Anesthesiology
V 39, No 5, Nov 1973

Antagonism of d-*Tubocurarine- and Pancuronium-induced Neuromuscular Blockades by Pyridostigmine in Man*

Richard P. Fogdall, M.D., and Ronald D. Miller, M.D.†*

Pyridostigmine was administered to 30 unpremedicated adult surgical patients anesthetized with nitrous oxide and halothane to antagonize neuromuscular blockade by *d*-tubocurarine (*d*Tc) or pancuronium. The mean doses of pyridostigmine necessary for 50 per cent recovery of depressed twitch height and for sustained tetanus were 4.9 and 11.7 mg, respectively, for *d*Tc, and 4.2 and 9.1 mg, respectively, for pancuronium. Compared with results of a previous study of neostigmine, 5.8 and 5.4 times more pyridostigmine than neostigmine were needed for sustained tetanus during antagonism of blockades by *d*Tc and pancuronium. In 40 additional patients, atropine, 0.3, 0.6, or 1.0 mg, was administered concomitantly with neostigmine, 2.5 mg, or pyridostigmine, 14.5 mg, during antagonism of *d*Tc- or pancuronium-induced neuromuscular blockade. The bradycardia following pyridostigmine does not differ significantly from that following neostigmine when combined with these doses of atropine. (Key words: Pancuronium; *d*-Tubocurarine; Neostigmine; Pyridostigmine; Atropine; Antagonism of neuromuscular blockade; Heart rate.)

PYRIDOSTIGMINE BROMIDE (Mestinon), an inhibitor of acetylcholinesterase, has been used primarily as an oral medication for the control of symptoms of myasthenia gravis. Because of an apparent longer duration of action and lesser muscarinic effects in myasthenic patients,[1-3] pyridostigmine has been suggested as possibly superior to neostigmine as an antagonist of nondepolarizing neuromuscular blockade.[4-6] Accordingly, we evaluated the abilities of intravenously administered pyridostigmine (Regonol‡) and neostigmine to antagonize neuromuscular blockades by *d*-tubocurarine (*d*Tc) and pancuronium. We also compared the heart-rate changes following equipotent doses of pyridostigmine and neostigmine given with various doses of atropine, and in two patients without atropine. Although this study confirms the effectiveness of pyridostigmine as an antagonist of *d*Tc- and pancuronium-induced neuromuscular blockades, its muscarinic cardiac effects do not appear to be significantly different from those of neostigmine.

Methods

Seventy-two unpremedicated adult surgical patients, ASA classifications I and II, were studied intraoperatively. Their mean body surface area and mean age were 1.75 ± 0.02 (SE) m^2 and 49.0 ± 2.25 years. The operative procedures were repair of hip fractures (37), cranioplasty (2), ear, nose, throat, and plastic surgery (5), intra-abdominal operations (15), and operations on extremities (13).

Anesthesia was induced with halothane and 60 per cent nitrous oxide, and the trachea intubated without the use of any other drug. End-tidal concentrations of halothane, determined by gas chromatography, were held between 0.45 and 0.8 per cent. Anesthesia was maintained for 30 minutes before the first injection of a muscle relaxant was made. Controlled ventilation kept Pa_{CO_2} at 34.0 ± 0.62 torr. Mean esophageal temperature was 36.5 ± 0.07 C.

Neuromuscular transmission was evaluated by quantitating force of thumb adduction with

* Research Trainee in Anesthesia.

† Assistant Professor of Anesthesia/Pharmacology.

Received from the Department of Anesthesia, University of California, San Francisco, California 94122. Accepted for publication May 15, 1973. Supported in part by USPHS Grants 5T1 GM00063-15 and 1P01 GM155561-05, and Organon, Inc. Presented in part to Residents' Section, 26th Postgraduate Assembly in Anesthesiology of the New York State Society of Anesthesiologists, Inc., December 11, 1972, New York, N. Y.

Address reprint requests to: Ronald D. Miller, M.D., Department of Anesthesia, University of California Medical Center, San Francisco, California 94122.

