Neuromuscular effects of vecuronium and neostigmine in Montreal and Paris

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The potency of vecuronium was reported to be greater in Montréal than in Paris. This study was designed to determine whether there were differences in onset, duration, and reversibility with neostigmine between both centres. Twenty ASA I or II adults (ten men, ten women), aged 18–65 yr were studied in each of the two cities, during a standard thiopentone-fentanyl-nitrous oxide (60–70%) – isoflurane 0.5% end-tidal anaesthetic. Train-of-four stimulation was applied every 20 sec to the ulnar nerve at the wrist and the force of contraction of the adductor pollicis muscle was measured. Vecuronium, 0.1 mg · kg⁻¹, was given as a bolus, and neostigmine, 0.04 mg · kg⁻¹, was administered, with atropine 0.02 mg · kg⁻¹, at 25% first twitch height recovery. Onset time to maximum blockade was (mean ± SD) 3.9 ± 1.3 min in Paris vs 4.5 ± 1.3 min in Montréal (NS). Duration from injection to 25% first twitch recovery was shorter (28.5 ± 6.8 min) in Paris than in Montréal (39.1 ± 7.3 min) (P < 0.0001). Time from injection of neostigmine to a train-of-four ratio of 70% was not different in Paris (6.3 ± 2.2 min) from Montréal (5.6 ± 1.9 min). It is concluded that the duration of an "intubating" dose of vecuronium is longer in Montréal, but, when given at 25% first twitch recovery, neostigmine has the same efficacy in Montréal as in Paris.

Le vécuronium est plus puissant à Montréal qu'à Paris. On a voulu déterminer si l'on retrouvait des différences de temps d'installation, de durée et de neutralisation avec la néostigmine

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS:
neostigmine;

MONITORING: neuromuscular duration, train-of-four;
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entre les deux endroits. Dans chaque ville, on a recruté vingt adultes (dix hommes et dix femmes), âgés de 18 à 65 ans, et anesthésiés au thiopentone, protoxyde d'azote (60–70%) et isoflurane (0.5% télé-expiratoire). On a stimulé le nerf cubital toutes les 20 sec en utilisant le train-de-quatre et on a mesuré la force de contraction de l'adducteur du pouce. Une dose de 0,1 mg · kg⁻¹ de vécuronium a été injectée, suivie de néostigmine, 0,04 mg · kg⁻¹ et d'atropine, 0,02 mg · kg⁻¹ lorsque le premier élément du train-de-quatre récupérait à 25% de sa valeur initiale. L'intervalle entre l'injection et le bloc maximum était de (moyenne ± ET) 3,9 ± 1,3 min à Paris et 4,5 ± 1,3 min à Montréal (NS). La durée d'action, c'est-à-dire le temps entre l'injection de vécuronium et la récupération de 25%, était plus courte à Paris (28,5 ± 6,8 min) qu'à Montréal (39,1 ± 7,3 min) (P < 0,0001). Après administration de néostigmine, il fallait 6,3 ± 2,2 min à Paris pour atteindre un rapport quatrième: première réponse de 70%, et 5,6 ± 1,9 min à Montréal (NS). On en conclut que la durée d'une dose « d'intubation » est plus longue à Montréal, mais que si la néostigmine est donnée quand la récupération atteint 25%, elle est tout aussi efficace à Montréal qu'à Paris.

In 1969, Katz *et al.*¹ reported that the maximum blockade attained after a single dose of d-tubocurarine or succinylcholine was greater and the duration of action was longer in New York than in London. The study was performed before dose-response techniques became common practice in the evaluation of muscle relaxants, and before a standard mode of stimulation, the train-of-four,² was introduced into clinical use and research.

