Anesthesiology
54:399–402, 1981

Pharmacokinetics of Edrophonium and Neostigmine When Antagonizing d-*Tubocurarine Neuromuscular Blockade in Man*

Robert B. Morris, M.D., Roy Cronnelly, M.D., Ph.D.,† Ronald D. Miller, M.D.,‡ Donald R. Stanski, M.D.,§ Mark R. Fahey, M.D.**

The pharmacokinetics and effectiveness of edrophonium antagonism of *d*-tubocurarine neuromuscular blockade were compared with that of neostigmine in surgical patients anesthetized with halothane and nitrous oxide. After an intranveous (iv) injection of *d*-tubocurarine (0.3 mg/kg), the single twitch tension was allowed to return to five per cent of the control level. Edrophonium, 0.5 or 1.0 mg/kg (n = 12), or neostigmine, 0.07 mg/kg (n = 6), was then given iv in combination with atropine, 1.0 mg, as a 2-min controlled infusion. Train-of-four and single twitch tension were followed for 60 min in all patients. Twelve patients were monitored for 90 min, six patients for 120 min, four patients for 150 min, and two patients for 240 min. Blood was sampled intermittently for four hours and assayed for edrophonium or neostigmine using high-pressure liquid chromatography. Edrophonium was found to promptly antagonize the *d*-tubocurarine blockade. Twitch tension rapidly increased to a plateau (a rate of increase in twitch tension of less than 2 per cent of control per min) which was sustained in all cases. The mean time to plateau for edrophonium was 2.9 ± 0.21 (±SE) min as compared to 6.1 ± 0.75 min for neostigmine. Neuromuscular blockade did not reappear in any patient. The degree of antagonism of the neuromuscular blockade by neostigmine and edrophonium was not significantly different. Except for a longer distribution half-life, the pharmacokinetic variables for edrophonium did not differ significantly from those for neostigmine. The elimination half-lives of edrophonium and neostigmine were 110 ± 34 min (mean ± SD) and 77 ± 47 min, respectively. The authors therefore conclude that edrophonium, 0.5–1.0 mg/kg, has pharmacokinetic variables comparable to neostigmine and produces prompt, sustained, and effective antagonism of *d*-tubocurarine neuromuscular blockade. (Key words: Antagonists, neuromuscular: edrophonium; neostigmine. Measurement technique: neuromuscular blockade. Monitoring: stimulator, nerve. Neuromuscular relaxants: *d*-tubocurarine. Pharmacokinetics: edrophonium; neostigmine.)

EDROPHONIUM has not been the preferred antagonist of nondepolarizing neuromuscular blockade because of its apparently brief, unreliable antagonism and the possibility of recurarization.[1–6] In the only pharmacokinetic analysis of edrophonium in humans, a very short elimination half-life (mean $t_{1/2\beta}$ = 33 min) was found which supported the previously observed brief duration-of-action.[7] In the past, edrophonium has been used in doses of 10–20 mg; however, Bevan[8] and Kopman[9] recently found that larger doses (0.5–0.7 mg/kg) produced sustained antagonism of pancuronium neuromuscular blockade. However, Bevan[8] monitored neuromuscular function for only 30 min, and Kopman[9] monitored only ten of 40 patients for 60 min following edrophonium administration. This may be an inadequate time to assess whether neuromuscular blockade will reappear after edrophonium. In this study we confirmed that these larger doses of edrophonium do produce sustained antagonism. Also, we determined whether this sustained antagonism could be explained on a pharmacokinetic basis. Finally, these data were compared with those from a more commonly used antagonist, neostigmine.