‡ Trademark, Organon, Inc., West Orange, N. J.

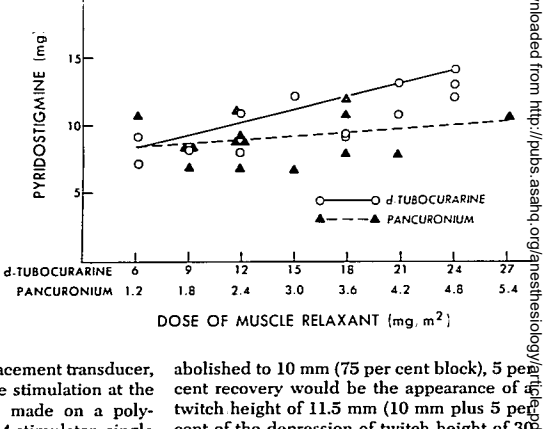

FIG. 1. Correlation between total doses of relaxants and doses of pyridostigmine needed for sustained tetanus at 50 Hz. Lines represent analysis of linear regression.

a Grass FT–10 force-displacement transducer, in response to ulnar-nerve stimulation at the wrist.[7] Recordings were made on a polygraph. From a Grass S–44 stimulator, single supramaximal stimuli of 0.1-msec duration were administered at a rate of 0.3 pulses per second through 22-gauge thin-wall needle electrodes. A continuous ECG was recorded.

Thirty patients received either *d*-tubocurarine chloride, 6, 12, or 18 mg/m², or pancuronium bromide, 1.2, 2.4, or 3.6 mg/m², iv. Five patients were studied at each dose of relaxant; each patient received only one relaxant. With spontaneous recovery of twitch height to the extent of 5 per cent of the total twitch-height depression, additional doses of either *d*Tc, 3 mg/m², or pancuronium, 0.6 mg/m², were given, unless the end of the surgical procedure was near. In the latter event, pyridostigmine, 1 mg, was given iv every 3 minutes until adduction of the thumb in response to a tetanic stimulus of 50 Hz was sustained for 5 seconds (sustained tetanus). When this occurred, neuromuscular blockade was considered to be antagonized.[7] Five per cent recovery refers to spontaneous recovery of 5 per cent of the loss in twitch height which followed administration of the relaxant. For example, if the control twitch height of 40 mm were completely obliterated by the relaxant (100 per cent depression of twitch height), 5 per cent recovery would represent the 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), 5 per cent recovery would be the appearance of a twitch height of 11.5 mm (10 mm plus 5 per cent of the depression of twitch height of 30 mm). Atropine was administered to ten of these 30 patients because their heart rates fell below 55 beats/min. The mean doses of pyridostigmine needed for 50 per cent recovery of the control twitch height and for sustained tetanus were determined.

To evaluate heart-rate changes resulting from pyridostigmine or neostigmine, the remaining 42 patients received *d*Tc, 12 mg/m² iv (32 patients), or pancuronium, 2.4 mg/m² iv (ten patients). With 5 per cent recovery of twitch height, additional doses of either *d*Tc, 3 mg/m², or pancuronium, 0.6 mg/m², were given unless the end of the surgical procedure was near. In that event, neostigmine, 2.5 mg, or pyridostigmine, 14.5 mg (equipotent doses in antagonizing a neuromuscular block, as determined by the potency ratio from the previous experiment) was given iv as a bolus. Each patient received only one relaxant and one antagonist. By random selection, atropine, 0.3 mg, 0.6 mg, or 1.0 mg, was given iv simultaneously with the administration of pyridostigmine or neostigmine, and the heart rate counted from the ECG tracing, 2, 4, 6, 8, 10, 15, and 20 minutes after injection. In none of our studies of muscarinic effects was the unreplaced blood loss greater than 100 ml, or systolic blood pressure lower than 100 torr. Control heart rate was the rate immediately

