BMC Anesthesiology

Research article

Effect of mivacurium 200 and 250 μg/kg in infants during isoflurane anesthesia: a randomized controlled trial [ISRCTN07742712]

Alejandro A Nava-Ocampo*[1,2], Ferel T Aguirre-Garay[3], Elvia Y Velázquez-Armenta[4] and Diana Moyao-García[2]

Address: [1]Unit of Medical Research in Pharmacology, Hospital de Especialidades, Centro Médico Nacional "Siglo XXI", Instituto Mexicano del Seguro Social, Mexico City, Mexico, [2]Department of Anesthesia and Respiratory Therapy, Hospital Infantil de México "Federico Gómez", Mexico City, Mexico, [3]Hospital de Gineco-Pediatría No. 48, IMSS, León, Guanajuato, Mexico and [4]Department of Clinical Pharmacology, Hospital Infantil de México "Federico Gómez", Mexico City, Mexico

E-mail: Alejandro A Nava-Ocampo* - navaocampo_aa@yahoo.com; Ferel T Aguirre-Garay - ferto@LatinMail.com; Elvia Y Velázquez-Armenta - velazquezyadira@yahoo.com; Diana Moyao-García - dianitamg@yahoo.com

*Corresponding author

Abstract

Background: Infants usually respond differently to a neuromuscular relaxant compared to children or adults. Isoflurane is commonly used as an anesthetic gas in infants. In an RCT design, we investigated whether a dose of mivacurium 250 μg/kg results in faster onset of action than 200 μg/kg in infants under isoflurane anesthesia. Spontaneous recovery times and cardiovascular response were also evaluated.

Methods: Twenty-four low surgical risk children, aged 6–24 months, undergoing an elective surgery and requiring tracheal intubation were selected. After anesthetic induction, patients randomly received an iv bolus dose of mivacurium 200 or 250 μg/kg. After maximal relaxation, the patient was intubated. Isoflurane was administered to maintain anesthetic level during the surgical procedure. Neuromuscular function was monitored by accelerometry (TOF-Guard) at the adductor pollicies. The first twitch (T) of the TOF and the T4/T1 were measured. The time-course of heart rate and systolic and diastolic blood pressure were analysed by transforming them into their respective areas under the curve.

Results: Mivacurium 250 μg/kg produced a maximal T block faster than 200 μg/kg, i.e. 2.4 ± 1.1 *vs.* 3.5 ± 1.4 min (p < 0.05). Spontaneous recovery times were similar in both groups. Heart rate was similar between doses while systolic and diastolic blood pressures were lower with the higher dose (p < 0.05). Flushing was observed in two cases, one in each group.

Conclusions: The maximal effect of mivacurium 250 μg/kg, in infants under isoflurane anesthesia, was present one minute faster than 200 μg/kg. However, it produced a significant cardiovascular response.

Background

Mivacurium is a short acting benzylisoquinoline non-de-

polarizing neuromuscular blocking agent, with a demonstrated safety and efficacy both in children and adults [1–

3]. It has been in clinical use for a long time and the clinical pharmacology has been widely documented.

In children, administration of isoflurane previous to and during the effect of vecuronium or mivacurium increases their spontaneous recovery times in a time-dependent manner [4,5]. However, these times are not modified if the anesthetic gas is administered after the peak effect of the neuromuscular relaxant is produced [6].

Furthermore, despite infants usually respond differently to the effects of a neuromuscular relaxant from children or adults do, and that isoflurane is commonly used in children including infants, only few studies have evaluated the effect of mivacurium during isoflurane anesthesia [4,7,8].

In the current study, we compared the effect of 200 and 250 μg/kg of mivacurium in infants during isoflurane anesthesia in order to investigate whether the higher dose resulted in a faster onset of action. Spontaneous recovery times and cardiovascular response to the neuromuscular relaxant were also compared.

