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

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To determine in infants and children the neuromuscular effect of pipecuronium during alfentanil–N₂O/O₂ 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% (which depression (ED₉₅). In children ED₉₀ and ED₃₀ of pipecuronium were 45.0 ± 5.8 μg/kg (mean ± SE) and 70.5 ± 9.5 μg/kg, respectively. In 3- to 12-month-old infants ED₉₀ and ED₃₀ 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 ED₉₀ and ED₃₀ 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; ED₉₀, ED₃₀.)

PIPECURONIUM BROMIDE is a long-acting, nondepolarizing neuromuscular blocking drug free of histamine release 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,⁶⁻⁷ but there are few data available in children⁸ and no data in neonates and infants.

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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–N₂O/O₂ 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 N₂O and O₂ (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 CO₂, O₂, and N₂O concentrations. Ventilation was controlled to keep end-tidal CO₂ 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 pipercuronium 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. 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 D75 (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 pipercuronium 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. To compare the potency of pipercuronium, ED50 and ED95 were calculated for each patient from individual linear regression analysis. Comparisons of ED50, ED95, clinical duration, recovery index, and D75 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 Pco2. For all statistical comparisons, differences were considered as significant if 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 pipercuronium did not significantly deviate from parallelism (fig. 1). Table 1 describes the potency of pipercuronium and the duration of the neuromuscular blockade in each group.

In children anesthetized with alfentanil–N2O/O2, ED50 and ED95 were 45.0 ± 5.8 μg/kg (mean ± SE) and 70.5 ± 9.5 μg/kg, respectively. In 3- to 12-month-old infants ED50 and ED95 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 ED50 and ED95 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-

<table>
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<tr>
<th></th>
<th>Infants</th>
<th>Children</th>
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<tbody>
<tr>
<td></td>
<td>0–3 Months (n = 12)</td>
<td>3–12 Months (n = 10)</td>
</tr>
<tr>
<td>ED50 (μg/kg)</td>
<td>23.7 ± 1.7*</td>
<td>25.8 ± 1.5*</td>
</tr>
<tr>
<td>ED95 (μg/kg)</td>
<td>46.5 ± 2.9*</td>
<td>48.7 ± 3.5*</td>
</tr>
<tr>
<td>TDP (μg/kg)</td>
<td>44.6 ± 2.8*</td>
<td>46.5 ± 2.8*</td>
</tr>
<tr>
<td>CD (min)</td>
<td>13.2 ± 1.8*</td>
<td>13.4 ± 2.2*</td>
</tr>
<tr>
<td>RI (min)</td>
<td>25.5 ± 4.6</td>
<td>30.4 ± 4.1</td>
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<tr>
<td>D75 (min)</td>
<td>38.7 ± 5.7*</td>
<td>43.8 ± 5.3*</td>
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Values are mean ± SE.

TDP = total dose of pipercuronium given; CD = clinical duration; RI = recovery index; D75 = duration to 75% recovery.

* Significantly different from children (P < 0.05).

**Table 1. The Potency of Pipercuronium and the Duration of the Neuromuscular Blockade in Infants and Children during N2O-Alfentanil Anesthesia**

**Fig. 1. Dose–response curves for pipercuronium in infants (0–3 months: A; 3–12 months: ●) and children (○) during alfentanil–N2O/O2 anesthesia. Data points represent mean ± SE depression of neuromuscular response following cumulative doses of pipercuronium; the three regression lines are the mean of 12 (0–3 months), ten (3–12 months), and ten (children) individual slopes calculated from ED50 and ED95 values for each patient in the three age groups.**
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, re-
spectively). Recovery index was similar in the three age
groups. \( D_{75} \) was 64.5 ± 8.8 min in children and signif-
icantly 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 \( P_{CO_2} \). Cardio-
vascular 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 elim-
nination of neuromuscular blockade significantly faster, in
infants compared with values measured in children.

To determine the neuromuscular effect of pipecuron-
iun, we used an electromyographic recording of twitch
responses. Although electromyography has been used in-
creasingly in clinical adult studies, the small size of
infants relative to the large electrode size (12.5 mm) may
make it technically difficult to use this technique. Moni-
toring of neuromuscular blockade could be liable to elec-
trical interference when transcutaneous electrodes have
to be placed near each other in small infants. In a pilot
study we found that satisfactory electromyographic recor-
dings were achieved with a minimal risk of system fail-
ure in small infants when placing the active recording
electrode on the adductor pollicis muscle rather than on
the hypothenar muscle and the indifferent recording elec-
trode at the base of one of the fingers. These findings
confirm the recently published data from Kalli 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
\( ED_{90} \) and \( ED_{95} \) of pipecuronium are of the same magni-

tude 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 neu-
romuscular blockade in children older than 2 yr are similar
to the values found in the same age group in a previous
study in which we compared the neuromuscular effect
of pipecuronium administered by the cumulative dose-
response technique in adults and children during fent-
anyl–\( N_2O \) anesthesia. Lower values of \( ED_{90} \) and \( ED_{95} \) in
infants compared with children have also been reported
for vecuronium and atracurium in studies using elec-
tromyography, although other studies did not detect
any difference between these age groups with mechano-
myography. In contrast, the dose requirement of long-
acting relaxants, such as \( d \)-tubocurarine, metocurine,
and pancuronium, is not modified by age. To explain
this fact, Fisher et al. 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 phar-
macokinetic data on pipecuronium available for infants
and children, we can expect that the increase in extra-
cellular fluid volume in infants influences the volume of
distribution of pipecuronium in a way similar to that of
other muscle relaxants. 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 sen-
sitivity 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 pi-
pecuronium 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 in-
fants compared with children and adolescents, 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 and \( d \)-tubocurarine 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.

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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