Recently, Fiset *et al.*³ performed another transatlantic study, and compared the dose-response curves for vecuronium between Montréal and Paris. In spite of similar demographic data in both centres and an identical anaesthetic and neuromuscular technique, the Paris dose-response curve was shifted to the right by 30%, that is, vecuronium was more potent in Montréal. The difference could not be explained by differences in age, sex, weight or body habitus, because these variables were similar in both cities. Disposition of the drug probably had little effect on these differences, because dose-response data are

obtained from twitch depression obtained shortly after drug administration. Thus, it is possible that the transatlantic differences might be due to a different relationship between plasma concentration and twitch height, i.e., a pharmacodynamic difference.

These data do not necessarily imply that onset is longer and duration is shorter in Paris than in Montréal, because pharmacokinetic differences could be present. It is also unclear whether differences in sensitivity extend beyond the dose range (0.02 – 0.04 $\text{mg} \cdot \text{kg}^{-1}$) used for dose-response data, and also apply to intubating doses (0.1 – 0.15 $\text{mg} \cdot \text{kg}^{-1}$). In addition, differences in sensitivity to vecuronium could also imply differences in the response to neostigmine. Therefore, this study was designed to examine the neuromuscular effects of clinically useful doses of vecuronium and neostigmine under identical anaesthetic conditions in Montréal and in Paris.

Methods

The protocol was approved by the Ethics Committee at the Royal Victoria Hospital in Montréal, and at Institut Gustave Roussy in Villejuif, located in the suburbs of Paris, France. At each centre, an equal number of men and women, ASA status I or II, aged 18–65 yr, and scheduled for elective surgery requiring tracheal intubation, were entered in the study. There was a total of 40 patients, 20 from each location. Exclusion criteria were ASA status III or greater, emergency surgery, anticipated difficulty with the airway, deviation from ideal body weight by more than 30%, renal, hepatic or neuromuscular disease, and acute or chronic ingestion of drugs for which an interaction with neuromuscular function is known or suspected. Premedication, when given, consisted of an opioid or a benzodiazepine, and was at the discretion of the anaesthetist.

In the operating theatre, standard monitoring equipment was used and consisted of ECG, pulse oximetry, non-invasive arterial blood pressure measurement, end-tidal PCO_2 , inspired oxygen fraction and end-tidal vapour pressure. Surface electrodes were applied to the ulnar nerve at the wrist and the force of contraction of the adductor pollicis muscle was measured with a Grass FT-10 transducer (Grass Instruments, Quincy, Mass, USA) in Montréal and a Bioindustry Curamètre transducer (Bioindustry, Boulogne-sur-Mer, France) in Paris. Anaesthesia was induced with thiopentone, 5 – 7 $\text{mg} \cdot \text{kg}^{-1}$, and fentanyl, 1 – 2 $\mu\text{g} \cdot \text{kg}^{-1}$, *iv*. Then, the lungs were ventilated manually with 100% oxygen. Supra-maximal train-of-four stimulation was applied after loss of consciousness, using a Datex NMT-221 (Datex, Helsinki, Finland) in Montréal, and a Bioindustry Curamètre in Paris, after the calibration of the stimulators was made. Within two minutes after calibration was obtained, vecuronium, 0.1

$\text{mg} \cdot \text{kg}^{-1}$ was injected *iv* as a rapid bolus. Tracheal intubation was performed when maximum blockade was obtained. Then, mechanical ventilation was initiated, and adjusted to keep end-tidal PCO_2 in the range 30–35 mmHg.

Anaesthesia was maintained with nitrous oxide (60–70%), isoflurane, 0.5% end-tidal concentration, and fentanyl, 1 – 2 $\mu\text{g} \cdot \text{kg}^{-1}$ as required. No incremental doses of vecuronium were administered. When first twitch height (T_1) in the train-of-four reached 25% of pre-vecuronium control, neostigmine, 0.04 $\text{mg} \cdot \text{kg}^{-1}$, with atropine, 0.02 $\text{mg} \cdot \text{kg}^{-1}$ was injected *iv*. Neuromuscular blockade was monitored for an additional ten minutes, during which time the end-tidal nitrous oxide and isoflurane concentrations were maintained constant.