Materials and Methods

Informed consent, approved by our Committee on Human Research, was obtained from eighteen surgical patients, aged 19–63 years. All patients were ASA class I or II and had normal laboratory values for serum electrolytes, BUN, creatinine, bilirubin, SGOT, and alkaline phosphatase. Diazepam (10 mg orally) was given 60–90 min before anesthesia. Anesthesia was induced with thiopental (3–4 mg/kg), and maintained with halothane (0.5–0.7 per cent end tidal) and nitrous oxide (60 per cent inspired) as measured by a mass spectrometer. Endotracheal intubation was accomplished under halothane anesthesia without use of muscle relaxants. Normal blood gases and body temperatures were maintained. Supramaximal ulnar nerve stimulation was delivered by a Grass S44 stimulator through 27-gauge needle electrodes at the wrist. Stimuli were delivered continuously at 0.15 Hz and 0.15 ms duration except during train-of-four stimulation. Train-of-four stimulation (four supramaximal stimuli delivered at 2 Hz) was performed at 15-min intervals following antagonist infusion. The resultant force of thumb adduction was measured and recorded. Twitch tension was monitored in all cases for the entirety of the operative procedure.

An iv bolus of 0.3 mg/kg *d*-tubocurarine (*d*Tc) was

* Research Fellow in Anesthesia.
† Assistant Professor of Anesthesia and Pharmacology.
‡ Professor of Anesthesia and Pharmacology.
§ Assistant Professor of Anesthesia.

Received from the Departments of Anesthesia, University of California, San Francisco 94143, and Stanford University, School of Medicine, Stanford, California 94305. Accepted for publication October 27, 1980. Supported by NIH grant NIH Rol Gm 26403-02 and Anesthesia-Pharmacology Research Foundation. This paper received Third Prize in the 1980 ASA Residents' Research Essay Contest.

Address reprint requests to Dr. Robert B. Morris: Department of Anesthesia, C-214, University of California, San Francisco, California 94143.

0003-3022/81/0500/0399 $00.70

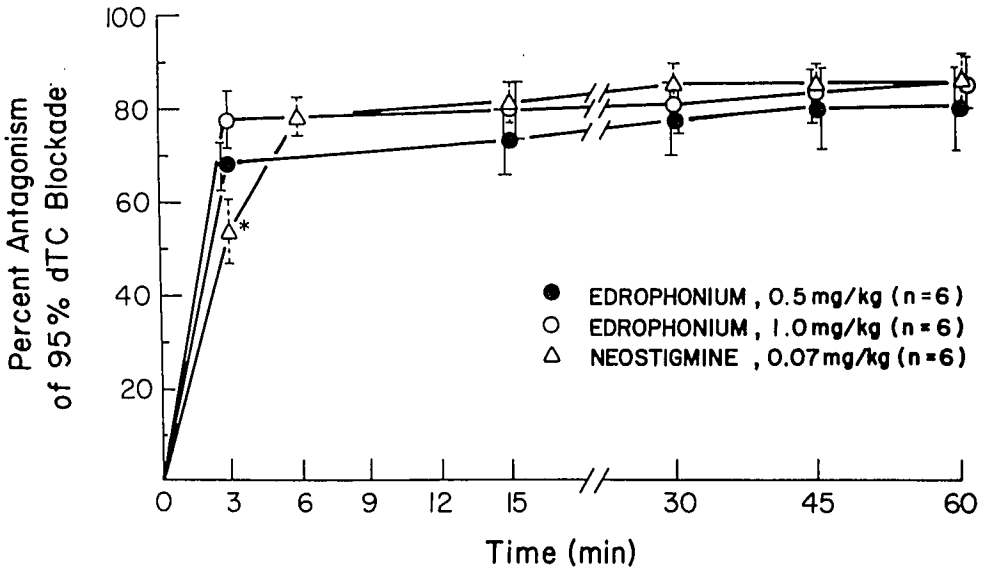

FIG. 1. Antagonism of a 95 per cent *d*Tc-induced depression in twitch tension in normal anesthetized patients. Points represent mean ± SE twitch tensions expressed as per cent of control (*Significantly different from edrophonium 1.0 mg/kg, $P < 0.05$)

administered, after which the neuromuscular blockade was allowed to spontaneously recover to 5 per cent of control. At this point edrophonium, 0.5 mg/kg (n = 6), 1.0 mg/kg (n = 6), or neostigmine, 0.07 mg/kg (n = 6), was infused over 2 min in combination with atropine, 1.0 mg. The length of the operative procedures permitted monitoring of all cases for at least 60 min following antagonist infusion. Twelve cases were monitored for 90 min, six cases for 120 min, four cases for 150 min, and two cases for 240 min. Venous blood was sampled from the contralateral arm at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min after beginning the antagonist infusion, and stored at −30° C until assayed. Samples were assayed for edrophonium or neostigmine using a high-pressure liquid chromatography technique which separates parent compounds from metabolites, and is sensitive to 1 ng/ml.[10] The data, appropriately

