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Neostigmine and Edrophonium as Antagonists of Pancuronium in Infants and Children

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The rates of recovery of neuromuscular activity following reversal of pancuronium-induced neuromuscular blockade with neostigmine or edrophonium were studied in three groups of 24 pediatric patients: "babies"—0–3 months, "infants"—3–12 months, and "children"—1–10 years.

Reversal was attempted at 10% spontaneous recovery of muscle twitch with neostigmine, 0.036 or 0.071 mg/kg, or edrophonium 0.71 or 1.43 mg/kg. Rapid, sustained recovery of function followed administration of either antagonist. Recovery was more rapid after edrophonium than neostigmine, was similar in all three age groups, but was significantly more rapid than reported previously in adults. Two minutes after neostigmine, the mean recovery of first twitch tension in pediatric patients was 58.6 ± 4.9% after 0.036 mg/kg and 70.6 ± 4.3% after 0.071 mg/kg, compared with 84.8 ± 3.2% and 92.6 ± 2% after edrophonium 0.71 and 1.43 mg/kg, respectively. In adults, recovery 2 min after similar doses of antagonist was 29.5 ± 4.9% and 55.7 ± 6.6% after neostigmine and 62.0 ± 3.5% and 71.2 ± 2.3% after edrophonium.

When the extent of recovery of first twitch tension was compared with recovery of train-of-four ratio, it was found that for the same tension the train-of-four ratio was greater with edrophonium than neostigmine and after the same antagonist was greater in babies and infants than in children and adults.

It is concluded that reversal of pancuronium can be achieved more rapidly in pediatric patients than adults, is more rapid after edrophonium than neostigmine, and that qualitative differences in the pattern of recovery are seen in subjects less than 1 year old. (Key words: Anesthesia: pediatric. Neuromuscular relaxants: pancuronium. Antagonists, neuromuscular relaxants: neostigmine; edrophonium.)

SEVERAL INVESTIGATORS have attempted to determine whether the response to neuromuscular blocking drugs in infants and small children differs from adults[1,2] but with conflicting results.[3] Surprisingly, little attention has been given to the reversal of nondepolarizing relaxants in this age group[4]; most pediatric anesthetists use large doses of antagonists, *e.g.*, neostigmine, 0.07 mg/kg, because of the severe consequences of respiratory inadequacy in infants.[2]

In adults, neostigmine is the reversal agent most commonly used, although it has been demonstrated recently that edrophonium is an effective antagonist with a more rapid onset of action when used in adequate dosage.[5,6] The present study is an extension of previous studies in adults[7] to pediatric patients. One of two doses of either edrophonium or neostigmine was given to 72 pediatric patients during nitrous-oxide–halothane anesthesia when 10% recovery from pancuronium had occurred spontaneously. The rates of recovery of neuromuscular function were measured and compared with those obtained previously in adults.

Methods

The protocol for the study was approved by the Hospital Ethics Committee. Seventy-two patients scheduled for surgical procedures lasting more than 1 h were studied. No patients with hepatic, renal, or neuromuscular disease, or any electrolyte abnormality, or who were receiving drugs known to interfere with neuromuscular transmission were included. Patients were studied in three groups of 24, according to age. Group 1 consisted of "babies" aged less than 3 months. Groups 2 and 3 consisted of "infants" aged from 3 months to 1 year and "children" from one to 10 years, respectively. Each group was subdivided randomly into four subgroups of six patients to receive one of two doses of either neostigmine, 0.036 or 0.071 mg/kg, or edrophonium, 0.71 or 1.43 mg/kg.

