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Edrophonium Antagonism of Pancuronium-induced Neuromuscular Blockade in Man:

A Reappraisal

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The ability of edrophonium to reverse the nondepolarizing neuromuscular blockade produced by pancuronium was studied in 40 adult patients during light nitrous oxide–enflurane anesthesia. Antagonism of paralysis was attempted when the train-of-four fade ratio had spontaneously recovered to various extents. Edrophonium was administered in incremental doses intravenously either until the fade ratio increased to 0.70 or more or until the total dose of drug amounted to 0.5 mg/kg. All patients who had spontaneous recovery of train-of-four fade ratios to at least 0.10 had adequate reversal with edrophonium. When the train-of-four count was three or fewer visible twitches, the response to edrophonium was unpredictable. No evidence of recurarization was seen. (Key words: Antagonists, neuromuscular relaxants: edrophonium. Neuromuscular relaxants: pancuronium. Neuromuscular transmission: train-of-four.)

THERE IS LITTLE SUPPORT in the recent anesthesia literature for the use of edrophonium as an antagonist to nondepolarizing neuromuscular blocking drugs. Katz,[1] more than a decade ago, found that the effectiveness of edrophonium depended in large measure upon the extent of spontaneous recovery from *d*-tubocurarine (*d*Tc). Because of his variable success in using edrophonium, Katz believed it was a poor choice as an antagonist to *d*Tc. More recently, Miller[2] and Waud[3] agreed that edrophonium, due to its short duration of action, has no role in the reversal of competitive neuromuscular blockade. While these opinions certainly express current thinking in this area, we believe that they should be re-examined, since the evidence on which they are based is not totally convincing.

With the exception of patients in renal failure paralyzed with gallamine, we have not been able to find a single well-documented case of recurarization following edrophonium reversal of a non-depolarizing neuromuscular blockade. As Lee *et al.*[4] point out, apparent recurrence of paralysis, as judged clinically, may in fact be the result of inadequate antagonism and subsequent fatigue. Unless the evoked EMG or muscle twitch tension response to neural stimulation is measured and recorded, any subjective report of recurarization must be viewed with skepticism. Katz, in the work quoted above, was unable to re-establish control twitch height in about half of the 50 patients he studied when antagonizing *d*Tc with edrophonium. His report, however, had several potential weaknesses. An unspecified number of his patients received very high doses of *d*Tc (0.6 mg/kg/hour); the time from the last incremental dose of relaxant was not recorded; and the doses of edrophonium employed in several of his failures (10–20 mg) may not have been adequate. In addition, in a lengthy operative procedure, spontaneous "changes" in twitch tension may occur due to small movements of the hand relative to the force transducer, or merely due to drift in the recording polygraph.

Since edrophonium might theoretically have several advantages over neostigmine or pyridostigmine (such as rapid onset of action and lack of long-term cardiovascular effects) if it were effective, we decided to restudy the adequacy of reversal produced by edrophonium at various stages of spontaneous recovery. The extent of fade on train-of-four stimulation (force of fourth twitch divided by force of first twitch) was used to determine the success of edrophonium in reversing neuromuscular blockade and to assess the extent of paralysis at the time reversal was attempted.

Methods

Forty patients undergoing elective surgical procedures were studied. Premedication consisted of either atropine or scopolamine, 0.4–0.6 mg, meperidine, 25–50 mg, and either diazepam, 5–10 mg, or secobarbital, 50–100 mg. Anesthesia was induced with thiamylal sodium and maintained with nitrous oxide and oxygen plus enflurane (average maintenance concentration 0.5–1.0 per cent). The tracheas of all patients were intubated with the aid of succinyl-choline, 40–80 mg, intravenously.

Evoked isometric twitch tension to ulnar-nerve stimulation was followed using a Grass FT-10® linear force transducer in the manner described by Ali and Savarese.[5] Results were recorded on a polygraph. Supramaximal stimulation was obtained using needle electrodes and a Professional Instruments® nerve stimulator (NS-2A or NS-3A). Control measurements of twitch height and percentage fade to train-of-four

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TABLE 1. Train-of-four Response as an Index of "Reversibility" with Edrophonium

Train-of-four Fade Ratio Prior to Reversal	Number of Patients	Maximum Train-of-four Fade Ratio Attained Immediately Following Edrophonium		
		<0.60	0.60–0.70	>0.70
<0.10	11	5	2	4
0.10–0.15	19	0	9	10
>0.15	10	0	1	9

stimulation were obtained before and after administration of succinylcholine. The initial dose of pancuronium was not given until twitch height had returned to baseline levels and remained there for at least 10 min. Control train-of-four fade ratio exceeded 0.95 just prior to the first injection of pancuronium. Tetanic stimulation was avoided during this study to prevent the occurrence of posttetanic facilitation.