Methods

The study was approved by the Institutional Investigation Committee of the *Hospital Infantil de México Frederico Gómez* and informed written consent was obtained from parents. The study design was a double blind randomized controlled trial comparing 200 and 250 μg/kg of mivacurium during isoflurane anesthesia. Patients aged 6 to 24 months, ASA I, were selected from those suffering any ophthalmic, oto-rhynologic, plastic or orthopedic disease and undergoing an elective surgery of a planned duration not longer than 1 h while requiring tracheal intubation during the procedure. Those patients undergoing any procedure requiring important mobilization potentially interfering with the neuromuscular monitor during surgery or receiving any drug known or suspected to interfere with neuromuscular transmission were not included. Premedication was not used in any patient. Selection and inclusion of patients was performed during a period of three months. Sample size was computed according to the following equation for estimating the sample size for the comparison of mean values of two independent samples [9]:

$$n > \frac{2\,K\,\sigma^2}{\Delta^2}$$

where K= 10.5 based on tables of the standard normal curve at an α level of 0.05 and β level of 0.10 for a two-
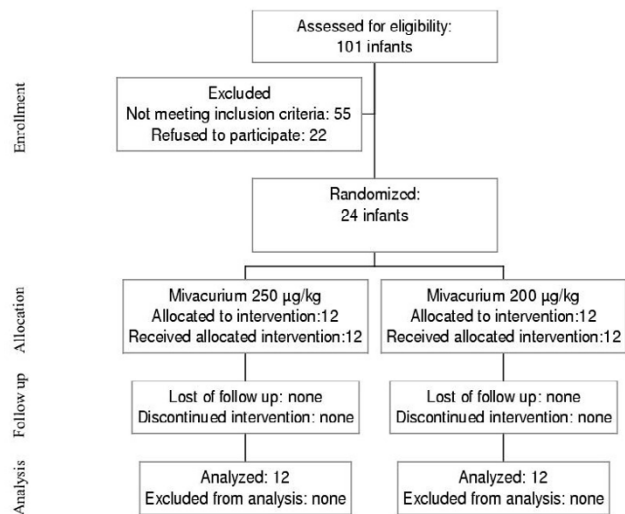

Figure 1
Flow chart of the progress of the study throughout the phases of a randomized trial, i.e. enrollment, intervention allocation, follow-up and data analysis.

sided test, $\sigma^2= 0.30^2$ min is the expected variance according to the standard deviation observed in 15 previous studies (range 0.06 to 1.26 min) administrating mivacurium in children under different clinical conditions, $\Delta^2 = 1^2$ min. Equation resulted in a sampling size of 1.9 patients in each group, we therefore arbitrarily increased the sample size to 12 subjects in each group that could satisfy the minimum significant difference of 1 min between two means associated to a standard deviation of 0.70 min.

One hundred and eighty-four patients were potentially eligible. However, because of the requirements of equipment, extra personnel and fasting period for patients, only 101 patients undergoing surgery between 8 and 12 a.m. were assessed for eligibility and were enough to obtain the required sample size. Fifty-five patients not meeting inclusion criteria and parents of 22 patients rejected participation into the study before randomization. After written consent was obtained, the selected 24 patients were randomized by means of a table of random numbers for two equal groups of 12 patients previously designed by a colleague without any participation in the study. For clarity and according to the CONSORT statement [10], a flow chart of the progress throughout the phases of the current randomized trial was constructed (Figure 1)

Procedures, previously used for other study [6], were as the following: on arrival at the operating room, children were cardiovascular monitored, i.e. ECG, pulse oxymetry

and non-invasive blood pressure by means of an automatic device. Anesthesia was induced using atropine (20 µg/kg), fentanyl (2 µg/kg) and propofol (3 mg/kg). Normocapnia and normal body temperature were maintained intra-operatively. After induction of anesthesia, children were ventilated with 100%-oxygen. Thereafter, using surgical tape, the acceleration transducer of a TOF-Guard neuromuscular transmission monitor (manufactured by Biometer International A/S, Odense, Denmark) was attached to the flexor aspect of the freely mobile thumb. The two cutaneous electrodes to stimulate the ulnar nerve were fixed to the anterior forearm just proximal to the wrist joint. The TOF-Guard was programmed to automatically deliver supramaximal train-of-four stimuli to the ulnar nerve in two phases. During the first, the stimuli were programmed to be delivered every 15 s from baseline to 5 min. Thereafter, the stimuli were delivered every minute until complete recovery (T ≥ 95%) was observed, and the stimuli sequence was stopped by the operator.

Mivacurium (commercialized in our country until 1999 by Glaxo-Wellcome de México, Mexico City, Mexico) was administered as a bolus dose into the T-connector of a rapidly running intravenous infusion. The TOF-Guard was calibrated by using its automatic start-up procedure, and the programmed sequence was started immediately before mivacurium administration. The T (%) and (T4/T1) of the TOF response were simultaneously measured. Time consumed from induction of anesthesia until mivacurium administration was 3 to 5 min.