Premedication for babies and infants consisted of intramuscular hyoscine, 0.01 mg/kg, and the children received pentobarbitone, 3 mg/kg, rectally 2 h preoperatively, followed by morphine, 0.1 mg/kg, and hyoscine, 0.01 mg/kg, im, 1 h preoperatively. Anesthesia was induced with thiopental, 3–5 mg/kg, followed by succinylcholine, 1–2 mg/kg, to facilitate endotracheal intubation and maintained with nitrous oxide (70%) in oxygen and halothane (0.5–1%). Ventilation was controlled using the Bain circuit and fresh gas flow rates were set to achieve normocapnia according to the recommendations of Rose and Froese.[8] Esophageal temperature was monitored and maintained between 35.5° and 37° C.

Neuromuscular transmission was monitored according to the method of Ali *et al.*[9] The ulnar nerve was stimulated supramaximally at the elbow or forearm using silver–silver-chloride electrodes. Trains-of-four with square pulses of 0.2 ms duration at a frequency of 2 Hz

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TABLE 1. Recovery of First Twitch as Percentage of Control

Recovery after Reversal %	Group 1 (<3 months)				Group 2 (3 months–1 year)				Group 3 (1–10 years)			
	A	B	C	D	A	B	C	D	A	B	C	D
1 min												
Mean	41.2	60.2	79.8	82.0	39.5	41.2	80.7	84.7	28.7	47.2	74.0	88.7
SEM	9.9	3.8	7.5	6.4	5.0	8.5	4.4	3.0	4.6	10.7	3.7	5.0
$P < 0.05$	CD	D	A	AB								
$P < 0.01$					CD	CD	AB	AB	CD	D	A	AB
2 min												
Mean	59.4	81.5	87.5	89.4	66.7	63.3	87.7	93.5	50.8	67.8	79.3	94.3
SEM	12.1	2.6	7.6	5.3	4.7	9.4	3.3	2.2	8.4	7.6	5.0	3.1
$P < 0.05$	B	A			D	D		AB	D			A
$P < 0.01$	D			A								
5 min												
Mean	78.6	96.0	95.0	96.0	92.0	84.8	92.8	98.7	81.3	93.7	84.7	99.7
SEM	8.3	5.4	7.4	3.3	3.5	3.6	2.9	2.7	7.0	3.4	7.1	1.9
10 min												
Mean	87.6	97.7	95.5	96.4	100.0	93.3	95.0	99.2	96.0	100.7	87.2	100.8
SEM	2.1	5.2	6.0	3.5	2.7	2.9	3.3	2.0	3.3	3.3	7.6	2.1
30 min												
Mean	90.7	99.3	88.8	100.0	101.2	102.4	95.3	101.7	104.5	104.0	91.5	102.5
SEM	3.8	2.3	7.1	3.0	1.8	3.2	3.0	1.8	2.2	2.8	8.1	1.4

A = neostigmine, 0.036 mg/kg; B = neostigmine, 0.071 mg/kg; C = edrophonium, 0.71 mg/kg; D = edrophonium, 1.43 mg/kg.

and a train duration of 2 s, were repeated every 10 s, using a Grass S48 stimulator and a SIU5 isolation unit. The hand and forearm were immobilized in a splint, and the force of adduction of the adductor pollicis was measured with a force displacement transducer (Grass FT 03) and recorded using a pen-and-ink recorder (Grass polygraph).

Recovery from the intubating dose of succinylcholine was monitored, and when it was complete, pancuronium was given in a dose of 0.04 mg/kg, with increments of 0.01 mg/kg, when necessary, to depress the first twitch height to less than 10% of control. When muscle-twitch activity, following pancuronium administration, had recovered spontaneously to 10% of control, atropine, 0.02 mg/kg, was given, followed 30 s later by one of the two doses of either edrophonium or neostigmine. Anesthesia, controlled ventilation, and neuromuscular transmission studies were continued for a further 30 min. Any decrease in heart rate, monitored with ECG, to less than 60% of the prereversal value was treated with atropine, 0.01 mg/kg, and this was necessary in four patients, all of whom had received neostigmine.

