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Pipecuronium-induced Neuromuscular Blockade during Nitrous Oxide-Fentanyl, Isoflurane, and Halothane Anesthesia in Adults and Children

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To determine in adults and children the dose-response relationship and the duration of action of pipecuronium bromide during fentanyl-nitrous oxide (N_2O), isoflurane, and halothane anesthesia, the authors studied 30 ASA Physical Status 1–2 adults (age: 16–55 yr) and 30 ASA Physical Status 1–2 children (age: 1.7–11.5 yr) during minor elective surgery. Patients were anesthetized with N_2O/O_2 (60:40) supplemented with either fentanyl (4 μg/kg), or isoflurane (adults, 0.9%; children, 1.2%), or halothane (adults, 0.6%; children, 0.7%). Neuromuscular (NM) blockade was measured by electromyography. Incremental iv doses of pipecuronium were administered to determine the cumulative dose-response relationship of pipecuronium until a 95% twitch depression (ED_{95}) had been obtained. In adults, ED_{50} was 31.7 ± 2.9 μg/kg (mean ± SE) during fentanyl-N_2O/O_2, reduced by isoflurane (18.0 ± 4.8 μg/kg, $P < 0.05$) but not by halothane (25.0 ± 2.6 μg/kg, NS). ED_{95} was 59.4 ± 5.4 μg/kg during fentanyl-N_2O/O_2, reduced by isoflurane (42.3 ± 2.5 μg/kg, $P < 0.05$), but not by halothane (49.7 ± 3.1 μg/kg, NS). In children, ED_{50} was 43.9 ± 4.7 μg/kg during fentanyl-N_2O/O_2, reduced by isoflurane (23.1 ± 1.6 μg/kg, $P < 0.05$), and halothane (33.2 ± 3.2 μg/kg, $P < 0.05$). ED_{95} was 79.3 ± 9.8 μg/kg during fentanyl-N_2O/O_2, and reduced by isoflurane (49.1 ± 3.1 μg/kg, $P < 0.05$), but not by halothane (62.5 ± 7.3 μg/kg, NS). Comparison between adults and children reveals no statistically significant differences, except for ED_{50} during fentanyl-N_2O/O_2 anesthesia which was increased in children. During fentanyl-N_2O/O_2 anesthesia, the time from the initial maximal blockade to 75% twitch height recovery (D_{75}) was 78.0 ± 9.1 min in adults and 61.8 ± 7.8 min in children (NS). D_{75} was not significantly changed during isoflurane and halothane anesthesia, neither in adults nor in children. The authors conclude that isoflurane but not halothane enhances the intensity of pipecuronium-induced NM blockade, both in adults and children. There is no significant difference in dose requirement for pipecuronium between children and adults. Finally, isoflurane and halothane do not change the duration of the pipecuronium-induced neuromuscular blockade neither in adults nor in children. (Key words: Age factors: adults; children. Analgesics, opioid: fentanyl. Anesthetics, volatile: halothane; isoflurane. Neuromuscular relaxants: pipecuronium bromide. Potency, anesthetics: ED_{50}; ED_{95}.)

PIPECURONIUM BROMIDE is a new long-acting nondepolarizing steroidal muscle relaxant that has been found to have a neuromuscular (NM) blocking action similar to pancuronium in young and middle aged patients.[1] A recent report indicates that the ED_{50} and ED_{90} (effective doses causing 50% and 90% NM depression, respectively) of pipecuronium is similar in the young adult patients and in the geriatric population during fentanyl-nitrous oxide/oxygen (N_2O/O_2) anesthesia.[2] Comparative data between children and adults are lacking, as well as data on the influence of inhaled anesthetic agents on pipecuronium-induced NM blockade. The purposes of the present study were, first, to examine the dose-response relationship of pipecuronium in adults and children during fentanyl-N_2O/O_2, isoflurane-N_2O/O_2, and halothane-N_2O/O_2 anesthesia; second, to determine the interactions between these inhaled anesthetic agents and pipecuronium on the NM blockade; and, third, to compare NM variables between the two age groups.

Materials and Methods

We obtained approval from the local ethic committee on human research and informed consent to study 60 ASA Physical Status 1 or 2 patients undergoing minor elective surgery. Two groups of patients were investigated: the first group included 30 adult patients, age 25 ± 12 yr (mean ± SD; range: 16–55 yr), weight 62 ± 12 kg; the second group included 30 children, age 4.8 ± 2.4 years (range: 1.7–11.5 years), weight 18.7 ± 6.2 kg. The patients were randomly assigned to one of the following anesthetic subgroups: N_2O-fentanyl, -isoflurane, or -halothane.

After receiving diazepam (0.15 mg/kg p.o. in adults, or 0.3 mg/kg rectal in children), anesthesia was induced with thiopental 4–5 mg/kg and fentanyl 2 μg/kg iv and was maintained by the administration of N_2O and O_2 (60:40) supplemented with either fentanyl (4 μg/kg) or isoflurane or halothane according to the treatment subgroup (ten patients in each). The end-tidal concentration of the volatile anesthetics (0.75 MAC excluding N_2O) was age adjusted: isoflurane, 0.9% for adults, 1.2% for children; and halothane, 0.6% for adults, 0.7% for children.[3,4] These concentrations were maintained during the entire study. The trachea was intubated using topical anesthesia (lidocaine 4%), without muscle relaxant. A multiple gas analyzer (Capnomac®, Datex Instrumentarium Corpo-

