4. Muir A. W., Marshall R. J., *Comparative neuromuscular blocking effects of vecuronium, pancuronium, Org 6368 and suxamethonium in the anaesthetized domestic pig*, Br. J. Anaesth., **59**, 622-9, 1987.
5. Secher N. H., Rube N., Secher O., *Effects of tubocurarine on human soleus and gastrocnemius muscle*, Acta Anaesthesiol. Scand., **26**, 231-4, 1982.
6. Meistelman C., Plaud B., Donati F., *Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans*, Can. J. Anaesth., **39**, 665-9, 1992.
7. Plaud B., Proost J. H., Wierda J. M., Barre J., Debaene B., Meistelman C., *Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans*, Clin. Pharmacol. Ther., **58**, 185-91, 1995.
8. Cantineau J. P., Porte F., D'Honneur G., Duvaldestin P., *Neuromuscular effects of rocuronium on the diaphragm and adductor pollicis in anesthetized patients*, Anesthesiology, **81**, 585-90, 1994.
9. Plaud B., Debaene B., Lequeau F., Meistelman C., Donati F., *Mivacurium neuromuscular block at the adductor muscles of the larynx and adductor pollicis in humans*, Anesthesiology, **85**, 77-81, 1996.
10. Goldberg M. E., Larijani G. E., Azad S. S., Sosis M., Seltzer J. L., Ascher J., Weakly J. N., *Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients*, Anesth. Analg., **69**, 93-9, 1989.
11. Shanks C. A., Fragen R. J., Pemberton D., Katz J. A., Risner M. E., *Mivacurium-induced neuromuscular blockade following single bolus doses and with continuous infusion during either balanced or enflurane anesthesia*, Anesthesiology, **71**, 362-6, 1989.
12. Van Aken H., Ory J. P., Vandermeersch E., Vertommen J. D., Crul J. F., *Intubating conditions and neuromuscular effects of mivacurium during propofol-alfentanil anaesthesia*, Acta Anaesthesiol. Scand., **39** (Suppl. 106), 26-9, 1995.
13. Debaene B., Billard V., Lieutaud T., Meistelman C., *Org 9487 induced neuromuscular block at the adductor pollicis muscle and laryngeal adductor muscles in humans*, Anesthesiology, **83**, A919, 1995.
14. Bowman W. C., Rodger W., Houston J., Marshall R. J., Mcindewar I., *Structure: action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat*, Anesthesiology, **69**, 57-62, 1988.
15. van den Broek L., Wierda J. M., Smeulers N. J., Proost J. H., *Pharmacodynamics and pharmacokinetics of an infusion of Org 9487, a new short-acting steroidal neuromuscular blocking agent*, Br. J. Anaesth., **73**, 331-5, 1994.
16. Wierda J. M., van den Broek L., Proost J. H., Verbaan B. W., Hennis P. J., *Time course of action and endotracheal intubating conditions of Org 9487, a new short-acting steroidal muscle relaxant; a comparison with succinylcholine*, Anesth. Analg., **77**, 579-84, 1994.

Onset time of neuromuscular block and intubating conditions : influence of different stimulation patterns

P. Hans (*), W. Dewé (**) and A. Albert (**)

(Acta Anaesth. Belg., 1997, 48, 15-21).

Background

The onset time of a given drug administered intravenously (IV) is defined as the time elapsed between end of injection and peak effect. Ideally, the onset time should be as short as possible to avoid the physician for waiting before the drug effect becomes effective and to prevent him from injecting an additional dose, and thus possibly exposing the patient to overdosage. In the case of muscle relaxants, a short onset time is also highly desirable to reduce the time between induction of anesthesia and tracheal intubation, and hence the risk of aspiration of gastric contents and the possibility of awareness. Basically, the onset of action of non-depolarising muscle relaxants depends on the arrival at the motor end-plate of molecules in suffcient amount to prevent acetylcholine from reaching enough receptors to cause neuromuscular transmission. The speed of onset of neuromuscular block may be affected by different factors related to the patient or to the muscle relaxant itself.

