Reversal of doxacurium and pancuronium neuromuscular blockade with neostigmine in children

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Recovery after doxacurium and pancuronium neuromuscular blockade and their acceleration by neostigmine have not been compared in children. Therefore, 60 paediatric surgical patients aged 2–10 yr (ASA 1–2) were studied. They were randomized to receive doxacurium 30 $\mu g \cdot kg^{-1}$ or pancuronium 70 $\mu g \cdot kg^{-1}$ iv during propofol, fentanyl, isoflurane and nitrous oxide anaesthesia. Electromyographic (EMG) responses of the adductor pollicis to train-of-four (TOF) stimulation of the ulnar nerve were recorded every ten seconds using a Datex NMT monitor. Six patients in each relaxant group received neostigmine (0, 5, 10, 20 or 40 $\mu g \cdot kg^{-1}$) with atropine by random allocation when first twitch height (T_1) had recovered to 25% of control. Spontaneous recovery after ten minutes was similar following doxacurium (mean ± SEM values of 45.0 ± 3.9 vs 49.5 ± 10.0 % for T_1 and 25.2 ± 3.8 vs 14.8 ± 3.6% for TOF ratios). Dose-responses to neostigmine were calculated from the log dose vs logit of T_1 or TOF ratio after ten minutes. Neostigmine-assisted recovery was not different in the two groups, with ED_{70} and ED_{90} doses for T_1 of 14.3 ± 1.8 and 25.7 ± 2.7 $\mu g \cdot kg^{-1}$ for doxacurium and 12.5 ± 1.7 and 25.3 ± 2.3 $\mu g \cdot kg^{-1}$ for pancuronium. Time to recovery of TOF ratio to 70% after neostigmine 40 $\mu g \cdot kg^{-1}$ was 2.3 ± 1.0 and 4.2 ± 1.7 min (P = NS) following pancuronium and doxacurium, respectively. Adjusted recovery due to neostigmine alone (spontaneous recovery subtracted from the total) required two to three times higher doses of neostigmine. Thus, in children, the spontaneous recovery and reversal of neuromuscular blockade is similar with doxacurium and pancuronium. However, compared with previous adult studies, they recover twice as quickly from doxacurium neuromuscular blockade and neostigmine antagonism is achieved at 25–50% of the adult doses.

On n'a jamais comparé chez l'enfant l'antagonisme du bloc neuromusculaire produit par le doxacurium avec celui du pancuronium et son accélération par la néostigmine. Dans ce but, 60 patients pédiatriques programmés pour la chirurgie sont étudiés. Ils sont répartis au hasard pour recevoir soit du doxacurium 30 $\mu g \cdot kg^{-1}$ ou du pancuronium 70 $\mu g \cdot kg^{-1}$ pendant une anesthésie générale au propofol, fentanyl, isoflurane et protoxyde d'azote. La réponse électromyographique à la stimulation par train de quatre (TOF) du nerf cubital est enregistrée toutes les dix secondes sur un moniteur NMT de Datex. Six patients dans chacun des groupes reçoivent néostigmine (0, 5, 10, 20 ou 40) avec de l'atropine au moment du retour de l'amplitude de la première secousse (T_1) à 25% du contrôle. Après dix minutes, la décurarisation spontanée est identique après le doxacurium (moyenne ± SEM, 45.0 ± 3,9 vs 49,5 ± 10,0% pour le T_1 et 25,2 ± 3,8 vs 14,8 ± 3,6% pour le rapport TOF). Les relations dose-effet de la néostigmine sont calculées avec le log de la dose vs le logit de T_1 ou la rapport TOF après dix minutes. Avec des ED_{70} et ED_{90}, la décurarisation assistée par la néostigmine ne diffère pas entre les deux groupes au regard du T_1: de 14,3 ± 1,8 et 25,7 ± 2,7 $\mu g \cdot kg^{-1}$ pour le doxacurium et de 12,5 ± 1,7 et 25,3 ± 2,3 $\mu g \cdot kg^{-1}$ pour le pancuronium. Le délai de retour du rapport TOF à 70% après néostigmine 40 $\mu g \cdot kg^{-1}$ est de 2,3 ± 1,0 après le pancuronium et de 4,2 ± 1,7 min (P = NS) après le doxacurium. La décurarisation ajustée pour la néostigmine seule (la décurarisation spontanée soustraite du total) nécessite des doses de deux à trois fois plus importantes de néostigmine. Chez l'enfant, la décurarisation spontanée et l'antagonisme du bloc neuromusculaire sont identiques pour le doxacurium et le pancuronium. Cependant, comparativement aux adultes, les enfants récupèrent deux fois plus rapidement du bloc neuromusculaire produit par le doxacurium et l'antagonisme de la néostigmine est complet à doses de 25–50% inférieures à celles de l'adulte.