Finally, intubation was attempted in all infants when either T= 0% or T <25% with no changes during a one-minute period together with the presence of clinical satisfactory conditions for tracheal intubation were present. Clinical condition was evaluated by other of the authors also blinded for patient allocation group, by using the scale described by Fahey et al. [11].

After intubation and throughout a period of time not longer than 3 minutes, administration of isoflurane in oxygen was initiated and slowly increased until a dose of 1.5−2.0 MAC end-tidal adjusted for age was reached. A flow rate of 4 L/min of oxygen was administered through a semiopen Bain circuit and an end-tidal carbon dioxide tension was maintained between 32 and 38 mmHg. At ages of patients studied herein, one unit of MAC of isoflurane is equivalent to 1.6% [12]. End-tidal concentration of isoflurane was kept stable until the endpoint of neuromuscular monitoring had been attained (T ≥ 95%) in every patient. At the end of the surgical procedure, administration of the anesthetic gas was slowly discontinued, during a process of 5 to 10 minutes, until patient presented clinical conditions to be extubated. Oxygen

administration was maintained until a complete clinical recovery was observed and patient was able to self maintain the ventilatory function. No additional drug was required during the anesthetic procedure. Information was recovered and captured in a printed data collection form. This process was performed by one of the authors ignoring the dose of mivacurium. Thereafter, data were transferred to an electronic form (Microsoft® Excel 97). Computation of the onset and spontaneous recovery times and statistical analysis were performed by a blinded process.

Measurements and outcomes

For analysis of the effect, the neuromuscular response was divided in two phases. Response from the baseline until the maximal relaxation was observed and maintained was used to compute the times to a block of 90 (OA_{90}) and 99.9% (OA_{100}). Second, response starting with the maximal relaxation until it returned to baseline values was used to obtain the times to spontaneous recovery of 10, 25, 50, 75 and 90% of the neuromuscular function. To obtain these parameters, both T and T4/T1 responses were analyzed.

The time-course of T or T4/T1 in each phase was considered sigmoidally related to time, and equation used to fit them was the following [13]:

$$E = \left[\frac{(E_0 - E_{max})}{1 + (t / t_{50})^b} \right] + E_{max}$$

The model used is a logistic equation where E = the observed response, t = the time at which every response was registered, E_0 = response at zero time, b= slope factor, t_{50} = time at which half-maximal response is given, and E_{max} = maximal response. In all patients the maximal block and maximal recovery were > 96%. Therefore the E_{max} was obtained by transforming the maximal effect registered by the TOF-Guard into the 100%, a value fixed into the model. All the other values of the effect were then transformed according to the new 100%. Value of the E_0 was then also fixed to the model. The complete neuromuscular response was fitted to time by using the SigmaPlot 4.01 (SPSS México, Mexico City, Mexico) for Windows™ 95, and b and t_{50} were computed by iteration. Thereafter, calculated effect was obtained by proper arrangement of the equation described above. For each patient, the HR and SBP and DBP were transformed into the area under the heart rate-time curve (AUC-HR), and into the area under systolic and diastolic blood pressure-time curve (AUC-SBP and AUC-DBP, respectively). Each AUC was obtained with data obtained immediately after

mivacurium was administered until 30 min. The AUC's were computed by means of the Microsoft® Excel 97 using an adaptation of a standard procedure [14], as follows:

$$AUC(Y) = \left[\frac{Y_1 + Y_2}{2} * (X_2 - X_1)\right] + \left[\frac{Y_2 + Y_n}{2} * (X_n - X_1)\right]$$

where Y represents HR, SBP or DBP, the X is the time at which Y was measured, and 1,2...n are the progressive values until the last observation was performed. By using this equation, the overall response of HR, SBP and DBP is obtained and compared between groups, avoiding the time-by-time comparisons.

Finally, the onset of action was considered as the primary outcome of the study while spontaneous recovery times and cardiovascular response as secondary outcomes.

Statistical analysis
All data were presented as mean ± SD, ranges and when indicated the 95% confidence intervals for the difference for parametric data were computed. The Student *t* test was used to compare age and weight between the two groups of treatment, while the Fisher exact test was used for comparison of gender. The quality of fit of the pharmacodynamic (sigmoidal) model to the data was judged by correlation coefficient of observed to predicted effect automatically computed by SigmaPlot®. Visual examination of plots of the ratio of observed to predicted response and plots of observed *minus* predicted response in function of time was also performed, considering a good agreement between observed and predicted response when ratios approached 1 and differences approached 0.

