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Neuromuscular Effect of Pipecuronium Bromide in Infants and Children during Nitrous Oxide–Alfentanil Anesthesia

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To determine in infants and children the neuromuscular effect of pipecuronium during alfentanil–N_2O/O_2 anesthesia, the authors studied 32 ASA Physical Status 1 and 2 pediatric patients undergoing minor elective surgery, divided into three groups according to their age: group 1 included 12 infants, 1.9 ± 0.2 months old (mean ± SE; range, 20 days to 3 months), weighing 5.2 ± 0.3 kg; group 2, 10 infants, 6.1 ± 0.9 months old (range, 3–11 months), 6.9 ± 0.4 kg; and group 3, 10 children 5.6 ± 0.9 yr old (range, 2–9 yr), 19.6 ± 2.2 kg. Neuromuscular blockade at the ulnar nerve–adductor pollicis muscle was measured by electromyography. Incremental iv doses of pipecuronium were given (one 20 μg/kg first dose, followed by 10 μg/kg increments) to reach a 95 ± 2% twitch depression (ED_{95}). In children ED_{50} and ED_{95} of pipecuronium were 45.0 ± 5.8 μg/kg (mean ± SE) and 70.5 ± 9.3 μg/kg, respectively. In 3- to 12-month-old infants ED_{50} and ED_{95} were 25.8 ± 1.5 μg/kg and 48.7 ± 3.5 μg/kg, respectively, and both significantly ($P < 0.05$) less than those in children. In 0- to 3-month-old infants ED_{50} and ED_{95} were 23.7 ± 1.7 μg/kg and 46.5 ± 2.9 μg/kg, respectively, and also significantly ($P < 0.05$) less than those measured in children. Time from maximal initial neuromuscular blockade to 75% recovery was 64.5 ± 8.8 min in children and significantly shorter ($P < 0.05$) in the two infant groups (0- to 3-month-old: 38.7 ± 5.7 min, 3- to 12-month-old: 43.8 ± 5.3 min, respectively). In conclusion, this study demonstrates that the neuromuscular potency of pipecuronium is increased in both groups of infants compared with that in children older than 2 yr. Furthermore, whereas pipecuronium is a long-acting neuromuscular blocking agent in children (similar to what has been reported in adults), it has only an intermediate duration of action in infants. (Key words: Age factors: children; infants. Analgesics, opioid: alfentanil. Anesthetics, gases: nitrous oxide. Neuromuscular relaxants, pipecuronium bromide: ED_{50}, ED_{95}.)

PIPECURONIUM BROMIDE is a long-acting, nondepolarizing neuromuscular blocking drug free of histamine release[1] and devoid of cardiovascular side effects in adults, even after four times the therapeutic dose.[1,2] It is about 50% more potent than pancuronium, with the same onset and duration of action.[2–5] Pipecuronium has a larger steady state volume of distribution and a greater plasma clearance than pancuronium, but the time courses of neuromuscular blockade following injection of both drugs are similar.[5] This new muscle relaxant has widely been studied in adults,[5–7] but there are only few data available in children[8] and no data in neonates and infants.

The aim of the present study was to evaluate and compare the potency and duration of the pipecuronium-induced neuromuscular blockade in infants and children during alfentanil–N_2O/O_2 anesthesia.

Methods

We obtained approval from the local ethics committee on human research, and informed consent was obtained from parents to study 32 ASA Physical Status 1 or 2 pediatric patients undergoing minor elective surgery. Patients were grouped according to their age: group 1 included 12 infants, 1.9 ± 0.2 months old (mean ± SE; range, 20 days to 3 months), weighing 5.2 ± 0.3 kg; group 2, 10 infants, age 6.1 ± 0.9 months old (range, 3–11 months), 6.9 ± 0.4 kg, and group 3, 10 children 5.6 ± 0.9 yr old (range, 2–9 yr), 19.6 ± 2.2 kg.