Rates of recovery of neuromuscular function were determined by measurement of the height of the first twitch, expressed as a percentage of the control (T1), and the height of the fourth twitch, as a percentage of the first in each train-of-four (T4/T1) at 1, 2, 5, 10 and 30 min, following administration of the reversal agent. In order to compare the pattern of recovery with each drug in the different age groups, T4/T1 also was measured at equivalent levels of T1 recovery without regard of time.

Results are presented as the mean ± 1 SEM and statistical significance was determined by analysis of variance and Student's t test for unpaired data using Bonferroni's modification for multiple comparisons. The null hypothesis was rejected when $P < 0.05$.

Results

The general patterns of recovery after administration of neostigmine were similar in all patients. An increase in response to the first stimulus of the train (T1) was seen after 1 min, which increased rapidly to a plateau over 4–6 min (table 1). Doubling the dose of neostigmine did not alter the mean rates of recovery significantly, and there were no differences in the rates of recovery among the three age groups of children. However, when the data for the three groups were pooled, their recovery was significantly greater for each dose than previously reported in adults (fig. 1*A*). Recovery of T4/T1 ratio, the height of the fourth twitch as a percentage of the first in each train, showed a similar pattern but was slower than recovery of T1 (table 2).

Recovery after edrophonium was more rapid initially than after neostigmine (table 1). Doubling the dose of edrophonium did not increase significantly the rate of recovery of T1, and there were no differences between the mean rates of recovery of T1 in the three different age groups of children when given the same dose of