The times to OA and to spontaneous recovery of neuromuscular function were also compared between groups by the unpaired Student *t* test. The unpaired Student *t* test was also used to compare each AUC, i.e. AUC-HR, AUC-SBP and AUC-DBP, between groups.

Ancillary analyses
In every group, the HR and SBP and DBP data obtained 5 min after mivacurium was administered were compared to their respective baseline values by means of the paired Student *t* test. In order to evaluate the effect of age and weight into onset and recovery times (data from all children), a single linear regression analysis (y= mx+b) was performed between each of the onset and recovery times as the dependent or explained variable and age or weight as the independent variable.

Finally, descriptive statistics, paired and unpaired Student *t* test and linear regression analysis were performed using the software WinSTAT (R. Fitch Software, Cambridge, MA, USA) for Microsoft® Excel. A two-tailed probability of p < 0.05 was considered significant in every test or analysis.

Results
The two groups were similar in demographic data including gender, age and weight (Table 1), reflecting a successful randomized procedure. All patients reached the maximal (100%) relaxation response and received a Fahey scale 0 for tracheal intubation, and were extubated and discharged from the operating room with a full recovery of the neuromuscular function (T ≥ 95%) and without any complication of drug administration. All infants completed the study and data were analyzed in the group they were randomized (Figure 1).

Responses from all patients were successfully modeled. This was proved by regression coefficients always greater than 96%, by plots of ratio of observed to predicted response in function of time approaching 1, and plots of observed *minus* predicted response in function of time approaching 0. The times to OA and to spontaneous recovery of T and T4/T1 of the two groups were summarized in Tables 2 and 3, respectively. In relation to T response (Table 2), the maximal block with mivacurium 250 µg/kg appeared one minute faster than 200 µg/kg (p < 0.05), whereas spontaneous recovery times were similar between groups. However, analyzing T4/T1 response, similar times to OA and to spontaneous recovery were obtained with both doses (Table 3). Additionally, no relationship between age or weight and any of the OA or spontaneous recovery times was demonstrated by linear regression analysis.

In relation to the cardiovascular response, the AUC-HR was similar in the two groups (p > 0.05) while both AUC-SBP and AUC-DBP were significantly lower (p < 0.05) in patients receiving 250 µg/kg. The HR at 5 min after any dose of mivacurium was administered significantly increased in relation to baseline values (p < 0.05), while a similar time-course of the HR was observed with the two doses of mivacurium (Figure 2). The time-course of both SBP (Figure 3) and DBP (Figure 4) reflected the differences observed in their respective AUC's. Transient flushing was observed in two cases: one female patient, weighing 13 kg, aged 22 mo., and receiving mivacurium 200 µg/kg, and one male patient, weighing 8.3 kg, aged 8 mo., and receiving mivacurium 250 µg/kg.

Discussion
In this study patients underwent muscle relaxation with mivacurium. Anesthesia was intravenously induced and

Table 1: Demographic data

	DOSE (µg/kg)		95% CI for the difference
	200	**250**	
Gender (M:F)	7:5	6:6	-
Age (month)	18.0 ± 6.3 (6.0 – 24.0)	15.2 ± 6.4 (8.0 – 24.0)	- 2.4 to 8.0
Weight (kg)	11.1 ± 2.2 (7.0 – 15.0)	10.3 ± 2.3 (6.5 – 14.0)	-1.1 to 2.7

mean $\pm$ SD (ranges)

Table 2: Times to OA and to spontaneous recovery of T

	DOSE (µg/kg)		95% CI for the difference
	200	**250**	
OA_{90} (min)	2.0 ± 0.6 (1.4 – 3.6)	1.6 ± 0.6 (1.1 – 2.9)	-0.1 to 0.9
OA_{100} (min)	3.5 ± 1.4 (1.9 – 6.0)	$2.4 \pm 1.1^*$ (1.1 – 4.7)	0.1 to 2.1
T_{10} (min)	10.1 ± 2.2 (5.4 – 13.1)	11.0 ± 1.9 (8.2 – 13.8)	-2.6 to 0.8
T_{25} (min)	11.7 ± 2.5 (6.4 – 15.1)	12.5 ± 1.93 (9.5 – 15.9)	-2.6 to 1.0
T_{50} (min)	13.5 ± 2.9 (7.6 – 17.4)	14.2 ± 2.1 (10.9 – 18.3)	-2.8 to 1.4
T_{75} (min)	15.6 ± 3.6 (8.9 – 20.0)	16.2 ± 2.4 (12.6 – 21.1)	-3.1 to 1.9
T_{90} (min)	18.0 ± 4.5 (10.5 – 23.9)	18.4 ± 3.0 (14.5 – 24.3)	-3.6 to 2.8

