50 Hz. The lines represent analysis of linear regression.

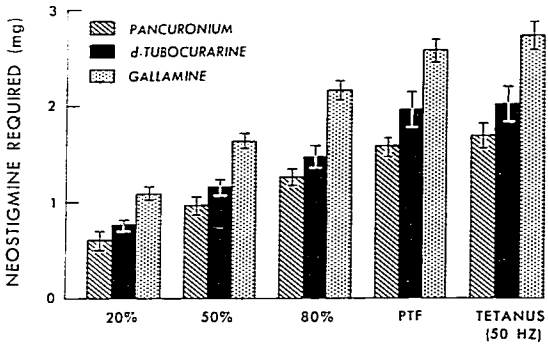


FIG. 4. Doses of neostigmine needed for 20, 50, and 80 per cent recovery of control twitch height, absence of posttetanic facilitation (PTF), and sustained tetanus with neuromuscular blockades produced by *d*-tubocurarine, gallamine, and pancuronium (mean ± SE).

barbiturate anesthesia, while we used halothane, which has been shown to augment the neuromuscular-depressant effects of pancuronium.[21] Norman *et al.*[19] administered several drugs, including succinylcholine, before administration of pancuronium. In some of their studies they used the Block-Aid stimulator instead of the Grass S-44 stimulator. All of these factors may account for the differences between our studies.[21-23]

With *d*Tc and pancuronium, only two patients needed more than 2.25 mg of neostigmine for reversal of neuromuscular blockade (tetanus 50 Hz sustained). These results are consistent with those of Katz, who found that 2.5 mg of neostigmine were necessary for about 85 per cent of the patients who received *d*Tc and for all the patients who received pancuronium.[11, 24] We are not necessarily recommending administration of neostigmine in the time sequence used in this study. This sequence was chosen for investigational reasons. In fact, it may be more efficient and time-saving to administer 2.5 mg of neostigmine as a bolus rather than in divided doses as we did.[24]

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TABLE 1. Durations (Mean Minutes ± 1 SD) of Neuromuscular Blockades without and with Neostigmine Compared*

| | Number of Patients | Per Cent Recovery of Control Twitch Height | | | Absence of Posttetanic Facilitation | Sustained Tetanus (50 Hz) |
|---|---|---|---|---|---|---|
| | | 20 | 50 | 80 | | |
| *d*Tc, 12 mg/m² | | | | | | |
| Without neostigmine | 5 | 78 ± 13 | 100 ± 13 | 116 ± 10 | 138 ± 12 | 142 ± 11 |
| With neostigmine | 3 | 75 ± 8 | 79 ± 6 | 83 ± 6 | 88 ± 4 | 91 ± 2 |
| Gallamine, 80 mg/m² | | | | | | |
| Without neostigmine | 5 | 76 ± 15 | 110 ± 30 | 131 ± 30 | 185 ± 44 | 168 ± 31 |
| With neostigmine | 4 | 72 ± 19 | 87 ± 20 | 91 ± 18 | 97 ± 17 | 95 ± 15 |
| Pancuronium, 2.4 mg/m² | | | | | | |
| Without neostigmine | 5 | 82 ± 14 | 119 ± 16 | 128 ± 18 | 160 ± 19 | 153 ± 20 |
| With neostigmine | 3 | 67 ± 4 | 70 ± 4 | 73 ± 4 | 76 ± 5 | 79 ± 9 |

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## References

1. Mushin WW, Wien R, Mason DFJ, et al: Curare-like actions of tri-(diethylaminoethoxy)-benzene triethyliodide. Lancet 1:726–728, 1949
2. Baird WLM: Some clinical experience with a new neuromuscular blocking drug—pancuronium bromide (Pavulon NA 97) Irish J Med Sci 1:559–563, 1968
3. Smith RM: Pediatric patients, Clinical Anesthesia: Muscle Relaxants. Edited by FF Foldes. Philadelphia, Davis, 1966, pp 38
4. Komesaroff D: Further clinical studies on pancuronium bromide: I. A comparison with other non-depolarizing muscle relaxants. Med J Aust 494–497, 1970
5. Lund I, Stovner J: Dose–response curves for tubocurarine, alcuronium and pancuronium. Acta Anaesth Scand 37:238–242, 1970
6. Miller RD, Eger EI II, Way WL, et al: Comparative neuromuscular effects of Forane and halothane alone and in combination with *d*-tubocurarine in man. ANESTHESIOLOGY 35:38–42, 1971
7. Miller RD, Way WL, Dolan WM, et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. ANESTHESIOLOGY 35:509–514, 1971
8. Waud BE, Waud DR: The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. ANESTHESIOLOGY 35:456–464, 1971
9. Katz RL, Ryan JF: The neuromuscular effects of suxamethonium in man. Br Anaesth 41: 381–390, 1969
10. Goldstein A: Biostatistics. New York, MacMillan, 1964, pp 70–72 and 135–154
11. Katz RL: Clinical neuromuscular pharmacology of pancuronium. ANESTHESIOLOGY 34: 550–556, 1971
12. Kasai M, Changeux JP: *In vitro* excitation of purified membrane fragments by cholinergic agonists. J Membrane Biol 6:1–23, 1971
13. Lu TC: Affinity of curare-like compounds and their potency in blocking neuromuscular transmission. J Pharmacol Exp Ther 174: 560–566, 1970
14. Gissen AJ, Karis JH: personal communication
15. Changeux JP: Responses to acetylcholinesterase from torpedo marmorata to salts and curarizing drugs. Mol Pharmacol 2:369–392, 1966
16. White RD, DeWeerd JH, Dawson B: Gallamine in anesthesia for patients with chronic renal failure undergoing bilateral nephrectomy. Anesth Analg (Cleve) 50:11–15, 1971
17. Walts LF, Dillon JB: Durations of action of *d*-tubocurarine and gallamine. ANESTHESIOLOGY 29:499–504, 1968
18. Walts LF, Dillon JB: The influence of the anesthetic agent on the action of curare in man. Anesth Analg (Cleve) 49:17–21, 1970
19. Norman J, Katz RL, Seed RF: The neuromuscular blocking action of pancuronium in man during anesthesia. Br J Anaesth 42:702–710, 1970
20. Foldes FF, Klonymus DH, Maisel W, et al: Studies of pancuronium in conscious and anesthetized man. ANESTHESIOLOGY 35:496–503, 1971
21. Katz RL: Modification of the action of pancuronium by succinylcholine and halothane. ANESTHESIOLOGY 35:602–606, 1971
22. Lebowitz MH, Blitt CD, Walts LF: Depression of twitch response to stimulation of the ulnar nerve during Ethrane anesthesia in man. ANESTHESIOLOGY 33:52–57, 1970
23. Miller RD, Way WL, Dolan WM, et al: The dependence of pancuronium and *d*-tubocurarine neuromuscular blockades on the alveolar concentration of halothane or Forane. ANESTHESIOLOGY (submitted for publication)
24. Katz RL: Neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine in man. ANESTHESIOLOGY 28:327–336, 1967