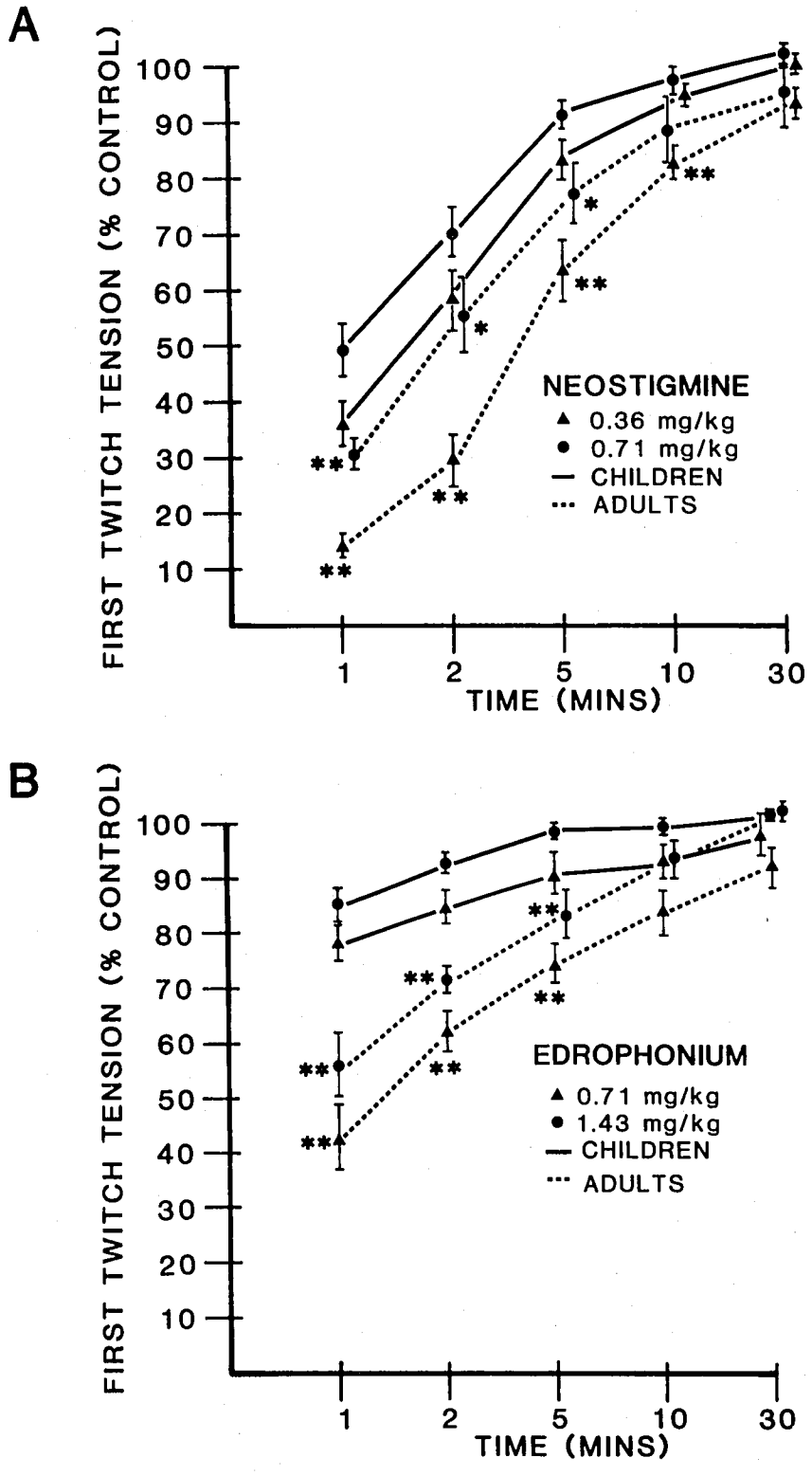

FIG. 1. Recovery of first twitch tension as percentage of control in pediatric patients (pooled data) compared with adults after, neostigmine (*A*) and edrophonium (*B*). Significant differences between adults and pediatric subjects after same dose of antagonist: $*P < 0.05$. $**P < 0.01$.

edrophonium. However, recovery of T1 after edrophonium in the pooled data for all three groups of children was significantly greater than in adults (fig. 1*B*). Recovery of T4 after edrophonium was slower than T1 but was significantly more rapid than after neostigmine (table 2).

The extent of recovery of T1 then was compared with the recovery of T4/T1. This relationship was not

TABLE 2. Recovery of Train-of-four

Recovery after Reversal %	Group 1 (<3 months)				Group 2 (3 months–1 year)				Group 3 (1–10 years)			
	A	B	C	D	A	B	C	D	A	B	C	D
1 min												
Mean	33.0	64.7	81.3	87.4	37.3	39.8	87.0	88.0	10.8	34.7	70.2	73.3
SEM	6.0	6.5	7.4	5.2	6.5	8.8	5.2	2.9	3.7	7.0	3.4	5.0
$P < 0.05$	B	A							B	A		
$P < 0.01$	CD		A	A	CD	CD	AB	AB	CD	CD	AB	AB
2 min												
Mean	52.4	81.3	84.0	87.6	66.0	59.3	88.0	92.7	30.8	47.0	73.5	78.7
SEM	10.2	3.6	6.5	5.0	7.2	6.7	4.7	1.7	3.5	8.5	4.1	2.2
$P < 0.05$	CD		A	A	D	CD	B	AB		CD	B	B
$P < 0.01$									CD		A	A
5 min												
Mean	78.8	89.7	85.2	90.6	91.5	81.0	89.2	93.8	57.8	73.8	76.5	89.2
SEM	8.7	2.6	6.4	5.0	2.4	3.7	3.3	2.1	6.1	6.2	3.7	3.0
10 min												
Mean	81.4	91.8	82.2	90.2	93.2	88.2	92.5	94.7	79.7	87.3	79.3	93.8
SEM	7.1	1.9	5.4	4.8	2.6	2.4	1.7	2.1	6.2	1.8	6.1	2.7
30 min												
Mean	92.3	91.7	82.8	96.0	96.0	92.5	95.5	95.0	92.3	97.3	88.0	98.2
SEM	3.2	4.5	5.0	1.0	2.0	3.3	3.1	2.0	2.2	1.3	6.7	1.8

A = neostigmine, 0.036 mg/kg; B = neostigmine, 0.071 mg/kg; C = edrophonium, 0.71 mg/kg; D = edrophonium, 1.43 mg/kg.

significantly different when comparing the two doses of edrophonium; with neostigmine, although the difference was statistically different, the actual difference was small. Thus, the results for the two doses of each antagonist for each age group were pooled and compared with adults.

