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Vecuronium is more potent in Montreal than in Paris

This study was undertaken to compare the potency of vecuronium in patients anaesthetized in Montreal or Paris. Anaesthesia was induced with thiopentone and maintained with N₂O, and intermittent boluses of thiopentone and fentanyl in 18 patients in Paris and 19 in Montreal. Neuromuscular blockade was measured using train-of-four stimulation of the ulnar nerve. The force of contraction of the adductor pollicis muscle was measured. Single doses of vecuronium, 20, 30, or 40 µg · kg⁻¹ were given by random allocation. Dose response curves were constructed by obtaining the linear regression of the logit of the first response (T1) neuromuscular blockade versus log dose. The patients in Paris required 27% more vecuronium (95% confidence limits 5–53%; $P = 0.01$) for the same intensity of blockade. In Montreal, the ED₅₀ and ED₉₀ ($\pm$ SEE for the mean) values were 26.0 ± 1.4 and 44.2 ± 2.5 µg · kg⁻¹ compared with 33.0 ± 3.3 and 71.9 ± 7.2 µg · kg⁻¹ in Paris respectively. The patients were comparable with respect to age, sex, height and weight. These results confirm, for vecuronium, the transatlantic difference in potency of neuromuscular blocking drugs which was previously observed with d-tubocurarine between London and New York.

Le but de cette étude était de comparer la puissance du vécuronium chez 19 sujets anesthésiés à Montréal et 18 sujets à Paris. Le thiopental a été utilisé pour induction de l'anesthésie, et l'entretien s'est effectué à l'aide de N₂O, en plus de doses intermittentes de thiopental et de fentanyl. On a mesuré la force de contraction de l'adducteur du pouce suite à des stimulations du nerf cubital en mode train-de-quatre. On a administré des doses uniques de 20, 30 ou 40 µg · kg⁻¹ de vécuronium, choisies au hasard. On a calculé des courbes de dose-action par

Key words

MONITORING: neuromuscular function;
NEUROMUSCULAR RELAXANTS: vecuronium.

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régression linéaire du logit du bloc du premier élément du train-de-quatre (T1) versus le logarithme de la dose. Les sujets anesthésiés à Paris ont eu besoin de 27% de plus de vécuronium pour le même bloc neuromusculaire (limites de confiance à 95% : 5–53% ; $P = 0.01$). A Montréal, les DA₅₀ et DA₉₅ s'établissaient à ($\pm$ SEE pour la moyenne) $26,0 \pm 1,4$ et $44,2 \pm 2,5$ µg · kg⁻¹, respectivement. A Paris, ces valeurs étaient de $33,0 \pm 3,3$ et $71,9 \pm 7,2$ µg · kg⁻¹, respectivement. Les groupes étaient sensiblement de même âge, sexe, poids et taille. Ces résultats confirment, pour le vécuronium, l'existence d'une différence de puissance de part et d'autre de l'Atlantique, semblable à celle qui avait été décrite pour la d-tubocurarine à Londres et à New-York.

Many factors influence the potency of neuromuscular blocking drugs. These include age,¹ disease states,^{2–4} and interaction with several drugs.^{5–8} In 1969, Katz *et al.* made the intriguing observation that there were transatlantic differences in sensitivity to muscle relaxants.⁹ They observed that, after administration of d-tubocurarine, 0.1 mg · kg⁻¹, to patients anaesthetized with nitrous oxide and halothane, the mean block of the adductor pollicis muscle in British patients in London was (mean $\pm$ SD) $43 \pm 21\%$ compared with $75 \pm 14\%$ in Americans anaesthetized in New York. In addition, the duration of the block (time to 90% recovery) was reduced from 31.2 ± 12.4 min in New York to 14.6 ± 8.8 min in London.

The duration of action of succinylcholine, 1 mg · kg⁻¹, was also reduced from 14.6 ± 3.6 min in New York to 9.1 ± 2.9 min in London. This transatlantic difference has never been confirmed with the same drugs, or with different neuromuscular blocking agents, or between different cities. Since dosage recommendations are based on potency data, it appears useful to determine whether there are geographical differences in the effect of relaxants used commonly in clinical practice. The present study was undertaken to compare the potency of vecuronium in patients anaesthetized in Montreal or Paris, using identical anaesthetic and neuromuscular monitoring techniques.

Methods

After approval by the hospitals' Ethics Committees, 19

patients were studied in Montreal and 18 in Villejuif, a suburb of Paris. All were ASA physical status I or II and were undergoing a variety of elective surgical procedures. Patients with hepatic, renal or neuromuscular diseases were excluded, as were those with malnutrition, electrolyte abnormalities, and those taking any medication known or suspected of interfering with neuromuscular function. Also excluded were patients who deviated from their ideal body weight by more than 20% and those with excessive alcohol intake. At each centre, patients were randomized to receive one of three doses of vecuronium in a dose range expected to produce only 20–90% neuromuscular block. An equal number of men and women received each dose. This investigation took place simultaneously in both centres involved, between September and December, 1989.