Anesthesia was induced with 5 mg/kg thiopental and 15 μg/kg alfentanil iv and was maintained by the administration of N_2O and O_2 (60:40) supplemented with repeated iv doses of alfentanil (10 μg/kg) every 10 min so that no patient responded with an increase in heart rate, mean systemic arterial pressure, sudation, or movement to the painful electromyographic stimulation applied before and during the administration of pipecuronium. The trachea was intubated without muscle relaxant. A multiple gas analyzer (Capnomac®, Datex Instrumentarium Corporation, Helsinki) was connected to the endotracheal tube to continuously measure the end-tidal CO_2, O_2, and N_2O concentrations. Ventilation was controlled to keep end-tidal CO_2 between 4.3 and 4.8 vol%. Rectal temperature was maintained between 36.0 and 37.5° C. Neuromuscular transmission was measured by electromyography (Relaxograph® NMT-100, Datex Instrumentarium Corporation, Helsinki) at the left ulnar nerve–adductor pollicis muscle, using transcutaneous electrodes. This device delivered supramaximal stimuli (0.1 ms duration) of train-of-four at 2 Hz every 20 s. The first of the four evoked responses was considered as the twitch height. To minimize movement-induced changes of twitch responses during electromyography measurement, the patient's hand was carefully restrained to avoid any displacement of the electrodes. The Relaxograph® was recalibrated 2–3 min before the administration of pipecuronium. To calculate the degree of neuromuscular blockade in per cent, all twitch heights were referred to those measured before the first injection of pipecuronium. Incremental iv doses

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of pipecuronium bromide were given (one 20 μg/kg first dose, followed by 10 μg/kg increments). After each dose two consecutive twitches of equal height were obtained before the next increment was given. In this manner the dose necessary to reach a 95 ± 2% suppression of the twitch was determined.[9] The time from the maximal initial blockade to 25% recovery of twitch height was defined as clinical duration. It does not include the time necessary to obtain maximal neuromuscular blockade. The time from 25% to 75% recovery of the twitch height was defined as recovery index. Clinical duration and recovery index together were defined as D_{75} (duration to 75% recovery). The study was ended when the twitch recovered to 75% of the prerelaxant control level. Spontaneous or neostigmine-induced (20 μg/kg, only in the children group) recovery of twitch height to control value was obtained. Patients in whom the twitch height did not recover to near 100% were excluded from the study.

Using linear regression analysis after logit transformation of twitch responses, we determined the dose–response relationship (logit effect *vs.* log dose) for pipecuronium in each patient of the three age groups. Regression slopes within and between each age group were tested with a one-way analysis of variance (ANOVA) to determine whether they deviated from parallelism. The positions of the three mean regression lines were compared by analysis of covariance.[10] To compare the potency of pipecuronium, ED_{50} and ED_{95} were calculated for each patient from individual linear regression analysis. Comparisons of ED_{50}, ED_{95}, clinical duration, recovery index, and D_{75} between each age group were made using a one-way ANOVA followed by a Duncan's multiple comparisons test. Finally, a one-way ANOVA determined whether significant differences existed between groups for rectal temperature or end-tidal P_{CO_2}. For all statistical comparisons, differences were considered as significant if $P < 0.05$.

