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Duration of Anesthesia before Muscle Relaxant Injection Influences Level of Paralysis

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Background: **Dosage guidelines for muscle relaxants are based on dose–response studies, normally performed after several minutes of stable nitrous oxide (N_2O)–opioid anesthesia. However, relaxants are used immediately after induction of anesthesia. The study was designed to determine the influence of the duration of anesthesia and N_2O on the onset time at the adductor pollicis (AP) and the corrugator supercilii (CS) muscles of maximum neuromuscular blockade after mivacurium.**

Methods: **After institutional approval and informed consent, patients were randomly allocated into three groups. Anesthesia was induced with alfentanil and propofol. Group A (n = 10) received mivacurium (0.1 mg/kg) immediately after loss of consciousness. Groups B (n = 10) and C (n = 10) received mivacurium after 15 min of anesthesia with propofol alone (B) or propofol with N_2O (C). The evoked response to train-of-four stimulation was measured by acceleromyography at the AP and the CS.**

Results: **Maximum neuromuscular blockade (%T1, median [range]) was significantly less in group A than in groups B and C ($P < 0.001$) at both the AP (81 [47–90]; 90 [35–100]; 100 [93–100], respectively) and the CS (19 [5–63]; 68 [61–100]; 89 [72–100], respectively). Maximum neuromuscular blockade was less in group B than in group C ($P < 0.001$) at the AP. Onset time of maximum neuromuscular blockade was not different between groups but was shorter at the CS than at the AP.**

Conclusions: **Duration of anesthesia and N_2O before mivacurium injection affect intensity of neuromuscular blockade but not onset time. Neuromuscular blockade obtained at the AP after several minutes of stable anesthesia with N_2O is greater than immediately after induction. This explains in part the discrepancy between the measured ED_{95} and the intubating dose.**

DOSAGE recommendations for neuromuscular blocking agents are based on dose–response studies. Several factors are known to influence dose–response relationships, such as the pattern and duration of nerve stimulation, the duration of stabilization of control responses, and the presence of inhalational agents.[1] For this purpose, a period of a few minutes of stable anesthesia to ensure signal stabilization with either thiopental or propofol and opioid–nitrous oxide is considered as the gold standard.[1] It is assumed that the duration of anesthesia (*i.e.*, for signal stabilization) and the introduction of nitrous oxide do not have any effect on the neuromuscular junction. However, this assumption has not been verified in humans.

Muscle relaxants used to facilitate tracheal intubation are normally injected immediately after induction of anesthesia, not after several minutes of anesthesia. The initial dose to provide deep paralysis required for tracheal intubation, is estimated at 2 to 3 times the ED_{95} measured at the adductor pollicis, and these measurements are performed after several minutes of anesthesia.[2] The requirement for a large intubating dose is usually attributed to the increased dose necessary to block the laryngeal muscles when compared with the adductor pollicis.[3] Kirkegaard-Nielsen *et al.*[4] demonstrated that the rocuronium dose that gives 95% probability of successful intubation at 60 s is 1.04 mg/kg, more than 3 times the ED_{95} at the adductor pollicis (0.3 mg/kg).[5] More recently, Plaud *et al.*[6] demonstrated that an estimate of laryngeal adductor muscle blockade can be obtained quantitatively by measuring the acceleromyographic response at the corrugator supercilii muscle. Nitrous oxide is recommended as part of the anesthetic for dose–response measurements,[1] but studies have suggested that it potentiates vecuronium[7] and succinylcholine[8] neuromuscular blockade in humans.

Therefore, it is important to determine the influence of the duration of anesthesia before muscle relaxant administration, with or without nitrous oxide (N_2O) on the response to these drugs. This study was designed to measure the onset and the intensity of mivacurium-induced neuromuscular blockade at both the adductor pollicis and the corrugator supercilii muscles immediately after induction of anesthesia, after 15 min of anesthesia without N_2O, and after the same duration of anesthesia with N_2O.

