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Importance of the Level of Paralysis Recovery for a Rapid Antagonism of Vecuronium with Neostigmine in Children during Halothane Anesthesia

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In children, neostigmine is an effective antagonist of paralysis induced by long-acting muscle relaxants as d-tubocurarine[1] or pancuronium,[2] but little attention has been given to the pharmacology of neostigmine when antagonizing a vecuronium neuromuscular blockade in pediatrics. We, therefore, studied the antagonism of vecuronium paralysis in children from three different predetermined degrees of neuromuscular blockade. In adults, Rupp *et al.*[3] and Hennart *et al.*[4] found that the speed and degree of reversal were dependant upon the prereversal level of neuromuscular blockade.

The aims of this study were to analyze the rate of recovery of vecuronium-induced neuromuscular blockade after administration of neostigmine in children during nitrous oxide, halothane anesthesia, and to determine whether recovery of neuromuscular blockade was affected by the degree of neuromuscular blockade prior to antagonism.

MATERIALS AND METHODS

The protocol was approved by our Human Ethics Committee and informed consent was obtained from the parents. Twenty-four children (ASA class I or II), aged 3–8 yr, undergoing genito-urinary surgery were studied. No child had any disease known to alter neuromuscular function. No premedication was used, and anesthesia was induced with halothane and 60% nitrous oxide (60%). Once the patient was unconscious, an indwelling catheter was inserted into a vein of the forearm and the ulnar nerve was stimulated at the wrist, using 2Hz train-of-four (TOF) every 20 s with supramaximal square wave stimuli through surface electrodes. The electromyographic (EMG) response was monitored through surface electrodes placed over the adductor pollicis. When the EMG response was stable, vecuronium was injected as an iv bolus (100 μg/kg). The trachea was intubated when the first twitch of the TOF reached 0% of the control value. Thereafter, ventilation was controlled to maintain end-tidal P_{CO_2}, as measured with capnography, within normal limits (30–40 mmHg). Anesthesia was maintained by inhalation of nitrous oxide (60%) and an age-adjusted[5] end-tidal concentration of halothane of 1 MAC. Body temperature was maintained by use of a warming mattress between 36–37° C. Heart rate and arterial blood pressure were monitored throughout with an electrocardiogram and an automatic blood pressure cuff.

Neostigmine (30 μg/kg) and atropine (10 μg/kg) were administered at a predetermined level of the first twitch height spontaneous recovery: either 1% (group A, n = 8), 10% (group B, n = 8), or 25% (group C, n = 8) of the control twitch height (TH). Assignment to groups was on a random basis. Both TH and TOF ratio were observed every minute during a 12-min period after administration of neostigmine. Recovery time was determined in the three groups by measuring the time from the beginning of spontaneous reappearance of TH (1%) to the return of TH to 90% of control. Time from the beginning of spontaneous reappearance of TH to a TOF ratio of 0.7 was also determined. To detect statistical differences between the three groups of children, analysis of variance (ANOVA) was used. If ANOVA showed significant differences between groups, Student-Newman-Keuls test was performed.[6] A value of $P < 0.05$ was considered to be significant. All the results are expressed as mean ± SD.

RESULTS

Age or weight of the children did not differ significantly in the three groups: for group A, 4.9 ± 2.1 yr and 19 ± 4 kg; for group B, 5.4 ± 2.6 yr and 19 ± 6 kg; and for group C, 5.8 ± 2.7 yr and 20 ± 7 kg. In all children, TH increased rapidly within the first minutes following neostigmine injection. TH reached 10 min after neostigmine values of 94 ± 6%, 99 ± 1%, and 100% of the initial control values in group A, group B, and group C, respectively. TH values of groups B and C were always

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significantly higher than those of group A up to and including the 10th minute after neostigmine, but there were no significant differences in TH between groups B and C beyond the second minute (fig. 1).