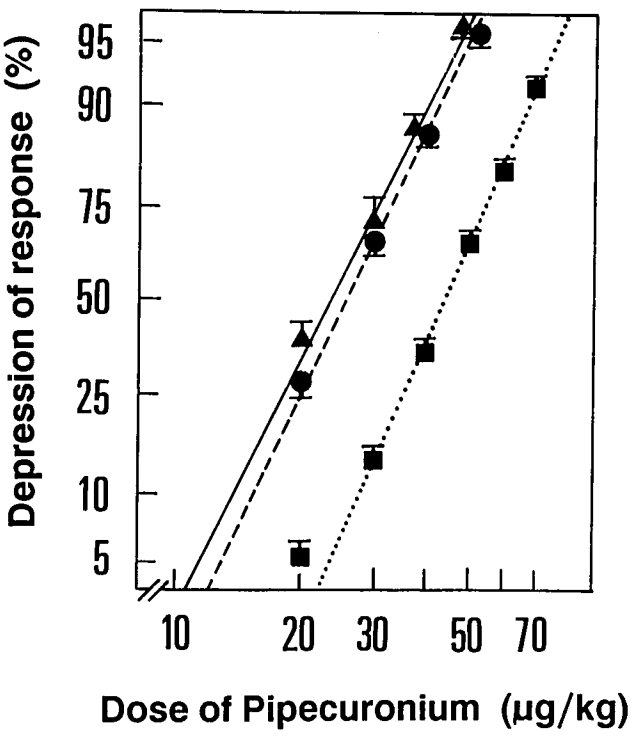

FIG. 1. Dose–response curves for pipecuronium in infants (0–3 months: ▲; 3–12 months: ●) and children (■) during alfentanil–N_2O/O_2 anesthesia. Data points represent mean ± SE depression of neuromuscular response following cumulative doses of pipecuronium; the three regression lines are the mean of 12 (0–3 months), ten (3–12 months), and ten (children) individual slopes calculated from ED_{50} and ED_{95} values for each patient in the three age groups.

TABLE 1. The Potency of Pipecuronium and the Duration of the Neuromuscular Blockade in Infants and Children during N_2O–Alfentanil Anesthesia

	Infants		
	0–3 Months (n = 12)	3–12 Months (n = 10)	Children (n = 10)
ED_{50} (μg/kg)	23.7 ± 1.7*	25.8 ± 1.5*	45.0 ± 5.8
ED_{95} (μg/kg)	46.5 ± 2.9*	48.7 ± 3.5*	70.5 ± 9.3
TDP (μg/kg)	44.6 ± 2.8*	46.5 ± 2.8*	69.5 ± 6.8
CD (min)	13.2 ± 1.8*	13.4 ± 2.2*	39.9 ± 6.4
RI (min)	25.5 ± 4.6	30.4 ± 4.1	24.6 ± 1.6
D_{75} (min)	38.7 ± 5.7*	43.8 ± 5.3*	64.5 ± 8.8

Values are mean ± SE.
TDP = total dose of pipecuronium given; CD = clinical duration; RI = recovery index; D_{75} = duration to 75% recovery.
* Significantly different from children ($P < 0.05$).

Results

In the three age groups the mean slopes of the regression lines of logit of twitch height *versus* log dose of pipecuronium did not significantly deviate from parallelism (fig. 1). Table 1 describes the potency of pipecuronium and the duration of the neuromuscular blockade in each group.

In children anesthetized with alfentanil–N_2O/O_2, ED_{50} and ED_{95} were 45.0 ± 5.8 μg/kg (mean ± SE) and 70.5 ± 9.3 μg/kg, respectively. In 3- to 12-month-old infants ED_{50} and ED_{95} were 25.8 ± 1.5 μg/kg and 48.7 ± 3.5 μg/kg, respectively, and both significantly ($P < 0.05$) less than those in children. In 0- to 3-month-old infants ED_{50} and ED_{95} were 23.7 ± 1.7 μg/kg and 46.5 ± 2.9 μg/kg, respectively, and also significantly ($P < 0.05$) less than those in children.

The mean time necessary to obtain maximal neuromuscular blockade was 11.0 ± 0.4 min in children (range, 8–12 min), 10.8 ± 1.1 min in 3- to 12-month-old infants (range, 8–13 min), and 8.4 ± 0.7 min in 0- to 3-month-old infants (range, 6–10 min). The time necessary to ob-

tain maximal neuromuscular blockade was not statistically different among the three groups. Clinical duration was 39.9 ± 6.4 min in children, and was significantly shorter ($P < 0.05$) in the two infant groups (0- to 3-month-old, 13.2 ± 1.8 min; 3- to 12-month-old, 13.4 ± 2.2 min, respectively). Recovery index was similar in the three age groups. D_{75} was 64.5 ± 8.8 min in children and significantly shorter ($P < 0.05$) in the two infant groups (0- to 3-month-old, 38.7 ± 5.7 min; 3- to 12-month-old, 43.8 ± 5.3 min, respectively).