Materials and Methods

The study was approved by the Center Hospitalier de Montréal Scientific Review Committee and Research Ethics Committee (Montreal, Quebec, Canada). Thirty patients with American Society of Anesthesiologists physical status I who were 18–56 yr old were included in the study after obtaining informed consent. Patients were scheduled for elective and nonhemorrhagic surgery (minor orthopedic procedures, or diagnostic gynecological laparoscopies). All patients were free of cardiovascular, hepatic, renal, or neuromuscular disease. They were not taking any drugs suspected to interfere with neuromus-

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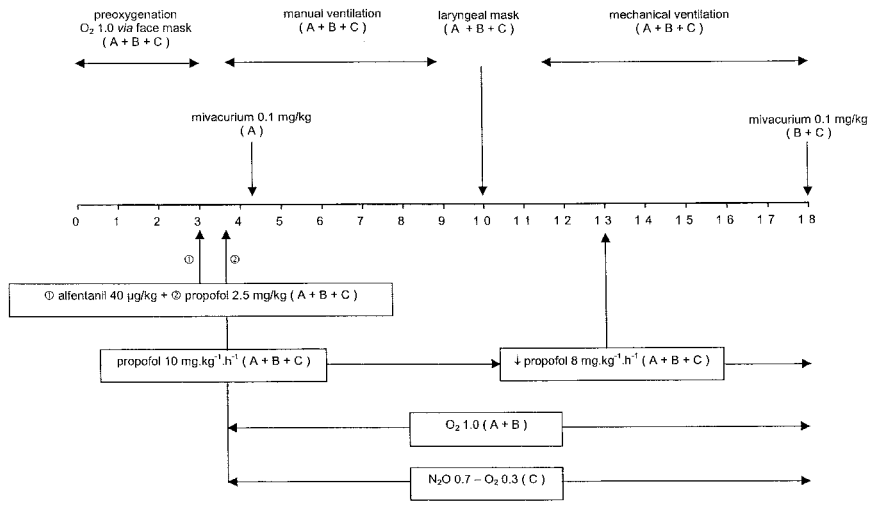

Fig. 1. Timing of the anesthetic procedure and mivacurium injection. Time in minutes. A, B, or C denotes group A, B, or C.

cular transmission or the cardiovascular system. Exclusion criteria included history of gastroesophageal reflux, anticipated abnormal airway, suspected allergy to muscle relaxants, and body weight more than 120% of ideal. On arrival in the operating room, an intravenous catheter was placed in the right antecubital fossa to administer fluids and drugs. Pulse oximetry, an electrocardiogram, and arterial blood pressure were monitored noninvasively. After 3 min, preoxygenation *via* face mask anesthesia was induced with 40 μg/kg alfentanil, and 2.5 mg/kg propofol 30 s later. Anesthesia was then maintained with 10 mg · kg^{-1} · h^{-1} propofol and 1.0 O_2 or with 10 mg · kg^{-1} · h^{-1} propofol and 0.7 N_2O–0.3 O_2. The propofol injection rate was adjusted to maintained hemodynamic stability defined as a 20% relative variation of control value (*e.g.*, before induction of anesthesia) of mean arterial pressure. A laryngeal mask airway was inserted under deep anesthesia without the aid of neuromuscular blocking drugs. The lungs were ventilated mechanically to keep end-tidal carbon dioxide tension within the range of 35–40 mmHg. Core temperature was monitored and maintained at normal levels.[9] After 10 min, propofol continuous infusion was decreased to 8 mg · kg^{-1} · h^{-1}.[10]

Patients were randomly allocated to three groups. In group A (n = 10), patients received 0.1 mg/kg mivacurium immediately after the loss of consciousness. Loss of consciousness was defined as unresponsiveness to both verbal and tactile stimuli.[11] In group B (n = 10), patients received 0.1 mg/kg mivacurium after 15 min of stable anesthesia with propofol only. In group C (n = 10), patients received 0.1 mg/kg mivacurium after 15 min of stable anesthesia with propofol and N_2O. Figure 1 depicts the anesthetic procedure and timing of mivacurium injection for each group.