Factors which are patient characteristics include cardiac output, circulation time and muscle blood flow (1). The onset of non-depolarising relaxants is shorter in infants, who have a relatively large cardiac output, than in older children, as well as in young subjects than in older individuals who have a decreased cardiac output (2, 3). Considering the circulation time between heart and the target organ, muscles of the larynx and respiratory system have a faster onset of block than peripheral muscles like the adductor pollicis which is frequently used in clinical practice for monitoring neuromuscular function (4, 5). Finally, access of drug at the receptor site depends also on the muscle blood flow, which can be modified by metabolic activity and evoked contractions (7).

Other factors which may affect onset are directly related to the muscle relaxant itself, such as organ affinity, potency, clearance and dose administered (1). Organ affinity depends on the ratio of muscle to blood relaxant concentrations at equilibrium. The effect of potency is related to the high proportion of receptors which need to be occupied by relaxant molecules to inhibit neuromuscular transmission. In case of potent relaxants, small doses are required to produce a given level of block. As small doses are associated with low plasma concentrations, the time needed

(*) Department of Anesthesia & Intensive Care Medicine, CHR de la Citadelle, University Hospital, 4000 Liège.
(**) Department of Biostatistics, University of Liège, CHU Liège, 4000 Liège.
Correspondence address : University Department of Anesthesia & Intensive Care Medicine, CHR de la Citadelle, boulevard du 12e de Ligne 1, 4000 Liège, Belgium.

to block the critical number of receptors will be longer. Consequently, high potency relaxants are expected to have longer onset times (8). A high clearance is associated with a more rapid decrease in plasma concentrations ; therefore, the peak concentration of the drug at the effect site occurs more early, resulting in a rapid onset. Finally, the onset time is independent of the dose if less than 100% block is attained. However, if paralysing doses are given, the time interval between injection and peak concentration at the effect site does not change but the concentration at the neuromuscular junction necessary to abolish transmission is reached before the peak concentration is achieved. Therefore, the onset time decreases with increasing doses of muscle relaxants (8).

Introduction

Beside patient characteristics and drug properties, the onset time of action of non-depolarising muscle relaxants may also be affected by technical factors related to the monitoring of neuromuscular function : the method of assessing the evoked muscle responses, the stimulation pattern, and the duration of stimulation prior to the administration of the relaxant drug.

The evoked responses to nerve stimulation can be monitored by mechanomyography, electromyography and acceleromyography. Acceleromyography has been compared with mechanomyography ; although both methods are reliable, they present some discrepancies and cannot necessarily be used interchangeably (9). On the other hand, neuromuscular transmission may be assessed using different patterns of stimulation among which the train of four (TOF) sequence is certainly the most commonly used. Increasing periods of control stimulation prior to the administration of atracurium, vecuronium and mivacurium has been shown to decrease the time to onset of block at the adductor pollicis (10). Finally, several studies have established that the onset time is also affected by the mode of stimulation, the neuromuscular function disappearing earlier with a high than with a slow frequency pattern (11, 12, 13).

In the present study, we decided to investigate the effect of three different patterns of stimulation, applied during a 2 minutes period, on the onset time of rocuronium, the speed of onset of block, and the conditions of intubation performed at 90% block at the adductor pollicis.

Patients and methods

The design of the study was approved by the Ethics Committee of the local University Hospital and informed consent was obtained from each patient.

Thirty adult, ASA class I or II patients scheduled to undergo elective surgery requiring tracheal intubation, were randomly enrolled in the study. Exclusion criteria included a history of renal, hepatic, cardiovascular, pulmonary or neuromuscular disease and an abnormal sensitivity to neuromuscular blocking agents. Patients with alcohol or narcotic addiction were also excluded from the study as well as patients outside 30% of their ideal body weight. Premedication consisted of hydroxyzine 1 mg kg^{-1} body weight, alprazolam 0.5 mg and atropine 0.5 mg given orally 1 h before the start of the procedure.