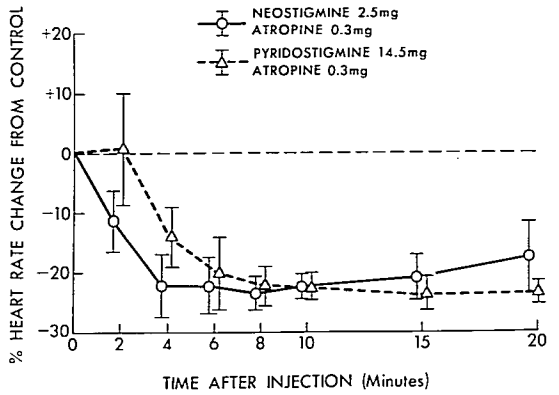

FIG. 2. Heart-rate changes during antagonism of *d*-tubocurarine-induced neuromuscular blockade by neostigmine and pyridostigmine with atropine, 0.3 mg.

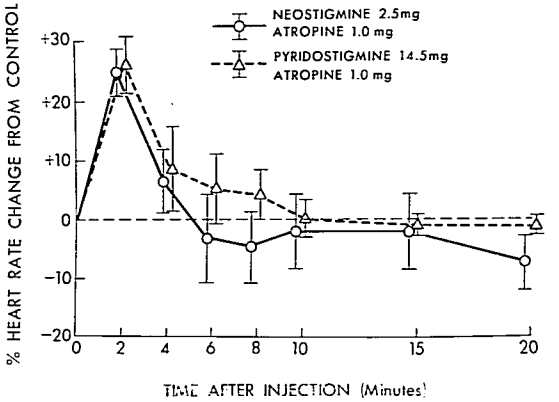

FIG. 3. Heart-rate changes during antagonism of *d*-tubocurarine-induced neuromuscular blockade by neostigmine and pyridostigmine with atropine, 1.0 mg.

prior to the administration of the drug mixture. Two patients received pyridostigmine, 14.5 mg, without atropine for *d*Tc antagonism.

In the recovery room, the pulse rate of each patient was counted every 10 minutes for approximately 2.5 hours to detect any pulse rates below 60 beats/min.

Analysis of variance and linear regression with correlation coefficient analysis were used for the statistical analyses.[8]

Results

More pyridostigmine was needed for antagonism of *d*Tc-induced neuromuscular blockade than for antagonism of pancuronium-induced blockade ($P < 0.05$). The mean doses of pyridostigmine necessary for 50 percent recovery of control twitch height and sustained tetanus were 4.9 ± 0.25 (SE) mg and 11.7 ± 0.98 mg (SE), respectively, for *d*Tc, and

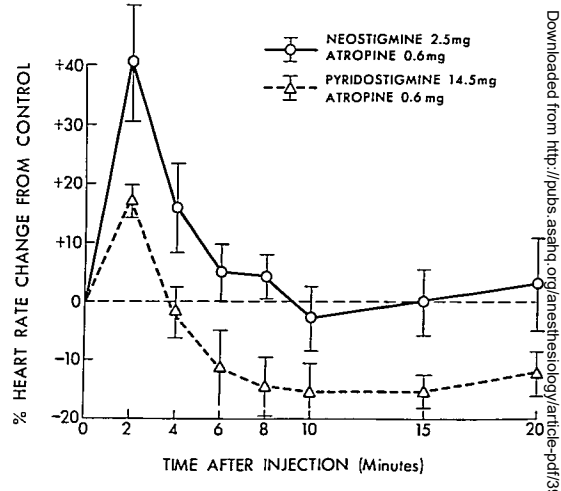

FIG. 4. Heart-rate changes during antagonism of *d*-tubocurarine-induced neuromuscular blockade by neostigmine and pyridostigmine with atropine, 0.6 mg.