No rigid dosage regimen for pancuronium was followed. For the majority of patients, however, the initial dose was approximately 0.03–0.05 mg/kg.

Additional doses of pancuronium were given as needed to maintain good clinical relaxation and operating conditions. Incremental doses were not administered unless at least two of four twitches were present in response to train-of-four stimulation. An attempt was made to time incremental doses of pancuronium so that a measurable train-of-four fade ratio was present at the termination of the procedure. For reversal of neuromuscular blockade, edrophonium, 10 mg, was injected intravenously and the response to 0.1-Hz stimulation and train-of-four fade ratio was followed for 2–3 min. Additional doses of edrophonium, 5 or 10 mg, were then given every 2 min either until the train-of-four fade ratio was 0.70 or greater or until the total dose of edrophonium reached 0.5 mg/kg. Atropine, 0.4 mg, was given intravenously prior to reversal, and repeated if the heart rate decreased to less than 60 beats/min.

In ten patients it was possible to follow the train-of-four fade ratio for at least an hour following the last dose of edrophonium. The degree of fade was measured every 5 min in these individuals in an attempt to see whether there was any evidence of recurarization in the postreversal period.

Results

The 40 patients in our series manifested various extents of spontaneous recovery from pancuronium-induced neuromuscular blockade at the time antagonism with edrophonium was attempted (table 1). In all patients who had a fade ratio of 0.10 or more it was possible to increase the ratio to more than 0.60 with edrophonium.

In five of the 11 patients who had spontaneously recovered to a fade ratio of less than 0.10 we were not able to produce satisfactory reversal with edrophonium (table 2). All five individuals received the maximum dose of edrophonium (0.5 mg/kg). The mean dose of relaxant administered to all 40 patients was 0.05 mg/kg, with a range of 0.03–0.11 mg/kg. Neither the durations of the operative procedures nor the times since the last incremental doses of relaxant for these five individuals varied from the norm. It is significant, however, that for four of five patients the train-of-four counts were less than 4, and in the remaining individual the fourth twitch was barely visible (train-of-four fade ratio 0.05).

The average dose of edrophonium administered in this study was 20 mg, and doses of 30 mg were frequently necessary to produce satisfactory recovery. Three patients needed 40 mg, but all of these individuals weighed more than 80 kg. There was no significant correlation between the extent of spontaneous recovery prior to antagonism and the dose of edrophonium needed for reversal.

In the ten patients evaluated for an hour or more, no evidence of recurarization was seen. The fade ratio either remained unchanged during the observation

TABLE 2. Data for Patients in Whom Blockade Was Inadequately Antagonized with Edrophonium

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Train-of-four fade ratio prior to reversal	0.05	0	0	0	0
Train-of-four count prior to reversal	4	3	2	3	2
Total dose of pancuronium (mg/kg)	0.043	0.043	0.042	0.044	0.08
Time from first dose of pancuronium to reversal (min)	65	115	100	80	82
Time since last dose of pancuronium (min)	35	20	35	25	82
Maximum train-of-four fade ratio attained with edrophonium	0.50	0.45	0.41	0.57	0.55