Upon arrival in the operating room, all patients were monitored with an electrocardiograph, a non-invasive blood pressure device (Dinamap) placed on the right arm, a pulse oximeter and 2 temperature probes. Neuromuscular transmission was assessed using a Biometer accelograph TOF-GUARD^R monitor connected to the patient by 2 electrodes used to stimulate indirectly the left ulnar nerve at the wrist, while a piezo-electric transducer was fastened to the thumb. Rectal temperature was maintained above 35°C, and palmer skin

temperature measured at the left hand using a cutaneous probe was kept at more than 32°C throughout the study. Sufentanil 0.3 μg kg^{-1} was given IV 5 minutes before induction of anesthesia. Anesthesia was induced with a bolus of propofol 2 mg kg^{-1} IV, immediately followed by a continuous infusion at 6-8 mg $kg^{-1}h^{-1}$.

Once the patients were asleep, the ulnar nerve was stimulated for a 2 min period prior to the administration of rocuronium 0.6 mg kg^{-1} IV over 5 s in an antecubital vein through a rapidly running infusion. Ten patients each were randomly allocated to one of three groups according to the pattern of stimulation delivered throughout the study : supramaximum stimuli of 0.2 ms duration were applied in a single twitch mode at 1Hz in group I (ST1), in a single twitch mode every 10 sec (0.1 Hz) in group II (ST0.1), and in a TOF mode at 2 Hz every 15 s in group III (TOF). Patients were given oxygen by mask, intubated by an experienced anesthetist at 90% block at the adductor pollicis, and then mechanically ventilated with an air/oxygen mixture. The anesthetist who intubated the patient was not aware of the stimulation pattern. The variables recorded were the onset time, the decrease in single or first twitch height value as a function of time, and the intubating conditions. Onset time was defined as time from the end of rocuronium injection until occurrence of 10% single or first twitch height (90% block). Intubating conditions were assessed according to the following scoring system : excellent (good jaw relaxation, vocal cords open, no response to intubation), good (good jaw relaxation, vocal cords open but minimal reaction to intubation), poor (moderate jaw relaxation, moving vocal cords, coughing and/or bucking), and inadequate (intubation impossible due to poor jaw relaxation or closed cords). For statistical analysis, intubating conditions were classified as clinically acceptable (excellent or good) or not (poor or inadequate).

Statistical analysis

Results were expressed as means ± SD. A log transform was used for the onset time to normalize the distribution, whereas a logit transform was applied to single or first twitch height values (expressed as % of control) to linearize their relationship with time, i.e. log $\{Y/(100 - Y)\} = a + b.t$. Thus, the slope «b» represents the speed of the onset of block and the intercept «a» may be viewed as the lag time between end of rocuronium injection and occurrence of a decrease in twitch height.

Treatment groups were compared by one way analysis of variance followed by multiple comparisons (Scheffe's method) for continuous variables and by a chi-square test for intubating conditions. To compare the speed of onset of neuromuscular block in the three groups, a generalized linear mixed model with random effects (SAS PROC MIXED) was applied to logits of twitch height values observed as a function of time.

All results were considered to be significant at the 5% critical level ($p < 0.05$). Statistical calculations were carried out using SAS (SAS Institute Inc., Cary, North Carolina, USA) and S-Plus (StatSci Europe, Oxford, U.K.) software packages.

Results

The 3 groups of patients did not differ significantly with respect to age, weight, height and gender (Table I). The onset times for the 3 groups are shown in Table II. Mean time ± SD to 90% block was 37.7 ± 8.9 s for ST1, 123 ± 60.2 s for ST0.1, and 84.5 ± 22.8 s for TOF. Analysis of variance applied to log values of onset times revealed to be highly significant ($P < 0.0001$). Multiple comparisons showed that onset time was significantly shorter in group I than in groups II and III, but did not significantly differ between the latter.