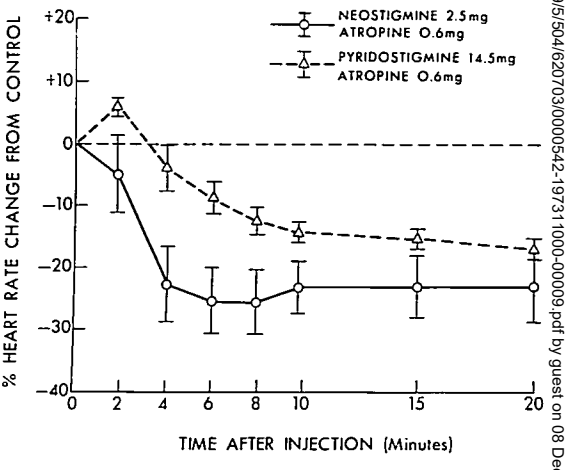

FIG. 5. Heart-rate changes during antagonism of pancuronium-induced neuromuscular blockade by neostigmine and pyridostigmine with atropine, 0.6 mg.

4.2 ± 0.22 mg (SE) and 9.1 ± 0.47 (SE) mg, respectively, for pancuronium. Our previous study demonstrated that 2.0 mg and 1.7 mg of neostigmine were needed for sustained tetanus during antagonism of *d*Tc- and pancuronium-induced neuromuscular blockades.[7] Thus, the pyridostigmine/neostigmine potency ratios for sustained tetanus are 5.8 (11.7 mg/2.0 mg) for antagonism of *d*Tc and 5.4 (9.1 mg/1.7 mg) for antagonism of pancuronium.

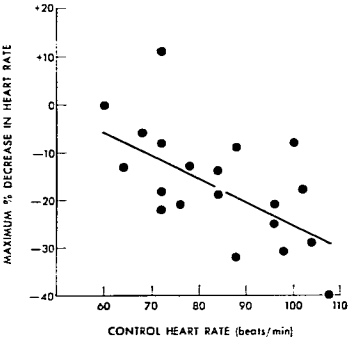

FIG. 6. Correlation between control heart rate for each of 20 patients who received atropine, 0.6 mg, and maximum per cent decrease in heart rate during antagonism. The line represents analysis of linear regression.

In mean age, body surface area, temperature, and Pa_{CO_2}, patients receiving *d*Tc did not differ significantly from patients receiving pancuronium, nor patients receiving pyridostigmine from those receiving neostigmine reported previously.[7]

The doses of pyridostigmine needed to antagonize *d*Tc- and pancuronium-induced neuromuscular blockades were independent of total dose of relaxant administered (fig. 1) (r = 0.52, r = 0.28, respectively). For this reason, the dose of relaxant was not considered when comparing the doses of pyridostigmine necessary for antagonism of the blockades produced by *d*Tc and pancuronium.

The heart-rate changes after either pyridostigmine or neostigmine given for *d*Tc antagonism were not significantly different when atropine, 0.3 mg or 1.0 mg, was concomitantly administered (figs. 2 and 3). There was no correlation between control heart rate and subsequent changes in heart rate in any of these groups. However, decreases in heart rate during *d*Tc antagonism were significantly greater with pyridostigmine than with neostigmine, when atropine, 0.6 mg, was concomitantly given (fig. 4) ($P < 0.05$). In contrast, decreases in heart rate during antagonism of pancuronium were significantly less with pyridostigmine than with neostigmine, when given with atropine, 0.6 mg (fig. 5) ($P < 0.05$). The heart-rate decreases observed with pyridostigmine or neostigmine when given with atropine, 0.6 mg, for antagonism of either *d*Tc- or pancuronium-induced neuromuscular blockade were directly related to control heart rates. Patients with higher control heart rates showed greater decreases from control than patients with lower control heart rates (fig. 6) (r = 0.67).

In the two patients given pyridostigmine, 14.5 mg, without atropine for antagonism of *d*Tc-induced neuromuscular blockade, heart rates decreased from a mean of 68/min to less than 48/min within 12 minutes, at which time atropine was given.

No patient had a pulse rate of less than 60/min during the 2.5-hour period of observation in the recovery room.