Neuromuscular monitoring was set up before induction of anesthesia. Surface electrodes were placed over the left temporal branch of the facial nerve at the external part of the superciliary arch to stimulate the corrugator supercilii.[6] Another pair of electrodes was applied over the left ulnar nerve at the wrist to obtain the response of the adductor pollicis. The evoked responses at the thumb and at the corrugator supercilii were measured by TOF-Guard® acceleromyographs (Organon-Teknika, Fresnes, France). Each probe was positioned on the distal ventral part of the left thumb and on the internal half of the left superciliary arch (corrugator supercilii) before induction of anesthesia. Both nerves were stimulated supramaximally with train-of-four stimulation (four pulses 0.2 ms in duration, at a frequency of 2 Hz, 2 s in duration) every 15 s. Typical current intensity was 20 mA for the facial nerve and 40 mA for the ulnar nerve. Due to low response for the corrugator supercilii, the signal from the acceleration transducer was amplified 5 times. Baseline measurement of neuromuscular response was obtained just after loss of the eyelash reflex in each group and consisted of only two train-of-four stimulations at both muscles. To avoid the confounding effect of different durations of baseline stimulation on neuromuscular blockade, stimulation was started again only at injection of mivacurium. Neuromuscular monitoring was continued until the maximum neuromuscular blockade of the first twitch (T1) was obtained at both muscles, as determined by three equal, consecutive T1s.

All neuromuscular parameters were defined according to the "good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents."[1] Lag time was the interval between injection of rocuronium and the first decrease of T1. If submaximal neuromuscular blockade (T1 < 95%) was reached, onset time was defined as the time elapsed between the beginning of the muscle relaxant injection and the first of three consecutive T1s with the same amplitude. If maximum T1 depression was from 95 to 100%, onset time was defined as the time until 95% T1 depression.

Table 1. Patient Characteristics

	Group A	Group B	Group C
Age (yr)	37 ± 11 (24–56)	41 ± 10 (18–51)	35 ± 12 (20–58)
Weight (kg)	63 ± 10 (50–75)	63 ± 8 (54–77)	61 ± 8 (47–69)
Height (cm)	165 ± 8 (155–178)	164 ± 3 (157–170)	163 ± 6 (150–170)
Gender (F/M)	10/0	10/0	10/0

Values are expressed as mean ± SD (range). No difference between each group for age, weight, and height (one-way analysis of variance, all variables are normally distributed).

Statistics

The major end point was maximum blockade, testing the influence of anesthesia duration with or without nitrous oxide. Secondary end points were comparing onset time at the both the adductor pollicis and the corrugator supercilii muscles for each group. A difference of 40% in maximum blockade, as obtained for succinylcholine in a previous study,[8] was considered clinically important. Mivacurium has been found to yield, for single-dose studies, an SD of 27%.[12] The number of patients per group[10] was then determined for a two-sided type I error of 0.05 and a power of 0.8. The results are presented as mean ± SD, median and range. Statistical analysis for neuromuscular parameters used a one-way analysis of variance on ranks (Kruskal-Wallis) following by a *post hoc* test for pairwise multiple comparison procedures if the differences in the median values among the treatment groups are greater than would be expected by chance. The differences were considered as statistically significant when $P < 0.05$.

Results

The patient characteristics are presented in table 1. All were women. The three groups did not differ significantly with respect to age, weight, or height. Median time (range) to loss of consciousness occurred at 44 (21–65), 47 (25–70), and 43 (20–63) seconds in groups A, B, and C, respectively. The time courses of neuromuscular blockade at the adductor pollicis and corrugator supercilii are shown in figures 2 and 3, respectively. Maximum neuromuscular blockade was significantly less when mivacurium was administered immediately after induction (group A) than in groups B and C at both the adductor pollicis and the corrugator supercilii muscles (tables 2 and 3). For the same duration of anesthesia, administration of nitrous oxide (C) increased maximum blockade compared with group B at both muscles, but the difference reached statistical significance only for the adductor pollicis (tables 2 and 3). After 0.1 mg/kg mivacurium, time to reach maximum neuromuscular blockade at the adductor pollicis and the corrugator supercilii muscles was not different among the three groups (tables 2 and 3, figs. 2 and 3).