The average decrease in single or first twitch height values as a function of time in

Table I

Patient characteristics (mean, SD) in the 3 groups defined according to the stimulation mode

Variable	ST1	ST 0.1	TOF	p
	n = 10	n = 10	n = 10	
Age (yr)	42.0 (2.2)	42.8 (2.2)	41.6 (2.2)	0.93
Weight (kg)	66.7 (3.6)	69.4 (3.6)	69.6 (3.6)	0.82
Height (cm)	169.5 (2.4)	169.7 (2.4)	171.0 (2.4)	0.90
Sex (m/f)	6/4	6/4	7/3	0.87

Table II

Mean and SD onset times and their log values in the 3 patient groups

Variable	ST 1	ST 0.1	TOF	p
Onset time (sec)	37.7 (8.8)	123 (60.2)	84.5 (22.8)	
Log onset	*3.6 (0.2)*	*4.7 (0.5)*	*4.4 (0.2)*	*0.0001*

F = 22.5 (2 and 27 df).

Table III

Intubating conditions at 90% block at the adductor pollicis according to stimulation mode

Conditions	ST1	ST 0.1	TOF
Clinically acceptable *(excellent + good)*	4	9	8
Clinically not acceptable *(poor + inadequate)*	6	1	2

$\chi^2 = 8.85$ (2 df) p = 0.012.

the three patient groups is illustrated in Figure 1. The slopes of the linear regression lines (b = –0.238 for ST1, b = –0.0259 for ST0. 1, and b = –0.0464 for TOF, respectively) were significantly different (*P < 0.001*) between the 3 groups, reflecting the highest speed of onset of block in group 1 and the lowest speed in group II. The intercept, assimilated to the lag time, revealed to be significantly higher (*P < 0.001*) in group I (a = 7.10) than in group II (a = 1.16) and in group III (a = 1.76) but did not differ significantly between the last 2 groups.

The results related to the assessment of intubating conditions are presented in Table III. The proportions of patients with excellent or good intubating conditions were significantly higher (*P = 0.012*) for ST0.1 and TOF than for ST1.

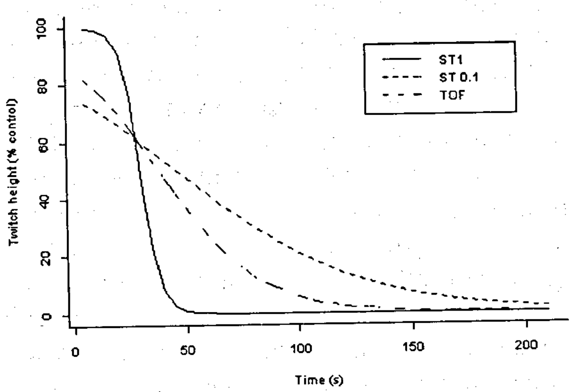

Fig. 1. — Average time response of single or first twitch height (% of control) in the three patient groups.

Discussion

The results of the study demonstrate that the pattern of nerve stimulation applied during a 2 min period prior to rocuronium administration can significantly affect the onset time, the speed of onset of block, and the conditions of intubation performed at 90% block at the adductor pollicis.

First, the onset time was more rapid when nerve stimulation was applied more frequently, since the number of impulses applied during the period of control stimulation was 12 in ST0.1 patients, 120 in ST1, and 32 in TOF. Thus, for the same stimulation duration, the higher the number of impulses, the shorter the onset time. The onset time was the most rapid in group I, but did not differ significantly between the last two groups, due to a larger variability in group II. The effect of stimulation pattern on onset time has already been investigated by comparing two modes of stimulation. After atracurium administration to patients who received, every 12 s, single twitch stimulation in one arm and tetanic stimulation for 1 s in the other, it has been demonstrated by Hughes and Payne that the neuromuscular function disappeared earlier with tetanic stimulation than with single twitch (11). According to Curran *et al.*, onset of atracurium and suxamethonium is more rapid with TOF than with single twitch stimulation applied at 0.08 Hz (12). Finally, Feldman and Khaw showed that increasing the rate of ulnar nerve stimulation from 0.1 Hz to 1 Hz results in an approximately 50% reduction in onset time of rocuronium (13). There is today a considerable body of evidence indicating that the onset of block is far more dependent on patient characteristics such as cardiac output, circulation time and muscle blood flow, than on properties of the muscle relaxants (1). Blood flow muscle is known to be affected by metabolic activity and can be markedly increased by evoked contractions due to nerve stimulation (7). Therefore, it is likely that the decrease in onset time observed with increasing stimulation rates is related to an increase in muscle blood flow resulting in a quicker delivery of drug to the stimulated muscle. Alternatively, it is also reasonable to speculate that the decrease in onset time according to the frequency of stimulation, as well as in case of prolonged stimulation, could result from a depletion of neurotransmitter at the motor end-plate (10). Indeed, if the number of acetylcholine molecules is decreased, the proportion or receptors which need to be occupied by the relaxant to inhibit neuromuscular transmission will be reached more rapidly. It has been previously shown that tetanic stimulation at 200-300 Hz in the presence of volatile anesthetics may provoke muscle fading without the use of muscle relaxants (14).