The mean values of T4/T1 for 10% increments of T1 are shown for each antagonist for each age group (fig. 2). There were no statistically significant differences in T4/T1 recovery between the antagonists when T1 exceeded 70% of control. However, below this, at the same T1 tension, the T4/T1 was greater with edrophonium than with neostigmine in each age group. In addition, the T4/T1 at the same T1 was greater in patients less than 1 year old than in older children and adults ($P < 0.01$).

Discussion

In the present study, rapid reversal of pancuronium-induced neuromuscular blockade was achieved with either edrophonium or neostigmine. The rate of reversal with both antagonists was significantly greater than in previous studies in adults,[7] and these observations are explained by the pharmacokinetic behavior of the anticholinesterases. Morris *et al.*[10] showed that the elimination half-lives of edrophonium and neostigmine in adults were similar, so that if their activity is dependent upon the plasma concentration, the durations of action also should be similar. More recently, Fisher *et al.*[11] demonstrated that the steady-state volume of distribution of neostigmine was smaller in infants and children. Thus, similar doses of neostigmine given to adults and children will achieve higher plasma concentrations in children, and this would enhance antagonism of neuromuscular blockade. In addition, the rapid circulation time with diversion of a greater portion of the cardiac output to the muscles in neonates[12] also would accelerate the onset of drugs acting at the neuromuscular junction.

The study confirmed the sustained antagonism that can be achieved when edrophonium is given in adequate dosage.[5–7] It is doubtful whether its more rapid reversal alone could justify the replacement of neostigmine by edrophonium in the reversal of nondepolarizing neuromuscular blocking drugs in children. However, in comparative doses, edrophonium has fewer muscarinic actions than neostigmine. In particular, there is decreased ileal smooth muscle stimulation and less vagal stimulation.[13] Thus, if the effectiveness of edrophonium is confirmed, its advantages include rapid reversal of muscle relaxants with fewer side effects.

In each age group, the T4/T1 at the same T1 tension following reversal with edrophonium was greater than observed after neostigmine until T1 exceeded 70% of control. These results are similar to those found in adults.[14] Both human and animal studies suggest that nondepolarizing muscle relaxants produce depression of T4 and decrease in T1 tension by independent actions at prejunctional and postjunctional receptors, re-