Times from vecuronium injection to 50%, 95% and maximum T_1 blockade were recorded. Times to 50% and 95% were interpolated if necessary. Maximum blockade was considered to occur at the first of three consecutive equal T_1 responses. With 100% blockade, maximum blockade was considered to take place at the first undetectable train-of-four response. Maximum blockade, duration from injection to 5% and 25% T_1 recovery, and duration from 5% to 25% were measured. The train-of-four ratio (T_4/T_1) was measured at 0, 2, 5 and 10 min after neostigmine administration. In addition, the time from injection of neostigmine to $T_4/T_1 = 70\%$ was noted. All measurements were recorded at each site and the tracings were subsequently reviewed by a single investigator (FD). Results are presented as mean $\pm$ standard deviation (SD) and range as indices of dispersion. A Student's *t* test was applied to comparisons between the two sites and differences associated with a *P* value < 0.05 were considered to be significantly different.

Results

Demographic data are presented in Table I. There were no differences in sex distribution, height and weight between both centres.

Onset times to 50%, 95% or maximum blockade were not different between both cities (Table II). Maximum blockade was 100% in all Montréal patients, and in 18 (95%) patients in Paris. The remaining two patients had blockades of 98 and 99%, respectively.

Times to 5% and 25% T_1 recovery were respectively 10.8 and 10.6 min longer in Montréal ($P < 0.0001$), but the recovery rate (5–25% T_1) was the same at both sites (Table III).

The train-of-four ratios before, and 2, 5 and 10 min after neostigmine administration were similar in both cities. Mean time from injection of neostigmine to $T_4/T_1 = 70\%$ was approximately six minutes in both centres (Table IV).

TABLE I Demographic data (mean $\pm$ SD)

	Montréal	Paris
Sex (M/F)	10/10	10/10
Age (yr)	39 $\pm$ 12	45 $\pm$ 13
Weight (kg)	69 $\pm$ 13	64 $\pm$ 12
Height (cm)	167 $\pm$ 2	165 $\pm$ 2

TABLE II Onset data (mean $\pm$ SD)

Time from injection to ... (min)	Montréal	Paris
50% T ₁ block	1.94 $\pm$ 0.53	1.61 $\pm$ 0.60
95% T ₁ block	3.39 $\pm$ 0.67	3.10 $\pm$ 0.73
100% T ₁ block	4.47 $\pm$ 1.28	3.93 $\pm$ 1.29

TABLE III Duration of effect (mean $\pm$ SD) (range)

Duration to	Montréal	Paris
5% recovery (min)	31.6 $\pm$ 7.0 (21.6–44.9)	20.8 $\pm$ 6.5 (6.2–31.5)
25% recovery (min)	39.1 $\pm$ 7.3 (27.6–58.9)	28.5 $\pm$ 6.8 (12.5–40.5)
Duration from 5–25% (min)	7.5 $\pm$ 1.4 (4.5–14)	7.7 $\pm$ 1.1 (4.7–11.3)

TABLE IV Effect of neostigmine (mean $\pm$ SD)

T ₄ /T ₁ following neostigmine	Montréal	Paris
after 0 min (%)	4 $\pm$ 4 (0–21)	6 $\pm$ 3 (0–11)
2 min (%)	41 $\pm$ 11 (11–55)	40 $\pm$ 9 (19–59)
5 min (%)	69 $\pm$ 7 (55–82)	68 $\pm$ 7 (49–77)
10 min (%)	81 $\pm$ 7 (70–91)	82 $\pm$ 6 (64–91)
Time to T ₄ /T ₁ = 70% (min)	5.6 $\pm$ 1.9 (3.7–10)	6.3 $\pm$ 2.2 (4–12)

Discussion

This study shows that the duration of action of vecuronium is longer in Montréal than in Paris. However, when neostigmine was given at the same level of recovery, its effect was the same at both sites. Onset data were more variable than duration measurements, and this probably explains the lack of differences in onset times. The coefficient of variation (standard deviation as a percentage of mean values) was 30–33% for time to maximum blockade and 18–24% for duration.