Within each group, no difference in lag time was found between the adductor pollicis and the corrugator supercilii (tables 2 and 3). However, onset time was shorter at the corrugator supercilii than at the adductor pollicis for the three groups ($P < 0.001$). Maximum neuromuscular blockade was less at the corrugator supercilii than at the adductor pollicis muscles in groups A, B, and C but reached statistical significance only in groups A and C ($P < 0.001$).

Discussion

This study shows that the duration of anesthesia before muscle relaxant injection increases mivacurium-induced neuromuscular blockade. This was observed both at the adductor pollicis and the corrugator supercilii muscles. Adding nitrous oxide to propofol further increases the degree of paralysis at the adductor pollicis when mivacurium was injected after 15 min of stable anesthesia.

The pattern and duration of nerve stimulation can influence onset time at the adductor pollicis,[13–15] so both of these variables were the same (train-of-four every 15 s) for the adductor pollicis and the corrugator supercilii. In all three groups, the number of stimulations before mivacurium injection was the same. The guidelines for good clinical research practice in pharmacody-

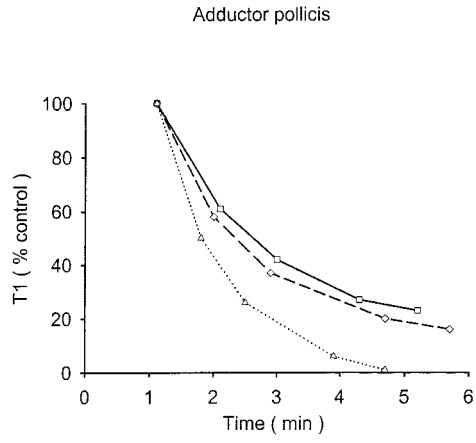

Fig. 2. Onset characteristics (mean %T1 against time) after 0.1 mg/kg mivacurium at the adductor pollicis. Mivacurium was either injected immediately after loss of consciousness (group A; solid line) or after 15 min of stable anesthesia with propofol–oxygen 1.0 (group B; dashed line) or propofol–nitrous oxide 0.7–oxygen 0.3 (group C; dotted line). The points on each line represent, from left to right, T1 and time to last 100% value (lag), T1 and time to 50, 75, 95 and 100% of maximum blockade, respectively.

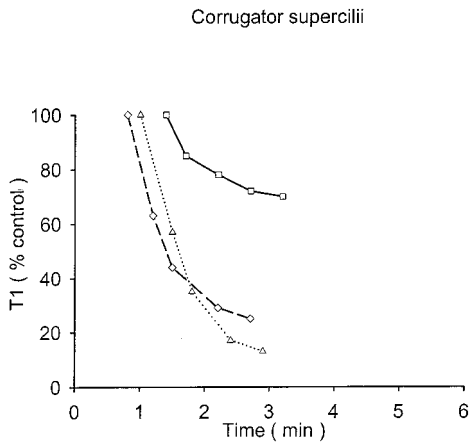

Fig. 3. Onset characteristics (mean %T1 against time) after 0.1 mg/kg mivacurium at the corrugator supercilii. Mivacurium was either injected immediately after loss of consciousness (group A; solid line) or after 15 min of stable anesthesia with propofol–oxygen 1.0 (group B; dashed line) or propofol–nitrous oxide 0.7–oxygen 0.3 (group C; dotted line). The points on each line represent, from left to right, T1 and time to last 100% value (lag), T1 and time to 50, 75, 95 and 100% of maximum blockade, respectively.

namic studies of neuromuscular blocking agents,[1] where a period of signal stabilization is recommended, could not be followed here because the hypothesis required mivacurium to be given immediately after induction, to mimic clinical practice. However, all patients were treated in the same way, with the same type of stimulation, the same interval between stimulations, and the same number of stimulations before injection of the relaxant.