Key words
AGE:
ANAESTHESIA: paediatric;
NEUROMUSCULAR RELAXANTS: doxacurium.

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Recovery from nondepolarizing neuromuscular blockade and its antagonism by neostigmine at the end of surgery are faster in children than in adults.[1] Pharmacodynamic differences in response result from altered sensitivity of the neuromuscular junction, extracellular fluid volume, cardiac output, renal and hepatic function. In children, a more rapid circulation time expedites drug delivery to the neuromuscular junction and its removal, accelerating the onset of action and shortening duration of effect. Higher doses of neostigmine used to be recommended in children,[2] but dose-response relationships for d-tubocurarine[3] and pancuronium[4] have proved the efficacy of neostigmine in doses half that of adult requirements.

Neostigmine-assisted recovery from neuromuscular blockade with doxacurium (a new long-acting nondepolarizing muscle relaxant which is devoid of cardiovascular side effects[5–8]), is slower in young and elderly adults than has previously been found after d-tubocurarine or pancuronium.[9,10] In children, antagonism of residual doxacurium blockade with neostigmine 60 $\mu g \cdot kg^{-1}$ and atropine 30 $\mu g \cdot kg^{-1}$ has been used at the end of surgery.[11–12] Direct comparisons of the recovery after doxacurium neuromuscular blockade with these other long-acting muscle relaxants have not been reported. Additionally, there has been no previous evaluation of the reversal of doxacurium neuromuscular blockade with neostigmine in children. Therefore, this study will examine recovery and its acceleration by neostigmine of equivalent degrees of neuromuscular blockade produced by doxacurium and pancuronium in children.

Methods

Institutional ethics approval and written parental consent to the study were obtained, with children assenting when possible. Sixty paediatric surgical patients (ASA physical status 1 or 2), aged two to ten years were studied. None had neuromuscular, cardiovascular, renal or hepatic diseases, mental of physical handicap, malnutrition or obesity, or were receiving medication that might interfere with neuromuscular function. All were scheduled for superficial surgery of two hours' duration.

No premedication was given and EMLA® local anaesthetic cream was applied to the dorsum of the hand to facilitate intravenous cannulation. On arrival in the operating room, an intravenous infusion of Ringer's lactate solution was established. Routine monitoring of ECG, blood pressure, oxygen saturation and end-tidal concentrations of carbon dioxide and volatile agents was performed. General anaesthesia was induced with propofol 3–5 $mg \cdot kg^{-1}$, atropine 20 $\mu g \cdot kg^{-1}$, lidocaine 30 $\mu g \cdot kg^{-1}$ and fentanyl 2 $\mu g \cdot kg^{-1}$ *iv*, followed by tracheal intubation. Mixtures of isoflurane (end-tidal concentration of 0.75–1.0%) in nitrous oxide:oxygen (2:1), with increments of fentanyl 1–2 $\mu g \cdot kg^{-1}$ *iv*, were used for maintenance of anaesthesia. Intermittent positive-pressure ventilation to maintain normocarbia during the period of muscle relaxation was applied.