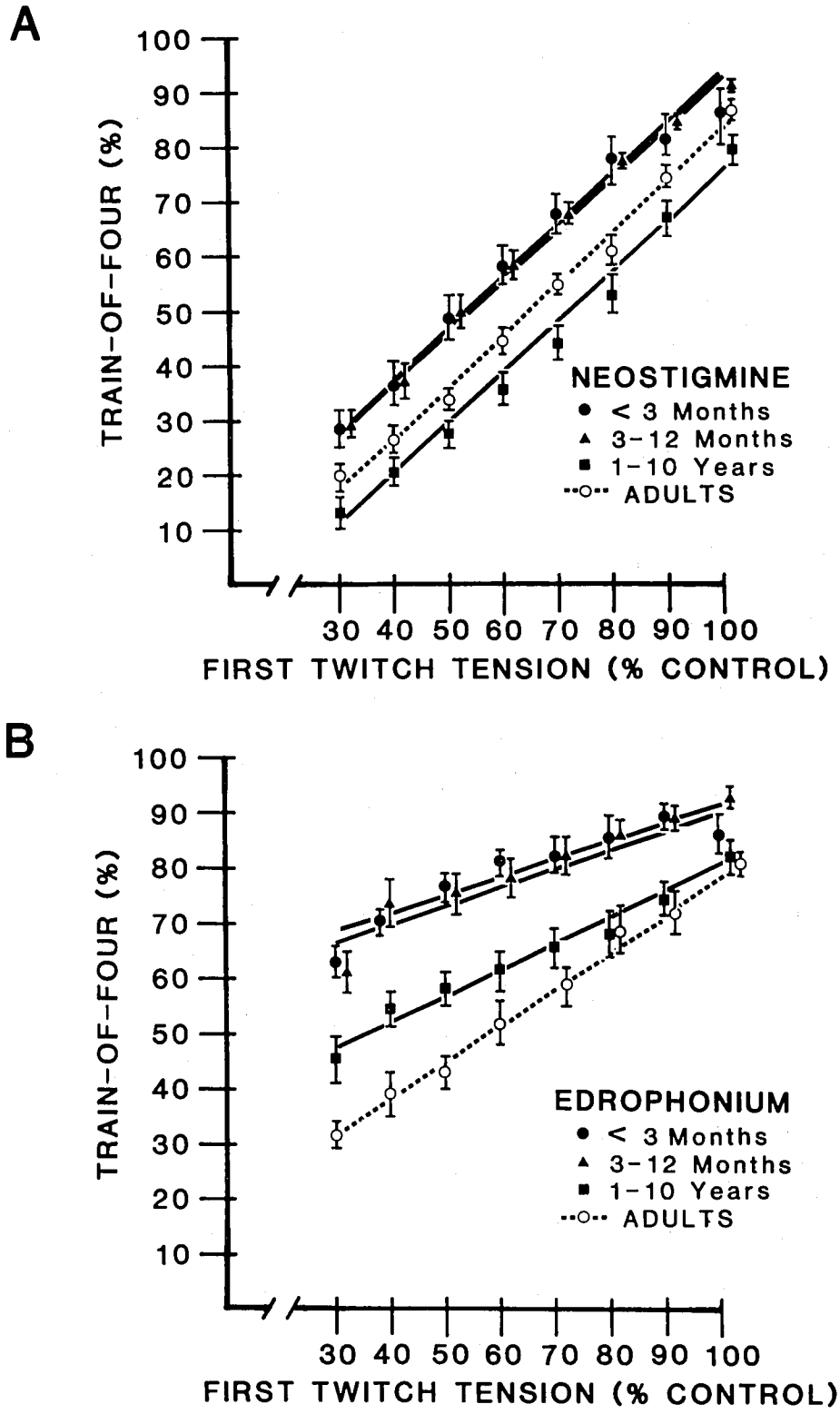

FIG. 2. Train-of-four ratio, T4/T1, *versus* first twitch height, T1, after reversal of pancuronium with neostigmine (*A*) or edrophonium (*B*).

spectively.[15] Thus, it was suggested that the differences between edrophonium and neostigmine reflect differences in the prejunctional and postjunctional activity of these drugs.[14] The results of the present study indicate that T4–T1 relationships also vary with age: the T4/T1 ratios at the same T1 tensions with both antagonists were greater in subjects less than 1 year of age than in older children or adults. This suggests either a de-

creased prejunctional action of pancuronium or more potent presynaptic antagonism in those under 1 year old. Previously, Goudsouzian[16] concluded that immaturity of the neuromuscular junction could be detected in infants less than 2 months of age because they showed an inability to sustain tetanic contraction and thus tended to have lower T4/T1 ratios. Although our results are qualitatively different, they confirm abnormal neuromuscular responses in the very young.

In conclusion, antagonism of nondepolarizing neuromuscular blocking drugs in pediatric patients is more rapid than in adults, can be achieved more quickly with edrophonium than neostigmine, and demonstrates qualitative differences in subjects less than 1 year old. These results do not support the use of larger doses of anticholinesterases in children than adults.

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