TOF ratio reached .68 ± .22, .95 ± .03, and .99 ± .01 in groups A, B, and C, respectively, 10 min after neostigmine. At each period of observation, TOF ratio of groups B and C was significantly higher than the TOF ratio recorded in group A ($P < 0.01$). Beyond the fourth minute, TOF ratio did not differ significantly in groups B and C (fig. 2).

Recovery time from beginning of spontaneous recovery of TH (1%) to the return of TH to 90% of control was similar whether neostigmine was injected at 1, 10, or 25% of control value of TH (table 1). Time from 1% spontaneous recovery of TH to a TOF ratio of 0.7 was also similar in the three groups (table 1).

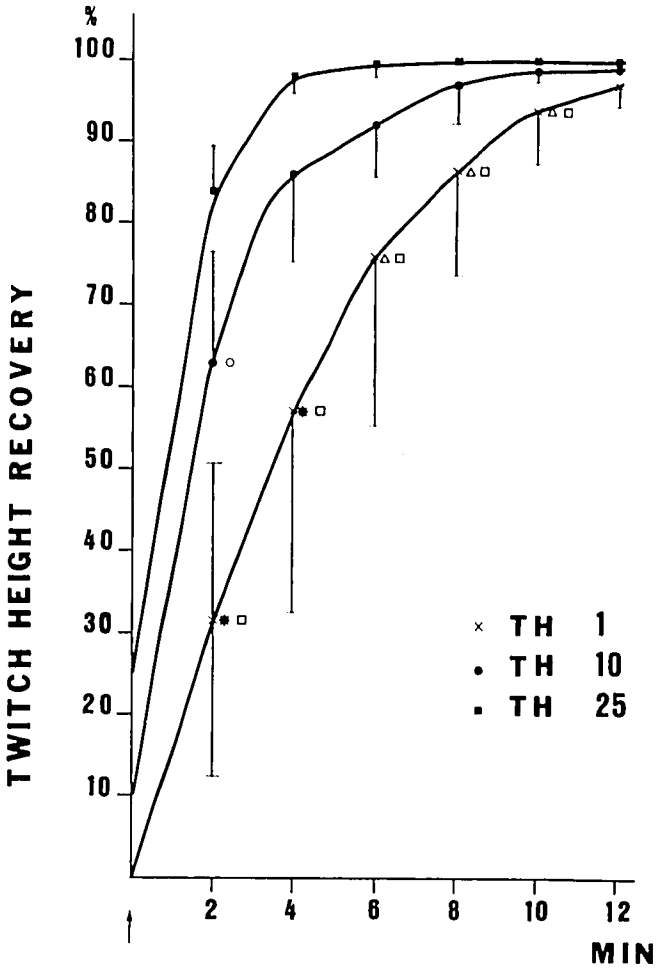

FIG. 1. Recovery characteristics of vecuronium TH after administration of neostigmine (30 μg/kg) and atropine (10 μg/kg) signified by the arrow at three predetermined TH values during nitrous oxide halothane anesthesia in children: TH 1 *versus* TH 10, △ $P < 0.05$, ✱ $P < 0.01$; TH 1 *versus* TH 25, □ $P < 0.01$; TH 10 *versus* TH 25, ○ $P < 0.01$.