Neuromuscular function monitoring was commenced using a Puritan Bennett Datex NMT Relaxograph to deliver supramaximal 0.1 msec, square wave, train-of-four (TOF) stimuli (2 Hz for two seconds at ten-second intervals) to the ulnar nerve in the forearm using cutaneous electrodes placed to obtain maximum twitch response. The hand and forearm were immobilized in a splint and the evoked responses of the adductor pollicis muscle recorded electromyographically. When the baseline response was stable, as judged by three consecutive equal responses, doxacurium 30 $\mu g \cdot kg^{-1}$ or pancuronium 70 $\mu g \cdot kg^{-1}$ was administered by random allocation to produce at least 90% depression of the first twitch in the train-of-four (T_1). Supplemental doses of doxacurium 10–15 $\mu g \cdot kg^{-1}$ or pancuronium 15–30 $\mu g \cdot kg^{-1}$ were given as needed to depress T_1 to $<10\%$ of control height. When T_1 had recovered spontaneously to 25%, neostigmine was administered in one of five doses (0, 5, 10, 20 or 40 $\mu g \cdot kg^{-1}$ with atropine 0–15 $\mu g \cdot kg^{-1}$) determined by random allocation in each relaxant group. The T_1 and train-of-four ratios (TOF ratios) were recorded as a percentage of control, every minute for the next ten minutes and then an additional dose of the reversal agents was administered to a total dose of neostigmine 60 $\mu g \cdot kg^{-1}$ with atropine 20 $\mu g \cdot kg^{-1}$. The EMG recording was continued until maximum recovery of neuromuscular function was evident by three consecutive equal readings of T_1 and TOF ratio. The time at which TOF ratio recovered to 70% after the injection of the first incremental dose of neostigmine was noted. Routine clinical anaesthetic care was provided for the completion of the procedure.

The T_1 values used for data analysis were the recorded values during the onset of neuromuscular blockade until 25% recovery of T_1 height. Those obtained during recovery, including that at administration of the initial dose of neostigmine, were recalculated using the final twitch height as the control value. Spontaneous recovery was defined as the recovery which occurred over the ten-minute study period in the absence of neostigmine (at the 0 $\mu g \cdot kg^{-1}$ dose). The term "total recovery" described the observed recovery following the various doses of neostigmine. The "adjusted recovery" is the recovery in T_1 resulting from neostigmine alone in the absence of continuing spontaneous recovery. It was calculated by subtraction of the T_1 recovery seen in the absence of neostigmine from the total recovery values ten minutes after the injection of neostigmine.

Dose-response curves for neostigmine for total and ad-

TABLE I Demographic data of patients receiving doxacurium or pancuronium

	DOX	*PAN*
Patients (*n*)	30	30
Age (yr)	4.5 ± 1.3	4.3 ± 1.8
Weight (kg)	17.4 ± 3.5	16.9 ± 3.6
Height (cm)	105.2 ± 10.6	103.2 ± 12.3
Sex (M:F)	21:9	17:13

Values for age, weight and height: means ± SD. M: male; F: female.

justed recovery following doxacurium and pancuronium were constructed using the log dose vs the logit of the amplitude of T_1 and TOF ratio at ten minutes after injection of the test dose. Linear regression analyses of these plots were used to calculate the effective doses of neostigmine required to achieve 50%, 70% and 80% recovery of T_1 and TOF ratio after ten minutes when administered at 25% spontaneous recovery of first twitch height after doxacurium or pancuronium, when administered at 25% spontaneous recovery of first twitch height. Results are expressed as mean ± SEM values.