On arrival in the operating room, the patients' ECG, blood pressure, and oxygen saturation were monitored. Anaesthesia was induced with thiopentone, 5–10 mg·kg⁻¹, and fentanyl, 1–3 µg·kg⁻¹, and the lungs were ventilated manually with nitrous oxide, 70%, in oxygen. Anaesthesia was maintained with N₂O and intermittent boluses of thiopentone and fentanyl.

The ulnar nerve was stimulated supramaximally at the wrist via surface electrodes at a frequency of 2 Hz for 2 sec, and repeated every 20 sec. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis was measured with a force displacement transducer (Grass FT10 in Montreal, Bioindustry Curamètre in Paris) and recorded on paper. Stimulation commenced four minutes after induction of anaesthesia and a baseline recording was established. One minute after the start of the stimulation, that is, five minutes after induction of anaesthesia, vecuronium (Norcuron®; Organon) (20, 30 or 40 µg·kg⁻¹) was injected by random allocation. The recording was continued until the response to the first stimulus in the train, T1, was stable for three consecutive trains. At the end of the recording, additional vecuronium was administered to facilitate tracheal intubation.

Dose response curves were constructed from the logit transformation of T1 depression versus the log of the dose of vecuronium, expressed in mg·kg⁻¹ actual body weight, at each location. The slopes of the curves were compared for parallelism and the groups of data were compared by analysis of covariance. The same analysis was made for logit transformation of T1 depression against log dose, in mg per kg ideal body weight, which was defined as the weight which made the body mass index (BMI) equal 22.5. The BMI is the weight in kg, divided by the square of the height in meters.¹⁰ A *P* value of <0.05 was considered to indicate a statistically significant difference. The results are expressed as mean

TABLE I Demographic data (mean ± SEM when applicable)

	Montreal	Paris
Number	19	18
Sex (M/F)	9/10	9/9
Age (yr)	44 ± 3	51 ± 3
Weight (kg)	65 ± 3	66 ± 2
Height (cm)	167 ± 3	168 ± 2

TABLE II Potency of vecuronium (mean ± standard error of estimate for the mean)

	Montreal	Paris
<i>Based on actual body weight:</i>		
ED ₅₀ (µg·kg ⁻¹)	26.0 ± 1.4	33.0 ± 3.3
ED ₉₅ (µg·kg ⁻¹)	44.2 ± 2.5	71.9 ± 7.2
<i>Based on ideal body weight:</i>		
ED ₅₀ (µg·kg ⁻¹)	26.1 ± 1.6	36.5 ± 2.5
ED ₉₅ (µg·kg ⁻¹)	48.2 ± 2.9	77.9 ± 5.4

values ± SEM, except for the ED₅₀ and ED₉₅ estimates, which are presented as mean values ± standard error of estimate for the mean.

Results

The demographic data are given in Table I. The patients in Paris were slightly older than those in Montreal, but the difference was not statistically different. There were no differences between the two groups regarding sex, weight or height. Both groups received comparable doses of thiopentone: 7.3 ± 0.8 mg·kg⁻¹ in Montreal, versus 6.8 ± 0.9 mg·kg⁻¹ in Paris (NS).

Dose response curves are shown in Figure 1. The slopes of the regression lines did not differ significantly from parallelism. The dose response relationship of the Paris patients was shifted to the right by 27% (95% confidence limits: 5–53%; *P* = 0.01) with respect to the Montreal patients. Estimates of ED₅₀ and ED₉₅ are presented in Table II. The time to maximum blockade was independent of dose and was comparable in both groups; i.e., 6.7 ± 0.3 min in Montreal, and 6.3 ± 0.3 min in Paris.

When the dose was expressed per kg ideal body weight, the difference between the groups was 41% (95% confidence limits 18–81%; *P* = 0.001) (Figure 2). Estimates of ED₅₀ and ED₉₅ based on ideal body weight are shown in Table II.

Discussion

The results demonstrated that patients in Paris required approximately 30% more vecuronium than patients in Montreal to achieve the same degree of neuromuscular

FIGURE 1 First twitch depression (logit scale) versus dose of vecuronium, in $\text{mg} \cdot \text{kg}^{-1}$ (log scale) for Montreal (solid line and filled circles) and Paris (dashed line and open circles) patients. Lines represent regression lines.

block. This difference cannot be attributed to a different anaesthetic technique, or to a different dose of induction agent. The results are qualitatively similar to the differences found previously by Katz *et al.*⁹ between New York and London for succinylcholine and d-tubocurarine, despite differences in anaesthetic and monitoring techniques between the two studies.

In the present study, agents which might modify the effects of vecuronium, such as succinylcholine,^{11,12} and anaesthetic vapours⁵ were avoided. Katz *et al.* used halothane in an inspired concentration of 0.75–1.5%.⁹ This would tend to potentiate d-tubocurarine and, in particular, prolong its duration of action because of the time taken for halothane to equilibrate in muscle.¹³ The net effect would be accentuated differences in duration of neuromuscular block. The d-tubocurarine was preceded by succinylcholine in half the patients studied by Katz *et al.* They observed that the magnitude and duration of the block produced by d-tubocurarine were increased in these patients. Overall, the administration of succinylcholine

FIGURE 2 First twitch depression (logit scale) versus dose of vecuronium, in $\text{mg} \cdot \text{kg}^{-1}$ ideal body weight (log scale) for Montreal (solid line and filled circles) and Paris (dashed line and open circles) patients. Lines represent regression lines.

may have contributed to their variation in the response to d-tubocurarine. Succinylcholine was avoided in the present study.