There were no significant differences among age groups in rectal temperature or end-tidal P_{CO_2}. Cardiovascular variables of the three groups of patients did not significantly change during the entire investigation.

Discussion

The results of the present study demonstrate that the neuromuscular potency of pipecuronium determined by electromyography is significantly increased, and the elimination of neuromuscular blockade significantly faster, in infants compared with values measured in children.

To determine the neuromuscular effect of pipecuronium, we used an electromyographic recording of twitch responses. Although electromyography has been used increasingly in clinical adult studies,[11,12] the small size of infants relative to the large electrode size (12.5 mm) may make it technically difficult to use this technique. Monitoring of neuromuscular blockade could be liable to electrical interference when transcutaneous electrodes have to be placed near each other in small infants. In a pilot study we found that satisfactory electromyographic recordings were achieved with a minimal risk of system failure in small infants when placing the active recording electrode on the adductor pollicis muscle rather than on hypothenar muscle and the indifferent recording electrode at the base of one of the fingers. These findings confirm the recently published data from Kalli[13] who demonstrated that electromyographic waveforms are similar in small infants as in older children. In contrast, the amplitude of evoked electromyography is smaller in younger than in older children.

The present investigation shows that body weight based ED_{50} and ED_{95} of pipecuronium are of the same magnitude for the two groups of patients younger than 1 yr and are significantly less than those for older children. Potency and duration of pipecuronium-induced neuromuscular blockade in children older than 2 yr are similar to the values found in the same age group in a previous study[8] in which we compared the neuromuscular effect of pipecuronium administered by the cumulative dose–response technique in adults and children during fentanyl–N_2O anesthesia. Lower values of ED_{50} and ED_{95} in infants compared with children have also been reported for vecuronium[14] and atracurium in studies using electromyography,[15] although other studies did not detect any difference between these age groups with mechanomyography.[16,17] In contrast, the dose requirement of long-acting relaxants, such as *d*-tubocurarine,[18] metocurine,[19] and pancuronium,[20] is not modified by age. To explain this fact, Fisher *et al.*[18] reported that a greater volume of distribution of *d*-tubocurarine in infants counterbalances the increased sensitivity of the neuromuscular junction observed in this age group. Although there are no pharmacokinetic data on pipecuronium available for infants and children, we can expect that the increase in extracellular fluid volume in infants influences the volume of distribution of pipecuronium in a way similar to that of other muscle relaxants.[16,21,22] Thus, differences in dose requirements for pipecuronium between infants and children are probably not only explained by age-related differences in pharmacokinetics of this muscle relaxant but also by a possible greater neuromuscular junction sensitivity for pipecuronium than for other muscle relaxants.

Clinical and total duration of action but not recovery index of pipecuronium were significantly shorter in both groups of infants compared with values measured in children. Our data suggest that the shorter duration of pipecuronium in infants is probably due to the lower doses given to infants because the recovery index was similar in the three age groups. Comparable results have been reported for the duration of action of atracurium in infants compared with children and adolescents,[15] which were explained by the unusual metabolic pathways of atracurium (Hofmann elimination and ester hydrolysis) resulting in the destruction of this drug in both tissue and plasma. In contrast to our results with pipecuronium, the duration of the neuromuscular blockade induced by vecuronium[16,23] and *d*-tubocurarine[18,24] has been reported to be significantly prolonged in infants compared with children. Prolonged clinical duration and recovery index of vecuronium may be due to the longer elimination half-life secondary to an increased steady state distribution volume.[25]

In conclusion, the present study demonstrates that the neuromuscular potency of pipecuronium determined by electromyography is increased in infants younger than 1 yr compared with children. Furthermore, contrary to what is observed in children, pipecuronium is not a long- but an intermediate-acting neuromuscular blocking agent in infants.

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