Demographic data were compared for between group differences using chi-square analysis for sex and two-factor analysis of variance for age, weight and height. Between group comparisons were performed on these variables: time to maximum T_1 depression after initial dose of doxacurium or pancuronium, time from injection to 25% T_1 recovery, time from maximum depression of T_1 to 25% T_1 recovery and time from injection of neostigmine test dose to 70% TOF ratio recovery. The following tests were used: analysis of variance, unpaired t tests and Mann-Whitney tests. Newman-Keul's test and Bonferroni's correction were applied when appropriate. Differences were considered statistically significant when $P < 0.05$.

Results

Sixty healthy paediatric dental surgical patients were studied. The demographic data of the two study groups, receiving doxacurium or pancuronium, are given in Table I. They were comparable for types of surgery, ages, weights and heights, but more boys than girls (38:22) were studied, with males predominating in the doxacurium group.

Characteristics of the neuromuscular blockade produced by doxacurium and pancuronium are shown in Table II. The initial bolus of doxacurium or pancuronium resulted in similar levels of neuromuscular blockade, with depression of T_1 to <10% of control in all but two patients after doxacurium. The T_1 values at maximum depression were 45% and 11% in these two patients and incremental doses of doxacurium of 15 and 3 $\mu g \cdot kg^{-1}$ were given to achieve T_1 values of 9% and 6%, respectively. The onset to T_1 maximum depression following the initial bolus was faster after pancuronium than doxacurium (3.2 ± 0.3 vs 6.1 ± 0.4 min, $P < 0.05$). The duration of action from T_1 at maximum depression (achieved with additional relaxant doses in two patients) to 25% recovery of control height was shorter after doxacurium (36.1 ± 3.1 min vs 49.3 ± 3.0 min, $P < 0.01$) than after pancuronium. These times, medians and (ranges) varied from 38 (13 to 70) min for doxacurium to 50 (15 to 88) min for pancuronium.

First twitch height did not always recover to the initial baseline level after administration of the final increment of neostigmine. Two patients in the doxacurium group had final T_1 values of only 60% and 70%, although TOF ratios had returned to 100% and 80%, so their data were excluded from all analyses. All others achieved T_1 values >80% with values of 90.6 ± 1.4% for doxacurium and 92.0 ± 1.4% for pancuronium.

During the study, neostigmine was injected when T_1 recovered to 25% of its initial height and onset data were referred to the initial value as control. For later analysis of reversal values, T_1 was recalculated using the final T_1 height for reference; which meant that neostigmine test doses were injected when the actual mean T_1 recovery was between 27% and 29% in different dosage groups. Spontaneous recovery at ten minutes after neostigmine was similar for both muscle relaxants, reaching T_1 recovery of 45.0 ± 3.9% for doxacurium and 49.5 ± 4.1% for pancuronium (P = NS). Corresponding values for TOF ratio were 25.2 ± 3.8% and 14.8 ± 3.6% (P = NS). Following the largest dose of neostigmine (40 $\mu g \cdot kg^{-1}$), all patients recovered to 70% TOF ratio within ten minutes. This took 4.2 ± 1.7 min after doxacurium and 2.3 ± 1.0 min after pancuronium (P = NS).

The dose-response curves for total recovery of T_1 and TOF ratio are parallel straight lines (Figures 1 and 2). Their slopes were compared using the t test for comparing slopes of two regression lines and no differences were found. The effective doses of neostigmine (EDs) for antagonism of doxacurium and pancuronium neuromuscular blockade estimated from these did not differ (Table III). The adjusted recovery dose-response curves resemble those of the total recovery with different intercepts and correspondingly higher doses. As no differences were detected between the doxacurium and pancuronium dose-responses to neostigmine in the patients studied, a power calculation was performed using pancuronium as the control ($\alpha = 0.05$, $\beta = 0.20$). This determined that a sample size per group of 815 for T_1 and 121 for TOF ratio would be needed to detect a 30% difference in ED_{70}s. These numbers increase to 1803 and 259 if a difference of 20% is sought.