mean $\pm$ SD (ranges) *p < 0.05

Table 3: Times to OA and to spontaneous recovery of T4/T1

	DOSE (µg/kg)		95% CI for the difference
	200	**250**	
OA_{90} (min)	1.9 ± 0.6 (1.4 – 3.6)	1.6 ± 0.5 (1.0 – 2.7)	-0.2 to 0.8
OA_{100} (min)	2.3 ± 1.1 (1.4 – 5.2)	2.1 ± 1.0 (1.0 – 4.5)	-0.7 to 1.1
$T4/T1_{10}$ (min)	10.3 ± 1.9 (5.3 – 12.8)	11.5 ± 2.1 (8.3 – 14.2)	-2.9 to 0.5
$T4/T1_{25}$ (min)	11.9 ± 2.0 (6.8 – 14.8)	13.0 ± 2.0 (9.9 – 15.5)	-2.8 to 0.6
$T4/T1_{50}$ (min)	13.9 ± 2.2 (8.6 – 17.1)	14.7 ± 1.9 (11.7 – 18.1)	-2.5 to 0.9
$T4/T1_{75}$ (min)	16.1 ± 2.6 (10.9 – 19.9)	16.7 ± 2.0 (13.8 – 21.2)	-2.5 to 1.3
$T4/T1_{90}$ (min)	18.8 ± 3.2 (13.8 – 23.1)	18.9 ± 2.5 (16.1 – 24.7)	-2.5 to 2.3

mean $\pm$ SD (ranges)

maintained with isoflurane administered when relaxation had reached a maximal response. The same clinical model was previously used to evaluate the effects of rocuronium [6], and clearly differs from other studies. Mainly, intubation followed by gas administration was performed after a maximum neuromuscular block was present, avoiding any effect of the anesthetic gas on the times to OA. However, isoflurane is able to increase twice the spontaneous recovery of vecuronium in children, and prolongs recovery times for more than 50% after 30 min of its administration [4,5]. In the present study similar spontaneous recovery was observed in the two groups, and our results are comparable to 15–20 min for T_{90} of Goudsouzian's review article [3]. Furthermore, our T_{25} values are longer than those obtained with 300 µg/kg of mivacurium under nitrous oxide-halothane or nitrous
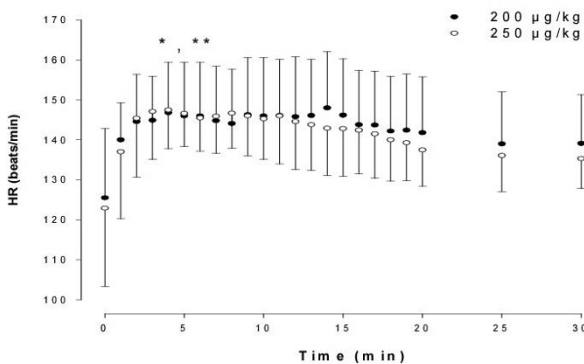
Figure 2
The time course of HR after administration of mivacurium. *P < 0.05, baseline *vs.* 5 min HR values of patients receiving mivacurium 200 µg/kg; **P < 0.05, baseline *vs.* 5 min HR values of patients receiving mivacurium 250 µg/kg
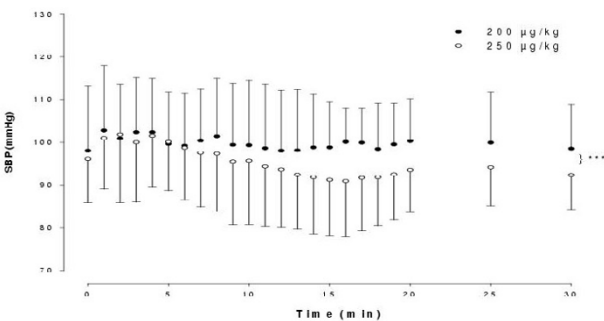