The anaesthetic technique and neuromuscular monitoring were the same for both centres, and they were intended to mimic clinical conditions. Vecuronium was

given shortly after induction, and the dose chosen, 0.1 mg $\cdot$ kg⁻¹, is administered commonly for tracheal intubation and for maintenance of relaxation during the first 30–45 min of surgery. The shorter duration observed in Paris suggests that the relative resistance recorded earlier with dose-response curves using doses in the range 0.02–0.04 mg $\cdot$ kg⁻¹ also applies to larger doses more commonly used in clinical practice.

Care was taken to control for the various factors which might influence the onset time or duration of neuromuscular blockade. The mode of stimulation and interval between train-of-four patterns was the same. The time between the start of stimulation and injection of the neuromuscular blocker can influence onset time, and to a lesser extent, duration of action.⁴ To avoid this confounding factor, vecuronium was injected shortly (approximately two minutes) after the start of stimulation. The anaesthetic agents were the same in both centres. End-tidal isoflurane concentration (0.5%) was measured and kept constant until at least ten minutes after neostigmine administration. The same muscle, the adductor pollicis, was monitored in both locations, and force of contraction was measured in both instances. Both force transducers had a linear response with an accuracy of approximately $\pm$ 2%. This possible error might be sufficient to affect measurement of time to 100% blockade, because blockade changes slowly when it approaches 100%.^{5,6} For this reason, onset times to 50% and 95% are probably more reliable. These two measures of onset time were not different between both centres. Duration data are even less likely to be affected by a measurement error. When the T₁ of Paris patients had recovered to 25% of control (at a mean time of 28.5 min), subjects studied in Montréal had reached less than 5% (which was attained at 31.6 min). Such a discrepancy cannot be attributed to the inaccuracy of measuring devices.

No attempt was made to keep core, muscle or skin temperature at any pre-determined level, thus mimicking clinical conditions. Core temperature was not measured systematically in all patients, and was found to be 30–45 min after induction of anaesthesia, 35.5–36.5°C in both centres. Thus, although mild core hypothermia (34–35°C) might prolong the duration of action of vecuronium,⁷ it is unlikely to have been a factor in the present study. Such levels of hypothermia were obtained only after 45–60 min of active cooling.⁷

It is unlikely that the transatlantic differences reported here are due to differences in the rate of distribution or elimination of vecuronium. Dose-response relationships depend on the initial concentration of the drug, and are relatively independent of disposition processes, unless these are very rapid. A previous study³ performed in the same hospitals showed a different dose-response

curve. In addition, the rate of recovery from 5 to 25% T_1 , which reflects the rate of redistribution metabolism and/or elimination of the drug, was the same at both centres, suggesting that altered elimination and/or redistribution are not responsible for the differences in duration. A 30% difference in the dose-response relationships³ and a 10.6 min in duration (this study) could be both explained by a difference in the plasma concentration vs effect relationship. Pharmacokinetic studies conducted on both sides of the Atlantic Ocean^{8,12} indicate that plasma concentrations decrease by approximately 30% between 28.5 and 39.1 min, i.e., the times corresponding to return of 25% T_1 in Paris and Montréal respectively. Thus, both the increased duration and increased potency observed in Montréal could be explained by a concentration response relationship shifted to the left. It remains to be seen whether these differences are due to the changes in protein binding, or to true differences in sensitivity at the neuromuscular junction. Such a study would require simultaneous measurement of vecuronium concentrations, both total and free, and twitch height. Given the inter-patient variability, such a pharmacokinetic-pharmacodynamic study would require a large number of patients.