Neuromuscular monitoring was performed using a standard methodology – train-of-four stimulation of the ulnar nerve at <0.1 Hz and measurement of the force of thumb adduction. Katz *et al.* used single pulse stimulation of the ulnar nerve at 0.25–0.3 Hz. Increasing the frequency above 0.1 Hz prevents full recovery of the neuromuscular junction between stimuli and, thus, exaggerates the apparent action of the neuromuscular blocking drug.¹⁴ Furthermore, onset of action of relaxants depends not only on the type of stimulation, but also on the duration of stimulation before injection of the relaxant.¹⁵ For this reason, the type of stimulation (train-of-four), the interval between trains (20 sec) and the time when the stimulation was started (5 min after induction and 1 min before injection of vecuronium) were standardized.

In the previous transatlantic study,⁹ maximum blockade and duration of a bolus dose were compared. In the present study, dose response relationships were obtained.

TABLE III Potency estimates (ED_{50} in $\mu\text{g} \cdot \text{kg}^{-1}$) for vecuronium found in literature

<i>Halothane N₂O or narcotic N₂O anaesthetic only</i>				
<i>Europe</i>		<i>North America</i>		
<i>Location</i>	<i>ED₅₀</i>	<i>Location</i>	<i>ED₅₀</i>	
Adults:				
UK ¹⁶	23.1	California ¹⁷	15.0	
Denmark ¹⁸	28.0	California ¹⁹	15.0	
Denmark ¹⁸	25.7	California ¹⁹	16.9	
Denmark ²¹	30.5	Illinois ²²	20.4	
France*	33.0	New York ⁷	28.0	
		Quebec ²³	31.0	
		Quebec ²⁴	23.0	
		Quebec*	26.0	
Adolescents:	Finland ²⁵	33.0	Massachusetts ²⁶	23.0
Children:	France ²⁷	31.0	Massachusetts ²⁶	33.0
	Finland ²⁵	45.0		
Mean (range):	31.2 (23.1–45.0)		23.1 (15.0–33.0)	

*This study.

This allows the determination of equipotent doses; i.e., those producing the same effect in both centres. For example, the present study suggests that $30 \mu\text{g} \cdot \text{kg}^{-1}$ in Montreal is equipotent with $42 \mu\text{g} \cdot \text{kg}^{-1}$ in Paris. The drug was provided by the same company (Organon) in both places, and a systematic discrepancy of this magnitude in manufacturing and packaging appears unlikely. Thus, the difference obtained between Montreal and Paris patients might be due either to different pharmacokinetics, or to different concentration-effect relationships. A kinetic-dynamic study could answer the question, but the number of subjects required would be high, considering the within-group variability.

Potency estimates for vecuronium reported in the literature vary by a factor greater than two (Table III), and North American researchers tend to report lower ED_{50} 's than European investigators. The present study suggests that geographical differences are important and might explain at least part of the discrepancies. Some drugs have been found to be metabolized differently in different ethnic groups,^{28–31} within a given population.³¹ However, metabolism cannot explain differences in the peak effect of a drug, as is the case here. Furthermore, the patient population in Montreal had various ethnic origins (Table IV). Paradoxically, half of the patients studied in Montreal were born in Europe. This suggests that the relative sensitivity of Montreal patients to vecuronium is acquired. This is corroborated by the fact that American citizens living in London for one or two years demonstrated a sensitivity to d-tubocurarine intermediate between

TABLE IV Ethnic backgrounds

<i>Montreal</i>		<i>Paris</i>	
European	9	French	14
		Italian	3
Quebec (French)	4		
Quebec (English)	3		
North African	1	North African	1
Indian	1		
Middle East	1		

native London and New York patients.⁹ In the Montreal study, six of the nine patients of European origin had been living in North America for more than ten years.

The differences reported in the present study cannot be attributed to differences in sex ratio, age, height or weight. The seven year age difference between both groups is too small to account for a 30–40% difference in potency. Height and weight were similar in both groups, suggesting that the relative sensitivity of North American patients was not related to a different body habitus. Furthermore, the difference between centres persists if the dose is expressed as $\text{mg} \cdot \text{kg}^{-1}$ ideal body weight.

Clinically, the 30–40% difference reported in the present study is much smaller than the inter-individual variability likely to be observed in a given population.³² However, the populations studied in Montreal and Paris do not necessarily lie at opposite ends of the potency spectrum. A survey of the literature (Table III) suggests that larger differences might be found. Thus, it is important to base potency estimates of neuromuscular relaxants on data obtained from different geographical areas. These data might lead to slightly different dosage recommendations in different countries.

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