Figure 3
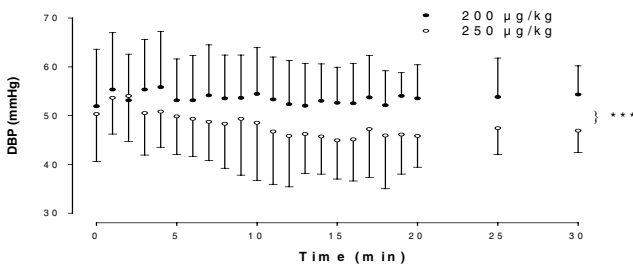The time course of SBP after administration of mivacurium. ***P < 0.05, 200 *vs.* 250 µg/kg

Figure 4
The time course of DBP after administration of mivacurium. ***P < 0.05, 200 *vs.* 250 µg/kg

oxide-opioid anesthesia [15]. These considerations suggest that isoflurane does affect the spontaneous recovery similar to or higher than other anesthetic techniques.

The duration of action of some non-depolarizing neuromuscular blocking agents differs with age, even when administered in equipotent doses [16]. Other studies have also demonstrated age differences of response to mivacurium [4,7,14,17,18]. In the current study, we obtained no significant relationship between age or weight and any of the OA or spontaneous recovery. The range of 6 to 24 months of our patients could be broad to study the effect of age in 24 patients. However, a Canadian group of pediatric anesthesiologists found similar neuromuscular effects of mivacurium in patients aged between 2 mo. to 10 yr. [19,20], supporting our results.

Additionally, extremely wide ranges of neuromuscular response in children have been described for other neuromuscular blocking, e.g. T_{75} ranged from 27.3 to 91.4 min with rocuronium 800 µg/kg and T_{25-75} ranged from 6.0–22.8 min with rocuronium 600 µg/kg [6,21]. In relation to mivacurium, cholinesterase activity level is a major determinant of the spontaneous recovery of mivacurium in pediatric population [8,22]. We did not quantify enzyme levels and therefore the inter-individual variations of spontaneous recovery times are difficult to be interpreted. However, coefficient of variations of T response to mivacurium varied from 14.8 to 45.8% and T_{75} response ranged from 8.9 to 20 min, representing a less markedly variation than rocuronium. Furthermore, an atypical response was not present in any patient. Therefore, we considered that our patients were a population without marked differences in plasmatic cholinesterase activity.

In relation to cardiovascular response, administration of mivacurium 200 to 300 µg/kg in infants and children has demonstrated minor changes or lack of significant changes in HR and blood pressure [14,18,19,23,24]. We observed an increment in HR at the first minute, reaching the top at 5 min in both groups. Agents having varying cardiovascular effects were administered in addition to and preceding the mivacurium, when assessing the cardiovascular response. Atropine administration and combination of fentanyl and propofol could certainly have an effect on heart rate and blood pressure in our patients. However, a drop in blood pressures indicated by lower AUC-SBP and AUC-DBP of patients receiving mivacurium 250 µg/kg was significant. The review article of Goudsouzian states that reported ED_{95} of mivacurium for infants ranges from 65–94 µg/kg [3]. The dose of 200 µg/kg will then be 2 to 3 times the referenced ED_{95}, and 250 will be 2.5 to approximately 4 times. We therefore considered that these changes could be mainly related to histamine release with both doses, probably more marked with the highest dose. Fortunately, in most cases the histamine release and cardiovascular changes have lacked clinical significance [25].

Table 4: The cardiovascular response

	DOSE (μg/kg)		
	200	**250**	**95% CI for the difference**
AUC-HR	$4,272.7 \pm 367.6$	$3,977.8 \pm 646.0$	-18.3 to 608.1
AUC-SBP	$2,964.6 \pm 646.0$	$2,682.9 \pm 435.9^{*}$	55.7 to 507.7
AUC-DBP	$1,599.0 \pm 201.8$	$1,344.7 \pm 244.3^{*}$	120.8 to 387.8