The "logit" transformation of single or twitch height values monitored as a function of time yielded a linear relationship in the three modes of stimulation. In these conditions, the slope of the linear relationship represents the speed of onset of the muscular block, and the intercept represents the time elapsed before a decrease in the twitch height was observed. Comparison of the slopes showed a significant difference between the three patient groups, indicating that the speed of onset was the most rapid for ST 1 and the lowest for ST0.1. These results may also be explained by the differences in drug delivery to the muscle and in reaching a critical concentration at the receptor site. Comparison of the intercepts indicated that the "lag time" was significantly longer for ST1 than for ST0.1 and TOF, but did not differ significantly between the last 2 groups. Although not explicitly mentioned, no significant difference in the lag time was reported by Curran *et al.*, when they compared single twitch and TOF stimulation, delivered every 12 s, on the onset of action of atracurium and suxamethonium (12). Neither, McCoy *et al.* did not find any difference in the lag time when studying the influence of the duration of control stimulation on the onset and recovery of neuromuscular block (10). The longer "lag time" in group I patients in the present study might be related to the high frequency of stimulation

© *Acta Anæsthesiologica Belgica*, 1997, 48, n° 1

and the release of acetylcholine in great amounts at the motor endplate before hydrolysis by acetylcholinesterase. Indeed, it is supposed that some of the released acetylcholine acts back on the prejunctional receptors of nerve endings to stimulate mobilisation of available transmitter and such a feedback control mechanism becomes more important as the frequency of nerve impulses increases (15).

Finally, the results of this study also showed a significance difference between groups regarding the intubating conditions. The higher proportion of clinically not acceptable intubating conditions in ST1 patients as compared with the 2 other groups is absolutely not surprising. The delay between end of rocuronium injection and tracheal intubation was 37.7 s on average in group I patients, 123 s in group II and 84.5 s in group III. The onset time of rocuronium measured in group I is artificially short when compared to that measured at the same muscle using more conventional patterns of stimulation. Using supramaximal stimuli of 0.2 ms duration delivered at the adductor pollicis either in a TOF sequence every 12 s, or in a single twitch mode at 0.1 Hz, it has been shown that clinically acceptable intubating conditions can be achieved 60 s following administration of a $2 \times ED_{95}$ of rocuronium (16, 17). In group I patients, a 90% block at the adductor pollicis is absolutely not indicative of relaxation of all muscles nor of adequate intubating conditions. In addition, the laryngeal adductors, which must be relaxed for intubation, are more resistant to the action of rocuronium than is the adductor pollicis (18, 19). Reviewing this problem, AGOSTON concluded recently that the onset time of neuromuscular block at the adductor pollicis should not be considered as a meaningful, quantifiable endpoint, defining optimal intubating conditions (20).

In conclusion, the onset time of rocuronium and the speed of onset of neuromuscular block at the adductor pollicis are affected by the pattern of nerve stimulation prior to drug administration ; both are more rapid when nerve stimulation is applied more frequently. Adductor pollicis monitoring using single twitch stimulation at 1 Hz frequency may not be used as a guide of muscle relaxation to perform tracheal intubation. Comparisons in onset times and intubating conditions should be considered only when the pattern of nerve stimulation used for assessing neuromuscular transmission is standardised and accurately defined.