TABLE II Characteristics of neuromuscular blockade following doxacurium and pancuronium

	DOX	*PAN*	*P*
Dose ($\mu g \cdot kg^{-1}$)	30	70	
T_1 at maximum depression (%)	3.6 ± 1.6	0.5 ± 0.3	
Time from injection to T_1 maximum depression (min)	6.1 ± 0.4	3.2 ± 0.3	0.00001
Time from injection to recovery of T_1 25% (min)	42.8 ± 2.9	52.5 ± 2.9	<0.05
Time from T_1 maximum depression to recovery of T_1 25% (min)	36.1 ± 3.1	49.3 ± 3.0	<0.01

Values: mean ± SEM.

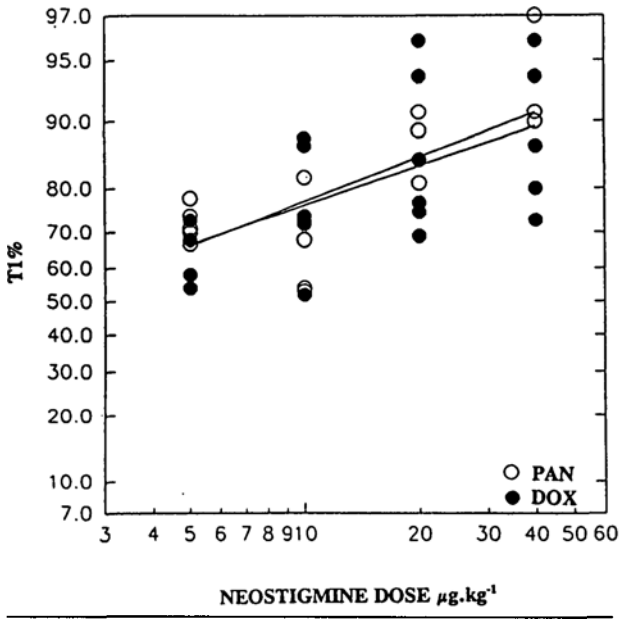

FIGURE 1 Dose-response curves for first twitch height (T_1) recovery after ten minutes (logit scale) for doxacurium and pancuronium neuromuscular blockade versus dose of neostigmine administered (log scale). Total recovery data used (observed recovery due to neostigmine in the presence of spontaneous recovery).

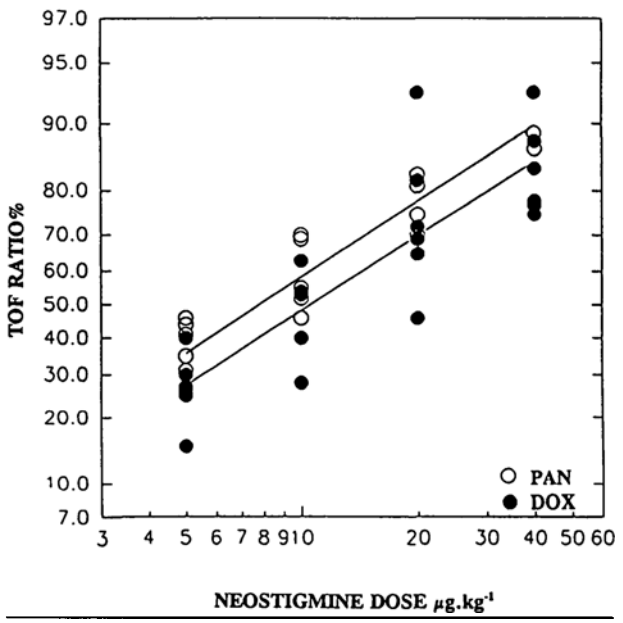

FIGURE 2 Dose-response curves for train-of-four ratio (TOF ratio) recovery after ten minutes (logit scale) for doxacurium and pancuronium neuromuscular blockade versus dose of neostigmine administered (log scale). Total recovery data used (observed recovery due to neostigmine in the presence of spontaneous recovery).