The duration of action of vecuronium is affected by many factors, such as age,¹² weight,^{13,14} pregnancy^{15,16} and end-organ function.^{9,10} The patients in our study had normal renal and hepatic function, were non-pregnant and had comparable heights and weights. The Montréal subjects were six years younger than the Paris patients. If anything, this should have produced a shorter duration in Montréal. The opposite was observed. The presence of a small end-tidal concentration of isoflurane probably had little effect, because the volatile agent did not have time to equilibrate with muscle tissue.¹⁷ A survey of the literature suggests that the duration of action of vecuronium, $0.1 \text{ mg} \cdot \text{kg}^{-1}$, might be more variable with geographical location than the differences between Paris and Montréal might indicate. In non-pregnant, ASA I or II young to middle-aged adults, the duration to 25% T_1 recovery was reported to be 26–30 min in Holland,¹⁷ 32 min in Austria,¹⁶ and 27.6 min in Norway,¹⁸ close to the value of 28.5 min reported here for Paris. Durations for the same vecuronium dose given to young adults in North America are somewhat more variable, ranging from 32–37.6 min in New York^{12–14} to 50–54 min in California^{9,10} (interestingly, 34 min was reported from the same institution,⁷ but from a limited number of subjects). Values of 35.3¹⁵ and approximately 40 min¹⁹ were reported in Texas and North Carolina, respectively. These values are close to the 39.1 min observed in Montréal. The absence of overlap between European and North American values suggests a different potency between

each continent. However, we do not suggest that the potency is uniform within each continent.

No difference in onset time could be demonstrated in this study. This is probably because onset times are more variable than durations and because increasing the dose does not change onset time markedly. For example, in one study,¹⁸ increasing the dose by 50%, from $0.1 \text{ mg} \cdot \text{kg}^{-1}$ to $0.15 \text{ mg} \cdot \text{kg}^{-1}$ decreased onset time from 169 to 146 sec, and the difference was not statistically significant. In Montréal, the potency of vecuronium was found to be 30% greater than in Paris, suggesting that the effect of the drug might mimic, in Montréal, that of a dose increased by 30% in Paris. This small increase in equivalent dose would be expected to produce little change in onset times.

There are few studies of the effect of neostigmine, $0.04 \text{ mg} \cdot \text{kg}^{-1}$, given at 25% first twitch height recovery after vecuronium. The values of train-of-four ratio reported here for five and ten minutes (68–69% and 81–82% respectively) compare well with the 82 and 84% reported by a Belgian group²⁰ at six and nine minutes respectively under nitrous oxide-narcotic anaesthesia. Addition of 1 MAC isoflurane was found to decrease the T_4/T_1 values by 10–15%.²¹ In the present study, approximately 0.4 MAC isoflurane was used, and the results are between those obtained with nitrous oxide-narcotic and nitrous oxide-isoflurane anaesthesia.²¹ The effect of neostigmine given at the same twitch height recovery was the same in Montréal and in Paris. This suggests that acetylcholinesterase function and the other mechanisms responsible for reversal of neuromuscular blockade operate similarly at both sites.

In summary, after an intubating dose of vecuronium, Montréal patients behave as if they were more sensitive to the drug than subjects with comparable demographic characteristics in Paris and duration of action is increased. Slight alterations in dosage and management of relaxation might be required. For example, all Paris patients recovered to 25% T_1 within 45 min while this level of recovery was not attained in 25% of Montréal patients. There is, however, no need to modify the dose of neostigmine depending on the site, provided the anticholinesterase drug is administered at 25% recovery.