Two muscles, the adductor pollicis and corrugator supercilii, were monitored in this study to rule out any effect specific to the adductor pollicis. The same method for neuromuscular monitoring (*e.g.*, acceleromyography) was used for both muscles. Both muscles behaved in the same way, that is blockade was less immediately after induction of anesthesia than after 15 min. In all groups, blockade was less at the corrugator supercilii than at the adductor pollicis (tables 2 and 3), which is in accordance with a previous study,[6] where rocuronium was used as muscle relaxant. The time course of blockade was found to be similar at the corrugator supercilii and at the laryngeal adductor muscles,[6] so it is reasonable to assume that the results of this study could apply to laryngeal muscles. The corrugator supercilii should not be confused with the orbicularis oculi. In spite of anatomical proximity, blockade at the orbicularis oculi is greater and duration is less than at the corrugator supercilii.[6]

The effect of nitrous oxide on neuromuscular blockade is uncertain,[1] but enhancement of vecuronium-[7] and succinylcholine-induced[8] neuromuscular blockade has been documented. The present study confirms these findings for mivacurium because maximum blockade was significantly less at the adductor pollicis in group B than in group C (table 2, figs. 2). The difference was not significant for the corrugator supercilii (table 3, Fig. 3), probably because of a greater variability and a small number of patients. The differences in mean maximum blockade were 15 and 12% at the adductor pollicis and the corrugator supercilii muscles, respectively, which is consistent with the 20% increase in vecuronium potency associated with nitrous oxide reported by Fiset *et al.*[6] The main difference between these two studies was the time exposure to nitrous oxide, 5 *versus* 15 min. When simulating (Gas Man® software, version 2.1.1, Understanding Anesthesia Uptake and Distribution, edited by Philip JH, Chestnut Hill, MA, Med Man Simulations), saturations of muscle tissue by nitrous oxide were only 0.1 and 0.3 of the pseudoplateau in the Fiset study and ours, respectively. This indicates that potentiation by nitrous oxide at the neuromuscular junction is unlikely. Thus, the effect of nitrous oxide is best explained by altered delivery of drug because of hemodynamic changes.

The hemodynamic effects of intravenous anesthetic agents influence onset time.[16] A decrease in cardiac output[17,18] and/or and increase in muscle blood flow[18,19] can increase maximum neuromuscular blockade. The enhanced neuromuscular blockade observed after 15 min of stable anesthesia with propofol alone could be the result of decreased cardiac output and increased peripheral vasodilatation.[20] Recently, cardiac output was found to influence the pharmacokinetic–pharmacodynamic relationship of rocuronium.[17] Contrary to what might be assumed, decreased cardiac output normally decreases the dose required for a given effect because of the higher and broader initial concentration peak.[21] Mivacurium given at induction might produce less blockade because it is administered before the depressant hemodynamic effects of propofol are

Table 2. Onset Time and Maximum Blockade after 0.1 mg/kg Mivacurium on the Adductor Pollicis

	Group A	Group B	Group C
Lag time (min)	1.1 ± 0.5; 1.2 (0.3–1.8)	1.1 ± 0.3; 1.2 (0.3–1.5)	1.1 ± 0.6; 1.0 (03–2.5)
Onset time (min)	5.4 ± 0.9; 5.2 (3.5–6.8)	5.7 ± 1.4; 5.3 (4.8–9.5)	4.7 ± 1.0; 5.2 (3.5–6.0)
Maximum blockade (%T1)	76 ± 15; 81* (47–90)	84 ± 19; 90† (35–100)	99 ± 2; 100 (93–100)

Values are expressed as mean ± SD; median (range). Lag time and onset time were not different among the three groups: $P = 0.896$ and 0.525, respectively.
* $P < 0.001$ *versus* groups B and C (Student–Newman–Keuls test after a Kruskal–Wallis one-way analysis of variance on ranks). † $P < 0.001$ *versus* group C (Student–Newman–Keuls test after a Kruskal–Wallis one-way analysis of variance on ranks).