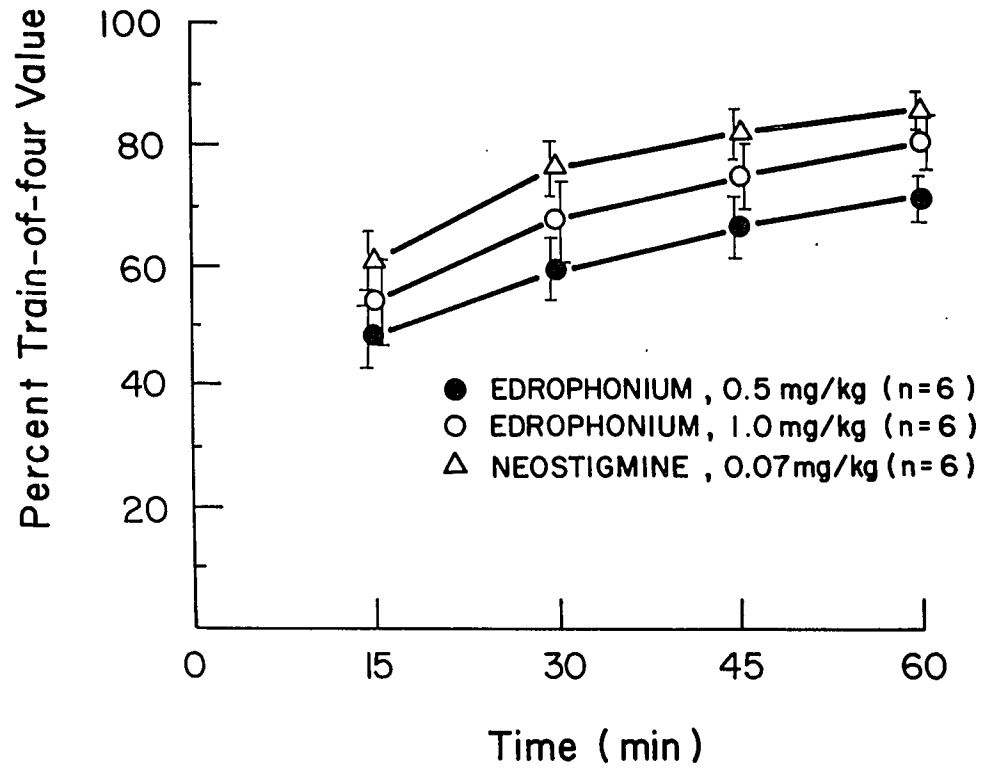

FIG. 2. Antagonism of a 95 per cent *d*Tc-induced depression in twitch tension in normal anesthetized patients. Points represent mean ± SE train-of-four ratios.

corrected for infusion period,[11] were analyzed by nonlinear least squares regression analysis and fitted to a two-compartment open pharmacokinetic model.¶ Computed pharmacokinetic variables were distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), volume of central compartment (V1), volume of distribution of steady state (VD_{SS}), and clearance (Cl). Variables for neostigmine and edrophonium were compared by Tukeys test.[12] Twitch tension data were compared by analysis of variance.[12]