Discussion

For sustained tetanus to occur, the amounts of pyridostigmine needed for antagonism of *d*Tc- and pancuronium-induced neuromuscular blockades were 5.8 and 5.4 times more than the amount of neostigmine needed in a previous study.[7] As was observed with neostigmine,[7] more pyridostigmine was necessary to antagonize blockades with *d*Tc than was needed to antagonize pancuronium-induced blockades. Also, as in the neostigmine study,[7] we found that if we administered the antagonist when 5 per cent recovery of twitch height occurred (see above), the dose of pyridostigmine needed was not related to the total dose of relaxant administered (fig. 1). Thus, the point in recovery from a neuromuscular blockade at which antagonism is initiated is a far more important determinant of pyridostigmine (or neostigmine) requirement than the total dose of relaxant administered. Miller *et al.*[8] suggested that the same number of receptors at the motor endplate is occupied by relaxant when the twitch height has spontaneously achieved 5 per cent recovery, without respect to the total dose of relaxant administered. If so, the comparison of pyridostigmine requirements for antagonism of these two relaxants is valid even if the relaxant doses are not equipotent.

Our data also demonstrate that neuromuscular antagonism with equipotent doses of neostigmine and pyridostigmine, combined with identical doses of atropine, resulted in heart-rate changes which were not significantly different with two of the three doses of atropine studied. With the third dose (0.6 mg), observed decreases in heart rate were partly related to control heart rates; several patients with high control heart rates had greater decreases in heart rate than patients with lower control heart rates (fig. 6). In any event, when given for antagonism of *d*Tc-induced neuromuscular blockade, the cardiac muscarinic effects of pyridostigmine appear similar to those of neostigmine.

Controversy regarding the questionable "central vagal stimulating effects" of small doses of atropine, which might lead to bradycardic episodes when peripheral vagolytic effect was negligible, continues. Since our patients given atropine, 0.3 mg, all had decreases in heart rates to approximately 20 per cent below control (fig. 2), we wished to test the possibility that the 0.3-mg dose of atropine contributed to the low heart rates. Two patients were given pyridostigmine, 14.5 mg, without atropine, and both promptly developed sinus bradycardia to less than 48/min, at which time atropine was given. Because of this profound bradycardia from pyridostigmine alone, we were reluctant to pursue this course of study in additional patients. This brief experience suggests that atropine, 0.3 mg, did not contribute to lower heart rates during *d*Tc antagonism, but instead had a moderate protective effect.

The results of this study suggest that there is no advantage in administering pyridostigmine in preference to neostigmine in terms of cardiac muscarinic effects for antagonism of *d*Tc- or pancuronium-induced neuromuscular blockade. However, this study did not evaluate the possibility that pyridostigmine might be longer-acting and might stimulate oropharyngeal secretions less than neostigmine.

The authors thank Edmond I. Eger, II, M.D., for his advice and counsel throughout the study. Both Dr. Eger and William K. Hamilton, M.D., assisted with the preparation of this manuscript.

References

1. Randall LO: Pharmacology of the anticholinesterase drugs Mestinon, Prostigmine, Tensilon and TEPP. Am J Med 19:673–678, 1955
2. Osserman KE: Progress report on Mestinon bromide (pyridostigmine bromide). Am J Med 19:737–739, 1955
3. Foldes FF, McNall PG: Myasthenia gravis: A guide for anesthesiologists. ANESTHESIOLOGY 23:837–872, 1962
4. Katz RL: Pyridostigmine (Mestinon) as an antagonist of *d*-tubocurarine. ANESTHESIOLOGY 28:528–534, 1967
5. McNall PG, Wolfson B, Tuazon JG, et al: Use of pyridostigmine for the reversal of neuromuscular blockade. Anesth Analg (Cleve) 48:1026–1032, 1969
6. Zsigmond EK: Pyridostigmine: A safe and effective antagonist to *d*-tubocurarine in anesthetized man (abstract). Clin Pharmacol Ther 13:155–156, 1972
7. Miller RD, Larson CP Jr, Way WL: Comparative antagonism of *d*-tubocurarine-, gallamine-, and pancuronium-induced neuromuscular blockades by neostigmine. ANESTHESIOLOGY 37:503–509, 1972
8. Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa State University Press, 1967, pp 258–298, 135–171