$^{*}p < 0.05$

The TOF-Guard was used to evaluate the neuromuscular response. Some studies have supported its use by finding that acceleromyography compares closely with other more sophisticated equipment [26,27], whereas clinical trials using the TOF-Guard to measure neuromuscular function have been increased. However, it is not yet accepted as a monitor of definitive studies of neuromuscular blocking agents in anesthesia probably because it does not register the neuromuscular function in a continuous fashion, and can generate "noise" in the measurement of the effect [20]. Previously, we utilized it to evaluate the pharmacodynamics of rocuronium [6,28]. When used for rocuronium, data acquisition every 5 min in the recovery period was enough to model the recovery phase. Because of a fast recovery after mivacurium administration, data acquisition in the recovery phase was now performed every minute and the effect was also successfully modeled, and results agreed with those previously published in the literature. We therefore considered that, if any, the noise generated by TOF-Guard measurements did not affect data modeling nor results and conclusions of the current study. Unfortunately and despite its relative low cost, capacity to retain data sets and its easy-to-use, TOF-Guard is worldwide no longer commercially available. It is being replaced by the manufacturer company with equivalent equipment named the TOF-Watch series (written personal communication from Biometer International A/S, Odense, Denmark, 1999), unable to retain data and therefore require to be connected into a computer.

Finally, we simultaneously registered T and T4/T1. It has been proposed that the T4/T1 is more sensitive than evaluation of any single twitch of the TOF response [29,30], and does not need an established control. By evaluating the T response, significantly faster OA times were identified with mivacurium 250 μg/kg, while all the T1/T4 were similar between the two groups. This controversy deserves further investigation.

Conclusions
The maximal effect of mivacurium 250 μg/kg was produced one minute faster than 200 μg/kg. However, it was associated to a significant cardiovascular response. We therefore conclude that the higher dose does not offer a satisfactory clinical advantage over the lower dose in infants under general anesthesia with isoflurane.

Abbreviations
AUC-HR, AUC-SBP and AUC-DBP: Respectively, the area under the time-course of heart rate, systolic and diastolic blood pressure; b: the slope factor; E_0: response at zero time; E_{max}: maximal response; OA: Onset of action; OA_{90} and OA_{100}: Time to a block of 90 and 99.9% at onset of action, respectively; T: The first twitch of the TOF, expressed as % of control values; TOF: Train-of-four; T4/T1: The ratio between the fourth and the first stimuli of the TOF; T_{10}, T_{25}, T_{50}, T_{75}, T_{90}: Respectively, the time to spontaneous recovery of 10, 25, 50, 75 and 90% of T; $T4/T1_{10}$, $T4/T1_{25}$, $T4/T1_{50}$, $T4/T1_{75}$, $T4/T1_{90}$: Respectively, the time to spontaneous recovery of 10, 25, 50, 75 and 90% of T4/T1

Competing interests
None declared

Acknowledgements

References
1. Plaud B, Debaene B, Lequeau F, Meistelman C, Donati F: **Mivacurium neuromuscular block at the adductor muscles of the larynx and adductor pollicies in human.** *Anesthesiology* 1996, **85**:77-81

2. Wierda JM, Hommes FD, Nap HJ, van den Broek L: **Time course of action and intubating conditions following vecuronium, rocuronium and mivacurium.** *Anaesthesia* 1995, **50**:393-396