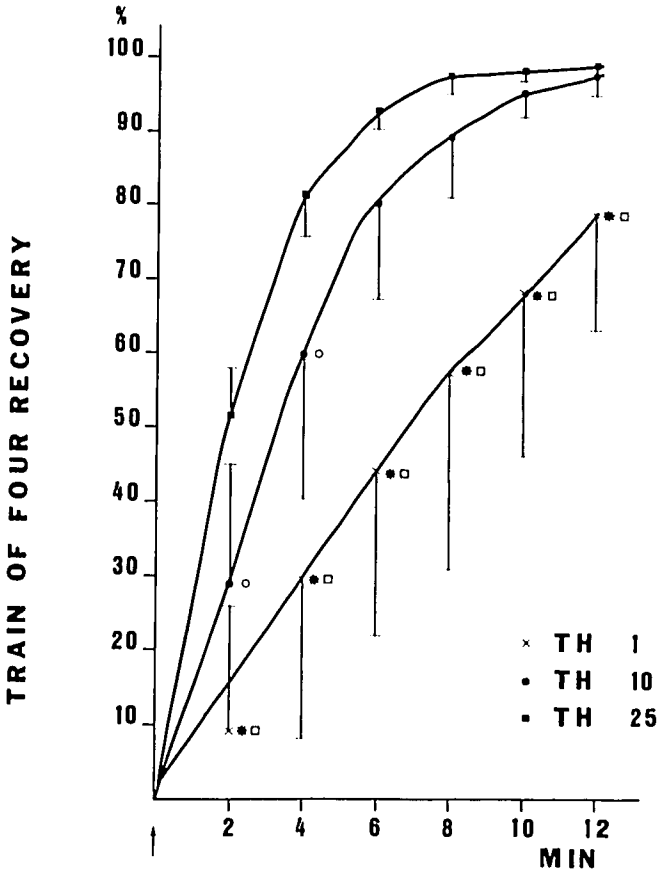

FIG. 2. Recovery characteristics of vecuronium TOF after administration of neostigmine (30 μg/kg) and atropine (10 μg/kg) at three predetermined TH values during nitrous oxide halothane anesthesia in children: TH 1 *versus* TH 10, ✱ $P < 0.01$; TH 1 *versus* TH 25, □ $P < 0.01$; TH 10 *versus* TH 25, ○ $P < 0.01$.

DISCUSSION

The degree and the speed of the antagonism of neuromuscular blockade by neuromuscular antagonists appears to be dependant on at least four factors: 1) the degree of paralysis at time of antagonism;[3,4,7] 2) the pharmacokinetics and pharmacodynamics of the muscle relaxant;[1,3] 3) the type of cholinesterase inhibitor molecule;[2,3] and 4) the dose of the antagonist.[3,8]

TABLE 1. Recovery Times from Beginning of Spontaneous Reappearance of TH (1%). Mean ± SD

	Time to 90% of Control TH (Min)	Time to 0.7 TOF Ratio (Min)
Group A (TH: 1%)	8.3 ± 1.9	9.4 ± 3.2
Group B (TH: 10%)	8.1 ± 2.0	9.0 ± 1.9
Group C (TH: 25%)	9.0 ± 1.0	9.8 ± 1.1

Initially, large doses of neostigmine (70 μg/kg) were recommended to antagonize neuromuscular blockade in children.[9] Fisher *et al.*[1] recently demonstrated that children require two-thirds the dose of neostigmine as compared with adults, and that a dose of 30 μg/kg in children is quite comparable to the usual dose of 40 μg/kg in adults.