Table 3. Onset Time and Maximum Blockade after 0.1 mg/kg Mivacurium on the Corrugator Supercilii

	Group A	Group B	Group C
Lag time (min)	1.4 ± 0.6; 1.3* (0.8–2.8)	0.8 ± 0.3; 0.8 (0.3–1.5)	1.0 ± 0.5; 1.0 (0.3–1.8)
Onset time (min)	3.2 ± 1.1; 3.0 (1.8–5.5)	2.7 ± 0.3; 2.5 (2.3–3.3)	2.9 ± 0.5; 2.8 (2.0–3.8)
Maximum blockade (%T1)	30 ± 22; 19† (5–63)	75 ± 15; 68 (61–100)	87 ± 9; 89 (72–100)

Values are expressed as mean ± SD; median (range). Onset time was not different among the three groups: $P = 0.373$.

* $P = 0.014$ *versus* group B (Student–Newman–Keuls test after a Kruskal–Wallis one-way analysis of variance on ranks). † $P < 0.001$ *versus* groups B and C (Student–Newman–Keuls test after a Kruskal–Wallis one-way analysis of variance on ranks).

manifest. Pharmacokinetic–pharmacodynamic analyses are needed to confirm this assumption.

Mivacurium was selected for this investigation because the intubating conditions reported with 0.15 mg/kg, that is, twice the ED_{95} of 0.07–0.08 mg/kg,[12] are much worse than expected. A dose of 0.1 mg/kg was chosen because it was expected to yield approximately 95–100% neuromuscular blockade at the adductor pollicis with N_2O–opioid anesthesia.[22] If, as expected, the effect were less immediately after induction of anesthesia and at the adductor pollicis, maximum blockade would likely be in the range 1–95%, and measurable. The mean value of 99% obtained at the adductor pollicis is compatible with an ED_{95} between 0.07 and 0.08 mg/kg, as reported in other studies.[12]

The study involved administration of a single dose instead of performing a full dose–response study. The dose chosen, 0.1 mg/kg, was expected to yield a measurable degree of block, that is, 0% and 100% values were avoided in all situations. Although the exact value of the ED_{95} cannot be obtained, estimates can be made at the adductor pollicis. In group B (anesthesia without N_2O), mean block was 84% after 0.1 mg/kg. It follows that without N_2O, the ED_{95} (dose giving 95% block on average) is greater than 0.1 mg/kg. When mivacurium is injected immediately after loss of consciousness, mean maximum blockade was 76% at the adductor pollicis. This indicates an even greater ED_{95}. Assuming a slope factor of 4 for dose–response curves,[23] the ED_{95} at the adductor pollicis could be approximately 0.14 mg/kg during anesthesia without N_2O and 0.16 mg/kg immediately after induction of anesthesia, greater than the accepted values of 0.07–0.08 mg/kg obtained under stable anesthesia with N_2O.

The study was performed on two muscles located in two separate locations to rule out any local effect, such as blood flow, on the adductor pollicis. In addition, the corrugator supercilii has special significance, because it is a good indicator of laryngeal blockade.[6] In all three groups of the present study, blockade was markedly less at the corrugator supercilii than at the adductor pollicis, and duration of anesthesia increased blockade at both muscles. Maximum blockade was only 30% at the corrugator supercilii immediately after induction of anesthesia, which suggests an ED_{50} greater than 0.10 mg/kg, and an even greater ED_{95}. This provides an explanation why a high percentage of excellent intubating conditions is not attained unless the dose of mivacurium is as high as 0.25 mg/kg.

It is concluded that the duration of anesthesia prior to mivacurium injection has a major influence on the level of paralysis at both the adductor pollicis and the corrugator supercilii. Nitrous oxide also enhanced neuromuscular blockade at the adductor pollicis. These results have major implications. Dose–response studies performed under stable N_2O–opioid anesthesia are likely to underestimate the ED_{95} that applies immediately after induction. This explains, at least in part, why it may be necessary to administer many times the ED_{95} at the adductor pollicis under stable propofol–opioid–N_2O anesthesia to obtain excellent intubating conditions.

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