References

- 1 Katz RL, Norman J, Seed RF, Conrad L. A comparison of the effects of suxamethonium and tubocurarine in patients in London and New York. *Br J Anaesth* 1969; 41: 1041–7.
- 2 Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block (Part I). *Br J Anaesth* 1971; 43: 473–7.
- 3 Fiset P, Donati F, Balendran P, Meistelman C, Lira E,

- Bevan DR.* Vecuronium is more potent in Montreal than in Paris. *Can J Anaesth* 1991; 38: 717-21.
- 4 *Curran MJ, Donati F, Bevan DR.* Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. *Br J Anaesth* 1987; 59: 989-94.
 - 5 *Donati F.* Effect of dose and potency on onset. *Anaesthetic Pharmacology Review* 1993; 1: 34-43.
 - 6 *Koscielniak-Nielsen ZJ, Bevan JC, Popovic V, Baxter MRN, Donati F, Bevan DR.* Onset of maximum neuromuscular block following succinylcholine or vecuronium in four age groups. *Anesthesiology* 1993; 79: 229-34.
 - 7 *Heier T, Caldwell JE, Sessler DI, Miller RD.* Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology* 1991; 74: 815-9.
 - 8 *Sohn YJ, Bencini AF, Scaf AHJ, Kersten UW, Agoston S.* Comparative pharmacokinetics and dynamics of vecuronium and pancuronium in anesthetized patients. *Anesth Analg* 1986; 65: 233-9.
 - 9 *Arden JR, Lynam DP, Castagnoli KP, Canfell PC, Cannon JC, Miller RD.* Vecuronium in alcoholic liver disease: a pharmacokinetic and pharmacodynamic analysis. *Anesthesiology* 1988; 68: 771-6.
 - 10 *Lynam DP, Cronnelly R, Castagnoli KP, et al.* The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. *Anesthesiology* 1988; 69: 227-31.
 - 11 *Ducharme J, Varin F, Bevan DR, Donati F.* Importance of early blood sampling on vecuronium pharmacokinetic and pharmacodynamic parameters. *Clin Pharmacokinet* 1993; 24: 507-18.
 - 12 *Lien CA, Matteo RS, Ornstein E, Schwartz AE, Diaz J.* Distribution, elimination, and action of vecuronium in the elderly. *Anesth Analg* 1991; 73: 39-42.
 - 13 *Weinstein JA, Matteo RS, Ornstein E, Schwartz AE, Goldstoft M, Thal G.* Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg* 1988; 67: 1149-53.
 - 14 *Schwartz AE, Matteo RS, Ornstein E, Halevy JD, Diaz J.* Pharmacokinetics and pharmacodynamics of vecuronium in the obese surgical patient. *Anesth Analg* 1992; 74: 515-8.
 - 15 *Camp CE, Tessem J, Adenwala J, Joyce TH III.* Vecuronium and prolonged neuromuscular blockade in postpartum patients. *Anesthesiology* 1987; 67: 1006-8.
 - 16 *Khuentl-Brady KS, Koller J, Mair P, Pühringer F, Mitterschiffhaller G.* Comparison of vecuronium- and atracurium-induced neuromuscular blockade in postpartum and nonpregnant patients. *Anesth Analg* 1991; 72: 110-3.
 - 17 *Swen J, Rashkovsky OM, Ket JM, Koot HWJ, Hermans J, Agoston S.* Interaction between nondepolarizing neuromuscular blocking agents and inhalational anesthetics. *Anesth Analg* 1989; 69: 752-5.
 - 18 *Rørvik K, Husby P, Gramstad L, Vamnes JS, Bütsch-Larsen L, Koller M-E.* Comparison of large dose of vecuronium with pancuronium for prolonged neuromuscular blockade. *Br J Anaesth* 1988; 61: 180-5.
 - 19 *Ginsberg B, Glass PS, Quill T, Shafron D, Ossey KD.* Onset and duration of neuromuscular blockade following high-dose vecuronium administration. *Anesthesiology* 1989; 71: 201-5.
 - 20 *Baurain MJ, Dernovoi BS, d'Hollander AA, Barvais L.* The influence of atropine dose on recovery from vecuronium-induced neuromuscular blockade. *Anesthesiology* 1992; 77: 17-20.
 - 21 *Baurain MJ, d'Hollander AA, Melot C, Dernovoi BS, Barvais L.* Effects of residual concentrations of isoflurane on the reversal of vecuronium-induced neuromuscular blockade. *Anesthesiology* 1991; 74: 474-8.