Discussion

This study demonstrates that doxacurium and pancuronium have similar neuromuscular blocking effects and recovery profiles in children aged 2–10 yr and that neostigmine antagonism of doxacurium is faster in children than previously reported in adults. The doses of doxacurium 30 $\mu g \cdot kg^{-1}$ or pancuronium 70 $\mu g \cdot kg^{-1}$ administered were approximately equipotent. Recent estimates of ED_{95} doses for doxacurium[11,12] of 27.3 and 32 $\mu g \cdot kg^{-1}$ have been reported in 2–12 yr old children during halothane anaesthesia. For pancuronium, the doses were more variable and ranged from 60–62 $\mu g \cdot kg^{-1}$ during halothane anaesthesia in children from 5 wk to 7 yr[13,14] to 80 $\mu g \cdot kg^{-1}$ in 1–15 yr old children during narcotic anaesthesia.[15]

The variable response to doxacurium, resulting in maximum depression of twitch of 55–100%, agrees with previous findings of 61–100% blockade produced with the same dose in similar groups of children.[11,12] The onset time to maximum block (6.1 min) was similar, but time from injection to T_1 of 25% recovery after doxacurium (42.8 min) was longer than anticipated (27.8 and 25 min) from previous studies.[11,12] In individual patients these times were as short as 17 min, or as long as 77 min, which was similar to the variability seen earlier.[11,12] Recovery from doxacurium blockade was faster in all of these paediatric studies than in adults, who took 80 ± 13 (17–306) min to reach 25% recovery from the same dose.[10] None of the children exhibited the abnormal sensitivity to doxacurium (resulting in prolongation of re-

TABLE III Dose-response relationships for T_1 and TOF ratio recovery during neostigmine reversal of doxacurium and pancuronium neuromuscular blockade

NEOST ($\mu g \cdot kg^{-1}$)	*Total recovery*		*Adjusted recovery*	
	DOX	*PAN*	*DOX*	*PAN*
T_1				
ED_{50}	1.8 ± 3.7	1.9 ± 3.4	4.9 ± 7.6	7.3 ± 8.1
ED_{70}	7.1 ± 6.6	6.3 ± 5.5	31.8 ± 44.0	40.6 ± 59.7
ED_{80}	16.3 ± 13.0	12.8 ± 8.6		
TOF ratio				
ED_{50}	10.8 ± 4.0	7.9 ± 2.9	21.8 ± 8.3	13.4 ± 4.7
ED_{70}	21.6 ± 9.3	14.2 ± 4.8	42.2 ± 24.6	26.4 ± 12.0
ED_{80}	32.8 ± 18.6	20.4 ± 8.3		

Values: mean ± SEM.

$ED_{50,\ 70\ and\ 80}$ ($\mu g \cdot kg^{-1}$) required to produce 50%, 70% and 80% recovery of T_1 or TOF after 10 min when given at T_1 recovery of 25%.

Total recovery: observed recovery due to spontaneous recovery and neostigmine reversal together.

Adjusted recovery: recovery due to neostigmine alone. Obtained by subtraction of increase in control value for spontaneous recovery (0 $\mu g \cdot kg^{-1}$ dose) in ten minutes, from value for total recovery at ten minutes.

covery to >four hours) which occurred in two of the adult patients. However, this may reflect the variability in response around a shorter mean duration of action in the children.