Our results in children are consistent with previous studies in adults,[3,4] demonstrating that it takes longer to antagonize profound neuromuscular blockade than to antagonize moderate neuromuscular blockade, even with muscle relaxants of intermediate duration of action. Despite quite similar final TH values, 10 min after neostigmine injection, final TOF ratio remained markedly influenced by the prereversal TH level. In TH 10% and TH 25% groups, the antagonism of paralysis was rapid: a .70 TOF ratio was already present 4 min after neostimine in TH 25% group and 6 min after neostigmine in TH 10% group. In contrast, in TH 1% group, 12 min were required after neostigmine injection to obtain a TOF above 70%. Influence of halogenated anesthetics on the antagonism of non-depolarizing neuromuscular block has been reported.[10,11] Therefore, all the children were studied while receiving the same stable and age-adjusted end-tidal concentration of halothane. The rate of spontaneous recovery from vecuronium-induced paralysis is rapid in children.[12] Nevertheless, a .75 TOF ratio is obtained about 25 min after the start of spontaneous recovery from vecuronium neuromuscular blockade during halothane anesthesia in children.[13] The results of our study demonstrate that antagonism of vecuronium with moderate doses of neostigmine is adequate in children when the single twitch reappears. In this case, a .70 TOF ratio is obtained rapidly, in 10 min or less after neostigmine. The time from the beginning of mesurable spontaneous recovery (1% TH) until a 0.7 TOF ratio is obtained is unaltered, whether neostigmine is given at 1, 10, or 25% of spontaneous recovery of TH. Even if recovery time from 1% of TH to a 0.70 TOF ratio is similar in the three groups, transition from deep or moderate neuromuscular blockade to recovery is more rapid when neostigmine is administered at 10–25% of spontaneous recovery of TH. Fortunately, a level of 10–25% of control TH is easy to quantify because it coincides with successive reappearance of second, third, and fourth twitch of TOF, respectively.[14,15] Lastly, a TOF ratio of 0.7 was used as a measure of antagonism, since ventilation needed for recovery is associated with this level of the TOF ratio.

In conclusion, following vecuronium neuromuscular blockade, a 0.70 TOF ratio can be rapidly obtained in children with a moderate dose of neostigmine (30 μg/kg), even if it is administered at the beginning of reappearance of TH. However, when neostigmine is administered at 10–25% of control value of TH, transition from deep or moderate blockade to recovery is more rapid without increase in total time from 1% TH to 90% TH, or to 70% TOF recovery.

References

1. Fisher DM, Cronnelly R, Miller RD, Sharma M: The neuromuscular pharmacology of neostigmine in infants and children. ANESTHESIOLOGY 59:220–225, 1983
2. Meakin G, Sweet PT, Bevan JC, Bevan DR: Neostigmine and edrophonium as antagonists of pancuronium in infants and children. ANESTHESIOLOGY 59:316–321, 1983
3. Rupp SM, Mc Christian JW, Miller RD, Taboada J, Cronnelly R: Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium or vecuronium. ANESTHESIOLOGY 64:711–717, 1986
4. Hennart D, D'Hollander A, Plasman C, De Jonckheere M: Importance of the level of paralysis recovery for a rapid antagonism of atracurium neuromuscular blockade with moderate doses of edrophonium. ANESTHESIOLOGY 64:384–387, 1986
5. Gregory GA, Eger EI, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
6. Zar J: Biostatistical analysis. Englewood Cliffs, Prentice-Hall, 1974, pp 133–137, 151–155, 198–202
7. Katz RL: Clinical neuromuscular pharmacology of pancuronium. ANESTHESIOLOGY 34:550–556, 1971
8. Ferguson A, Egerszegi P, Bevan DR: Neostigmine, pyridostigmine and edrophonium as antagonists of pancuronium. ANESTHESIOLOGY 53:390–394, 1980
9. Cook DR: Muscle relaxants in infants and children. Anesth Analg 60:335–343, 1981
10. Delisle S, Bevan DR: Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. Br J Anaesth 54:441–445, 1982
11. Dernovoi B, Agoston S, Barvais L, Baurain M, Lefebvre R, D'Hollander A: Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane and enflurane anesthesia. ANESTHESIOLOGY 66:698–701, 1987
12. Fisher DM, Miller RD: Neuromuscular effects of vecuronium (Org NC45) in infants and children during N_2O halothane anesthesia. ANESTHESIOLOGY 58:519–523, 1983
13. Goudsouzian NG, Martyn JJA, Liu LMP, Gionfriddo M: Safety and efficacy of vecuronium in adolescents and children. Anesth Analg 62:1083–1088, 1983
14. Lee CM: Train of four quantitation of competitive neuromuscular block. Anesth Analg 54:649–653, 1975
15. Ali HH, Savarese JJ: Monitoring of neuromuscular function. ANESTHESIOLOGY 45:216–249, 1976