References

1. Donati P., *Onset of action of relaxants*, CAN. J. ANAESTH., **35**, S52-S58.
2. Bevan J. C., Donati F., Bevan D. R. *Attempted acceleration of the onset of pancuronium. Effect of divided doses in infants and children*, BR. J. ANAESTH., **57**, 1205-1208, 1985.
3. Donati F., Bevan D. R., *The influence of patients's sex, age and weight on pancuronium onset time*, CAN. ANESTH. SOC. J., **33**, S86, 1986.
4. Chauvin M., Lebreault C., Duvaldestin P., *The neuromuscular blocking effect of vecuronium on the human diaphragm*, ANESTH. ANALG., **66**, 117-122, 1987.
5. Donati F., Meistelman C., Plaud B., *Vecuronium neuromuscular blockade at the adductor pollicis*, ANESTHESIOLOGY, **74**, 833-837, 1991.
6. Goat V. A., Yeung M. L., Blakeney C., Feldman S. A., *The effect of blood flow upon the activity of gallamine triethiodide*, BR. J. ANAESTH., **48**, 69-73, 1976.
7. Saxena P. F., Dhasmana K. M., Prakash O., *A comparison of systemic and regional hemodynamic effects of d- tubocurarine, pancuronium, and vecuronium*, ANESTHESIOLOGY, **59**, 102-108, 1983.
8. Donati F., *Effect of dose and potency*, ANAESTH. PHARMACOL. REV., **1**, 34-43, 1993.
9. Harper N. J. N., Martlew R., Strang T., Wallace M., *Monitoring neuromuscular block by acceleromyography : comparison of the Mini-accelograph with the Myograph 2000*, BR. J. ANAESTH., **72**, 411-414, 1994.
10. McCoy M. E., Mirakhur R. K., Connolly F. M., Loan P. B., *The influence of the duration of control stimulation on the onset and recovery of neuromuscular block*, ANESTH. ANALG., **80**, 364-367, 1995.
11. Curran M. J., Donati F., Bevan R., *Onset and recovery of atracurium and suxamethoniuminduced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation*, BR. J. ANAESTH., **59** : 989-994, 1987.

12. Hughes R., Payne J. P., *Clinical assessment of atracurium using the single twitch and tetanic responses of the adductor pollicis muscles*, BR. J. ANAESTH., **55**, 47S, 1983.
13. Feldman S. A., Khaw K., *The effect of dose and the rate of stimulation on the action of rocuronium*, EUR. J. ANAESTH., **12** (suppl. 1), 15-17, 1995.
14. Cohen P. J., Heisterkamp C. V., Skovsted P., *The effect of general anesthesia and regional hemodynamic effects of d-tubocarine, pancuronium and vecuronium*, ANESTHESIOLOGY, **59**, 102-104, 1983.
15. Bowman W. C., *Physiology and pharmacology of neuromuscular transmission, with special reference to the possible consequences of prolonged blockade*, INTENSIVE CARE MED., **19** (suppl. 2), S45-S53, 1993.
16. Pühringer F. K., Khuenl-Brady K. S., Koller J., *Mitterschiffthaler G. Evaluation of the endotracheal intubation conditions of rocuronium (ORG 9426) and succinylcholine in outpatient surgery*, ANESTH. ANALG., **75**, 37-40, 1992.
17. Magorian T., Flannery K. B., Miller R. D., *Comparison of rocuronium, succinylcholine and vecuronium for rapid- sequence induction of anesthesia in adult patients*, ANESTHESIOLOGY, **79**, 913-918, 1993.
18. Meistelman C., Plaud B., Donati F., *Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans*, CAN. J. ANAESTH., **39** : 665-669, 1992.
19. Wright P. M. C., Caldwell J. E., Miller R. D., *Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized human*, ANESTHESIOLOGY, **81**, 1110-1115, 1994.
20. Agoston S., *Onset time and evaluation of intubating conditions : rocuronium in perspective*, BR. J. ANAESTH., **12** (suppl. 11), 31-37, 1995.