Interpretation of the EMG trace during recovery of neuromuscular transmission was made with reference to the final T_1 height as control. Although there is good correlation of the EMG with other methods of recording, such as mechanomyographic recording of the evoked twitch response,[16] thumb acceleration techniques reflect 10% greater block than simultaneous EMG recordings.[17] The sensitivity of the EMG remains stable during periods of prolonged stimulation, but is susceptible to changes in pH, electrolytes and skin and muscle temperature at the recording site. Decreases in skin temperature to 29°C cause as much as 20% reduction in T_1 height and TOF ratio in adults.[18,19] These observations were verified in cats and considerable variability was noted during prolonged cooling and rewarming: T_1 amplitude being more sensitive to changes, while TOF ratio remained unaffected over a wide range of temperatures.[20] None of the children had changes in axillary temperature of more than ±1°C. The EMG was monitored on the hand opposite to the one in which the intravenous infusion was placed and the arms were covered by drapes, but skin temperature at the hand was not recorded. Therefore, it is possible that undetected temperature variations resulted in the variability in final T_1 height observed. Agreement between mechanomyography and EMG is linearly related, with EMG recording values between 15% lower - 10% higher during onset and 40% lower - 45% higher during recovery.[21] Thus, electromyography is more variable and perhaps less reliable at the time that neostigmine antagonism of neuromuscular blockade was being studied. The recovery data from two patients in whom T_1 returned to <80% of the initial control value was excluded as this was likely due to a recording anomaly, of a magnitude which may have influenced the validity of the results.

Although doxacurium is long-acting, an appreciable amount of spontaneous recovery was observed. Spontaneous recovery of doxacurium was similar to that of pancuronium. In the ten-minute period studied, neuromuscular function was restored from 25% to almost 50%; close to the times of 8.6 min with doxacurium[12] and 9.3 min with pancuronium[13] required for the same degree of improvement in earlier studies in children. Thus, overall recovery of neuromuscular function after reversal with neostigmine depends also on the continuing spontaneous recovery, even with the longer-acting nondepolarizing relaxants.

No other studies in children are directly comparable with this study. However, when neostigmine 36 $\mu g \cdot kg^{-1}$ was administered at 10% recovery of T_1 following pancuronium, after two minutes, the values for T_1 were 58.6 ± 4.9% in children compared with 29.5 ± 4.9% in adults.[4] In the present study, a similar dose of neostigmine 40 $\mu g \cdot kg^{-1}$, given at 25% recovery of T_1, resulted in T_1 recovery of 78.5 ± 5.3% after pancuronium and 66.0 ± 14.3% after doxacurium in two minutes. These findings for pancuronium are in agreement with those for other nondepolarizing relaxants, showing that the level of blockade at which neostigmine reversal is attempted influences the efficacy of the antagonism.[22-27]

Although the recovery from doxacurium and pancuronium neuromuscular blockade was remarkably similar in these children, the contrast with earlier findings in adults is striking. The ED_{80} doses of neostigmine of 45 $\mu g \cdot kg^{-1}$ (given at 10% recovery of T_1) after d-tubocurarine and pancuronium in adults[28] are much higher than the ED_{80}s for either doxacurium or pancuronium determined in the paediatric patients. Even after the intermediate duration of action atracurium,[29] when given at the same level of recovery, equivalent neostigmine requirements in adults were still higher at 22–24 $\mu g \cdot kg^{-1}$.

When the neostigmine requirements for reversal of doxacurium in these children are compared with those in adults and elderly patients studied under similar conditions,[10] the differences are marked. The ED_{70} doses for T_1 and TOF ratio recovery in ten minutes in children were half those required in adults (14.3 ± 1.8 vs 28.4 ± 7.4 $\mu g \cdot kg^{-1}$ and 24.5 ± 1.7 vs 53.6 ± 7.5 $\mu g \cdot kg^{-1}$,

respectively). When adjusted to estimate the neostigmine requirements in the absence of spontaneous recovery, the equivalent ED_{70} doses increased to 36.1 ± 4.9 and 34.7 ± 30 $\mu g \cdot kg^{-1}$.

These results dispel the fear that neostigmine antagonism of doxacurium in children may be less effective than with another older longer-acting nondepolarizing relaxant, pancuronium. Variability in neostigmine dose-responsiveness was seen after both relaxants, but more rapid recovery in children ensured the efficacy of neostigmine reversal of doxacurium in doses less than half of those required in adults.

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