Results

After infusion of the antagonist, twitch tension promptly increased to a plateau (a rate of increase in twitch tension of less than 2 per cent of control per min). This plateau was sustained for the duration of all cases, including those lasting 240 min. The time to plateau (mean ± SE) was significantly shorter for edrophonium (2.9 ± 0.21 min) than for neostigmine (6.1 ± 0.75 min) ($P < 0.001$). The amount of antagonism of twitch tension (fig. 1) or train-of-four (fig. 2) following edrophonium was not significantly different from that obtained with neostigmine at any time period beyond 6 min (neostigmine plateau). Also, the 0.5 and 1.0 mg/kg dose of edrophonium were equally effective in antagonizing the *d*Tc neuromuscular blockade. Following the 2-min infusion of edrophonium, 0.5 mg/kg, serum concentrations ranged from 1700–7980 ng/ml and rapidly declined to 29–92 ng/ml after four hours (fig. 3). Since the kinetics of edrophonium are first-order processes, they are independent of administered dose, and therefore the data from the two doses were combined for computation of pharmacokinetic variables. With the exception of a longer distribution half-life, pharmacokinetic variables for edrophonium were not significantly different than those for neostigmine (table 1).

Heart rate (ECG) and blood pressure (cuff) were monitored in the standard fashion. Although these parameters were not monitored as part of this study, several observations were made. Usually, the heart rate slowed 10–15 per cent, thirty seconds following the start of the edrophonium infusion. Thirty seconds later, a tachycardia developed consistent with a 1.0-mg dose of atropine. This transient drop in heart rate was not seen after neostigmine infusion. Following the initial tachycardia, however, the heart rate gradually slowed and some patients receiving neostigmine required supplemental atropine after 15–20 min to maintain a pulse of 60 and an adequate blood pres-

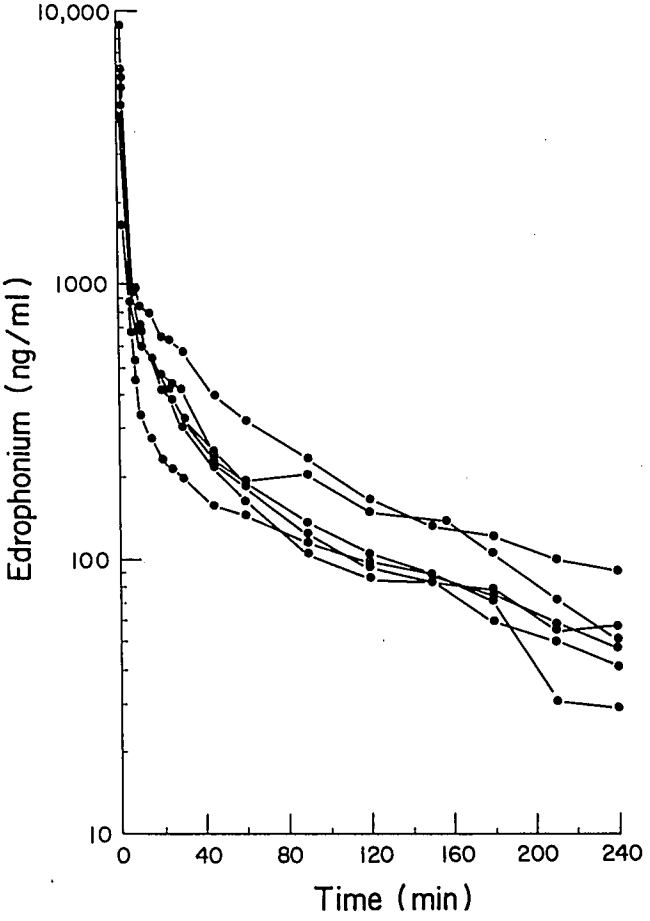

FIG. 3. Serum concentrations following 2-min intravenous infusion of edrophonium (0.5 mg/kg) for individual, normal anesthetized patients. Data for edrophonium, 1.0 mg/kg, are not shown. Similar curves were produced, however the serum concentrations were much higher than observed with 0.5 mg/kg.

¶ Netzler CM: NONLIN. Kalamazoo, The Upjohn Company, 1969.