TABLE 3. Train-of-four Responses after Edrophonium Reversal of Blockade

	Train-of-four Ratio Prior to Reversal	Dose of Pancuronium (mg/kg)	Dose of Edrophonium (mg)	Time from Initial Dose of Pancuronium (Min)	Train-of-four Fade Ratio after Reversal					
					5 Min	10 Min	20 Min	30 Min	45 Min	60 Min
Patient 1	0.12	0.05	15	42	0.86	0.90	0.90	0.91	0.94	0.94
Patient 2	0.15	0.05	20	44	0.78	0.77	0.82	0.81	0.83	0.91
Patient 3	0.11	0.05	20	55	0.70	0.70	0.73	0.77	0.82	0.88
Patient 4	0.16	0.05	25	59	0.72	0.70	0.73	0.71	0.71	0.70
Patient 5	0.00*	0.08	35	82	0.50	0.55	0.55	0.55	0.56	0.56
Patient 6	0.10	0.05	30	33	0.70	0.70	0.80	0.78	0.84	0.89
Patient 7	0.12	0.06	30	39	0.77	0.76	0.76	0.78	0.84	0.84
Patient 8	0.08	0.06	30	60	0.61	0.66	0.74	0.75	0.79	0.87
Patient 9	0.10	0.05	40	56	0.60	0.59	0.63	0.67	0.69	0.76
Patient 10	0.11	0.05	15	39	0.83	0.80	0.86	0.92	0.90	0.91

* Train-of-four count = 2.

period or, as was more commonly seen, improved slowly with the passage of time (table 3).

Discussion

We chose to monitor the mechanical response to train-of-four stimulation since this index correlates well with various tests of the adequacy of pulmonary function. Ali *et al.*[6] simultaneously recorded train-of-four response, vital capacity, inspiratory force, and peak expiratory flow rate in awake volunteers recovering from partial paralysis with *d*-tubocurarine. They found that at a train-of-four fade ratio of 0.70 or more all respiratory variables were indistinguishable from control values. At a fade ratio of 0.60, vital capacity was still in excess of 90 per cent of the control value, and all other indicies far exceeded minimal clinically acceptable limits.

Since the amounts of blockade in all of our patients who showed spontaneous recovery to train-of-four ratios of 0.10 or more could be antagonized to ratios of 0.60 or more with edrophonium, we were satisfied that all of these individuals had had adequate reversal. There was no clinical evidence of recurarization in the immediate postanesthetic period in any individual. In the ten patients in whom we were able to follow train-of-four responses for an hour or more into the postreversal period, this clinical impression was sustained.

Our results, therefore, support the findings of Lee *et al.*[4] and Katz[1] that when total neuromuscular blockade is avoided and some spontaneous recovery has commenced, even a short-acting anticholinesterase such as edrophonium can result in sustained reversal of a long-acting relaxant such as pancuronium. If one accepts the generally held view[7] that there is a rapid equilibration of relaxant between plasma and neuromuscular receptors and that the extent of paralysis is causally related to serum drug concentration, then the above results must be difficult to interpret. However, Feldman and Tyrell[8] have suggested an alternative hypothesis that may more satisfactorily explain these results. They postulate that a drug–receptor affinity constant exists for nondepolarizing blockers and that recovery is primarily related to the rate at which this drug–receptor binding is broken. In their view, the duration and intensity of neuromuscular blockade vary with the number of receptors initially occupied, and are relatively independent of serum concentration.

In the clinical setting, the decrease in plasma level of relaxant occurs slowly, but eventually a concentration gradient is established and drug begins to diffuse away from its site of action. During this recovery phase, although the serum concentration of relaxant may correlate with the extent of blockade, the level of circulating drug is insufficient to initiate the corresponding amount of paralysis. Once relaxant that has been liberated from its receptor is dispersed in this central pool, it will not redistribute back against a concentration gradient to the neuromuscular junction. Edrophonium, which may accelerate the dissociation between relaxant and receptor, should result in a permanent improvement in neuromuscular transmission so long as the plasma concentration of drug has decreased to less than a level sufficient to produce the existing neuromuscular blockade. Obviously, when the plasma level of relaxant is high, complete reversal with edrophonium cannot occur. However, any partial antagonism achieved should be long-lasting and not subject to recurarization.

When the train-of-four fade ratio is less than 0.1, or the train-of-four count is three or fewer easily visible twitches, edrophonium cannot be relied on to produce adequate reversal, and we would employ either neo-

stigmine or pyridostigmine. However, in those patients who are appropriate candidates for reversal with edrophonium (train-of-four ratio > 0.1 or four easily visible twitches on train-of-four stimulation), this short-acting anticholinesterase may offer several advantages over longer-acting drugs. First, because the peak neuromuscular effects of edrophonium are evident less than 2 min after intravenous injection, it is possible to titrate the dose of drug against response. Second, arrhythmias following the administration of long-acting anticholinesterases are not unknown, and may extend into the recovery-room period.[9] In view of the brief duration of action of edrophonium, any adverse cardiac effect should occur while the patient is still under close supervision in the operating room.

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