3. Goudsouzian NG: **Mivacurium in infants and children.** *Paediatr Anaesth* 1997, **7**:183-190
4. Jalkanen L, Meretoja OA: **The influence of the duration of isoflurane anaesthesia on neuromuscular effects of mivacurium.** *Acta Anaesthesiol Scand* 1997, **41**:248-251
5. Bazin JE, Dalens B, Veyret E, Picard P, Haberer JP: **Influence of isoflurane on the neuromuscular block induced by vecuronium in the child (French).** *Cah Anesthesiol* 1988, **36**:593-598
6. Villegas-Sánchez F, Charles-Torres JD, Moyao-García D, Nava-Ocampo AA, Velázquez-Armenta EY: **Rocuronium administration in children during isoflurane anesthesia: neuromuscular effects.** *Arch Med Res* 1999, **30**:307-314
7. Meretoja OA, Wirtavuori K, Taivainen T, Olkkola KT: **Time course of potentiation of mivacurium by halothane and isoflurane in children.** *Br J Anaesth* 1996, **76**:235-238
8. Markakis DA, Hart PS, Lau M, Brown R, Fisher DM: **Does age or pseudocholinesterase activity predict mivacurium infusion rate in children?** *Anesth Analg* 1996, **82**:39-43
9. Daly LE, Bourke GJ, McGilvray J: **Interpretation and uses of medical statistics.** *Oxford (UK), Blackwell Scientific Publications,* 1991425-427
10. Moher D, Schultz KF, Altman DG: **The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials.** *BMC Med Res Methodol* 2001, **1**:2
11. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P: **Clinical pharmacology of ORG NC45 (Norcuron™): A new nondepolarizing muscle relaxant.** *Anesthesiology* 1981, **55**:6-11
12. Coté CJ, Lugo RA, Ward RM: **Pharmacokinetics and pharmacology of drugs in children.** *In: A practice of anesthesia for infants and children (Edited by Coté CJ, Todres ID, Ryan JF, Goudsouzian NG) Philadelphia (USA), WB Saunders Co* 2001121-171
13. DeLean A, Munson PJ, Rodbard D: **Simultaneous analysis of families of sigmoidal curves: applications to bioassay, radioligand assay, and physiological dose-response curves.** *Am J Physiol* 1978, **235**:E97-E102
14. Ritschel WA: **Handbook of basic pharmacokinetics,** *Illinois (USA), Drug Intelligence Publications, Inc.,* 1992294
15. Brandom BW, Meretoja OA, Simhi E, Taivainen T, Wolfe SR, Woefel SK, Gronert BJ, Cook DR: **Age related variability in the effects of mivacurium in paediatric surgical patients.** *Can J Anesth* 1998, **45**:410-416
16. Meretoja OA: **Neuromuscular blocking agents in paediatric patients: influence of age on the response.** *Anaesth Intens Care* 1990, **18**:440-448
17. Meretoja OA, Olkkola KT: **Pharmacodynamics of mivacurium in children using a computer-controlled infusion.** *Br J Anaesth* 1993, **71**:232-237
18. Meretoja OA, Taivainen T, Wirtavuori K: **Pharmacodynamics of mivacurium in infants.** *Br J Anaesth* 1994, **73**:490-493
19. Woelfel SK, Brandom BW, McGowan FX Jr, Cook DR: **Clinical pharmacology of mivacurium in pediatric patients less than two years old during nitrous oxide-halothane anesthesia.** *Anesth Analg* 1993, **77**:713-720
20. Sarner JB, Brandom BW, Woelfel SK, Dong ML, Horn MC, Cook DR, McNulty BF, Foster VJ: **Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia.** *Anesth Analg* 1989, **68**:116-121
21. Woelfel SK, Brandom BW, Cook DR, Sarner JB: **Effects of bolus administration of ORG-9426 in children during nitrous oxide-halothane anesthesia.** *Anesthesiology* 1992, **76**:939-942
22. Bevan JC, Reimer EJ, Smith MF, de V Scheepers L, Bridge HS HS, Martin GR, Bevan DR: **Decreased mivacurium requirements and delayed neuromuscular recovery during sevoflurane anesthesia in children and adults.** *Anesth Analg* 1998, **87**:772-778
23. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miler V, McNulty BF, Savarese JJ: **Neuromuscular and cardiovascular effects of mivacurium in children.** *Anesthesiology* 1989, **70**:237-242
24. Gronert BJ, Woelfel SK, Cook DR: **Comparison of high equipotent doses of mivacurium and succinylcholine in children 2–12 years old.** *Anesthesiology* 1993, **79**:A966
25. Bevan DR: **Complications of muscle relaxants.** *Semin Anesth* 1995, **14**:63-70
26. Ansermino JM, Sanderson PM, Bevan JC, Bevan DR: **Acceleromyography improves detection of residual neuromuscular blockade in children.** *Can J Anaesth* 1996, **43**:589-594
27. Loan PB, Paxton LD, Mirakhur RK, Connolly FM, McCoy EP: **The TOF-Guard neuromuscular transmission monitor. A comparison with the Myograph 2000.** *Anaesthesia* 1995, **50**:699-702
28. Velázquez-Armenta EY, Nava-Ocampo AA: **Pharmacodynamic modeling without plasma concentrations of rocuronium administrated to children during isoflurane anesthesia.** *Rev Mex Anest* 1999, **22**:225-229
29. Lee CM: **Train-of-4 quantitation of competitive neuromuscular block.** *Anesth Analg* 1975, **54**:649-653
30. Waud BE, Waud DR: **The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block.** *Anesthesiology* 1972, **37**:413-416