TABLE 1. Pharmacokinetic Variables (Means ± SD) in Normal Anesthetized Patients

	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V1 (l/kg)	VD_{SS} (l/kg)	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)
Edrophonium (n = 10)	7.2 ± 3.9	110 ± 34	0.32 ± 0.09	1.10 ± 0.2	9.6 ± 2.7
Neostigmine (n = 6)	3.4 ± 1.1*	77 ± 47	0.22 ± 0.07	0.74 ± 0.2	9.2 ± 2.6

* Significantly different from edrophonium.

sure. All patients were observed in the recovery room for a period of at least four hours following antagonist infusion. There was no evidence for inadequate or unsustained antagonism of neuromuscular blockade in any patient involved in the study.

Discussion

Our finding of sustained antagonism of nondepolarizing neuromuscular blockade by edrophonium is in agreement with the observations of Kopman[8] and Bevan.[9] The unsustained and unreliable antagonism described by early observers may be explained by inadequate dosage, imprecise monitoring of neuromuscular function, or administration of edrophonium during the distribution phase of the muscle relaxant.[1–6]

The elimination half-life that we found for edrophonium was much longer than previously reported.[7] With the exception of a longer distribution half-life, the pharmacokinetics of edrophonium are similar to those for neostigmine and do not differ from those previously reported for pyridostigmine.[13] Several factors contribute to the apparent discrepancy between our data and those of Calvey *et al.*[7] Their indirect assay utilizing erythrocyte cholinesterase did not allow adequate detection of edrophonium over an extended sample period.[7] The high-pressure liquid chromatography technique[10] which we used permitted direct sensitive measurement of the specific antagonist for six hours following drug administration. This allowed the pharmacokinetic model to better characterize the data and provide more accurate estimates of elimination half-lives and clearance.

MacFarlane compared neostigmine and edrophonium at a dose ratio comparable to our 0.07 mg/kg and 1.0 mg/kg, respectively, and found the muscarinic activity of edrophonium to be significantly less.[4] It is unknown whether this difference in muscarinic activity would be found at the doses utilized to antagonize neuromuscular blockade in this and recent studies.[8,9] However, the potential for diminished muscarinic activity, coupled with the shorter time to sustained plateau of antagonism by edrophonium, may represent an advantage over neostigmine as an antagonist of nondepolarizing neuromuscular blockade.

References

1. Artusio JF, Riker WF, Wescoe WC: Studies on the interrelationship of certain cholinergic compounds. J Pharmacol Exp Ther 100:227–237, 1950
2. Hunter AR: Tensilon: a new anti-curare agent. Br J Anaesth 24:175–186, 1952
3. Hobbiger F: Mechanism of anticurare action of certain neostigmine analogues. Br J Pharmacol 7:223–236, 1952
4. MacFarlane DW, Pelikan EW, Unna KR: Evaluation of curarizing drugs in man. J Pharmacol Exp Ther 100:382–392, 1950
5. Doughty AG, Wylie WD: Antidotes to "true" curarizing agents. Br J Anaesth 24:66–80, 1952
6. Katz RL: Neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine in man. ANESTHESIOLOGY 28:327–336, 1967
7. Calvey TN, Williams NE, Muir KT, et al: Plasma concentration of edrophonium in man. Clin Pharmacol Ther 19: 813–820, 1976
8. Bevan DR: Reversal of pancuronium with edrophonium. Anaesthesia 34:614–619, 1979
9. Kopman AF: Edrophonium antagonism of pancuronium-induced neuromuscular blockade in man. ANESTHESIOLOGY 51:139–142, 1979
10. De Ruyter MGM, Cronnelly R, Castagnoli N: Reversed-phase, ion-pair liquid chromatography of quaternary ammonium compounds. Determination of pyridostigmine, neostigmine, and edrophonium in biological fluids. J Chromatogr 183: 193–201, 1980
11. Loo JCK, Riegelman S: Assessment of pharmacokinetic constants from post infusion blood curves obtained after iv infusion. J Pharm Sci 59:53–55, 1970
12. Snedecor GW: Statistical Methods. Ames, Iowa State University Press, 1962, pp 251–254
13. Cronnelly R, Stanski MD, Miller RD: Pyridostigmine kinetics with and without renal function. Clin Pharmacol Ther 28: 78–81, 1980