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ration, Helsinki) was connected to the endotracheal tube to continuously measure the end-tidal CO_2, O_2, N_2O, and halothane or isoflurane concentrations. Ventilation was controlled to keep end-tidal CO_2 between 4.3 and 4.8 vol%. Temperature was maintained between 35.5–37.5° C. NM transmission was measured by electromyography (Relaxograph®, Datex Instrumentarium Corporation, Helsinki), at the left ulnar nerve-hypothenar muscle, using transcutaneous electrodes. This device delivered supramaximal stimuli (0.1 msec 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 (EMG) measurement, the patient's hand was carefully fixed to avoid any displacement of the electrodes. The Relaxograph was recalibrated 2–3 min before the administration of pipecuronium, when a stable anesthetic concentration had been established, after a 30-min period of unchanged end-tidal concentration of the volatile agent. To calculate the degree of NM blockade in percent, all twitch heights were referred to those measured before the first injection of pipecuronium. Incremental iv doses of pipecuronium were given (one 20 μg/kg first dose, followed by 10 μg/kg increments). After each dose, two to three 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 titrated.[5] The time from this point to 25% recovery of twitch height was defined as clinical duration (CD). It does not include the time necessary to obtain maximal NM blockade. The time from 25% to 75% recovery of the twitch height was defined as recovery index (RI). CD and RI together was defined as D_{75} (duration to 75% recovery). The study was ended when the twitch recovered to 75% of the prerelaxant control level. Then, the administration of the volatile agent was stopped. Spontaneous or neostigmine-induced (20 μg/kg) 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 both groups. Regression slopes within and between each age group were tested with a one-way analysis of variance to determine whether they deviated from parallelism. 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}, CD, RI, and D_{75} between each subgroup were made using a one-way analysis of variance followed by a Duncan's multiple comparisons test. An unpaired Student's *t* test was used to compare data between both age groups. Finally, a one-way analysis of variance determined whether significant differences existed between subgroups for age, body weight, rectal temperature, dose of thiopental, or end-tidal P_{CO_2}. For all statistical comparisons, differences were considered as significant if $P < 0.05$.

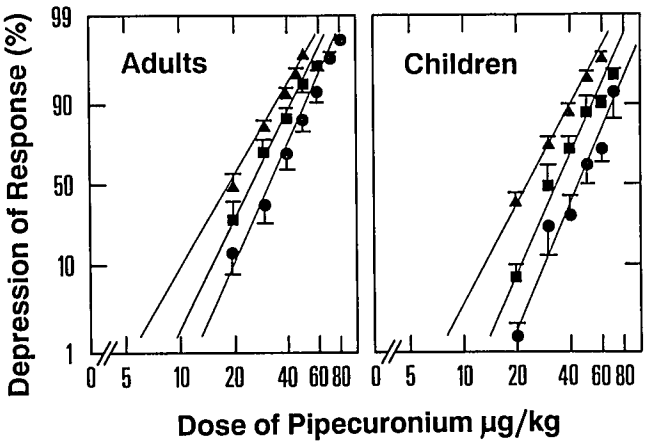

FIG. 1. Dose-response curves for pipecuronium in adults and children during N_2O/O_2 anesthesia supplemented with fentanyl (●), halothane (■), or isoflurane (▲). Data points represent mean ± SE depression of NM response following cumulative doses of pipecuronium; the six regression lines are the mean of ten individual slopes calculated from ED_{50} and ED_{95} values for each anesthetics in adults and children.

Results

For all treatments in both age groups, the mean slopes of the linear regression analysis 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 NM blockade in each group.

In adults, during fentanyl-N_2O/O_2 anesthesia, ED_{50} and ED_{95} were 31.7 ± 2.9 μg/kg (mean ± SE) and 59.4 ± 5.4 μg/kg, respectively. During isoflurane anesthesia, ED_{50} (18.0 ± 4.8 μg/kg) and ED_{95} (42.3 ± 2.5 μg/kg) were both significantly less than with fentanyl-N_2O/O_2. In contrast, ED_{50} and ED_{95} during halothane were not significantly less than those during fentanyl-N_2O/O_2.

In children, during fentanyl-N_2O/O_2 anesthesia, ED_{50} and ED_{95} were 43.9 ± 4.7 μg/kg and 79.3 ± 9.8 μg/kg, respectively. During isoflurane anesthesia, ED_{50} (23.1 ± 1.6 μg/kg) and ED_{95} (49.1 ± 3.1 μg/kg) were both significantly lower than with fentanyl-N_2O/O_2. During halothane anesthesia, ED_{50} was also lower (33.2 ± 3.2 μg/kg, $P < 0.05$) than with fentanyl-N_2O/O_2, whereas ED_{95} was not.

Comparison between adults and children reveals no statistically significant differences in ED_{50}s and ED_{95}s, except for ED_{50} during fentanyl-N_2O/O_2 anesthesia which was increased in children (table 1).

TABLE 1. The Potency of Pipecuronium and the Duration of the Neuromuscular Blockade in Adults and Children during Fentanyl (F), Isoflurane (I), and Halothane (H) Anesthesia

Variables	Adults			Children		
	F	I	H	F	I	H
ED_{50} (μg/kg)	31.7 ± 2.9	18.0 ± 4.8*	25.0 ± 2.6	43.9 ± 4.7†	23.1 ± 1.6*	33.2 ± 3.2*
ED_{95} (μg/kg)	59.4 ± 5.4	42.3 ± 2.5*	49.7 ± 3.1	79.3 ± 9.8	49.1 ± 3.1*	62.5 ± 7.3
Total dose of pipecuronium (μg/kg)	57.5 ± 5.0	41.0 ± 2.1*	46.5 ± 3.2	70.0 ± 6.8	48.0 ± 2.5*	57.0 ± 4.1
CD (min)	45.0 ± 5.0	41.6 ± 4.2	38.5 ± 4.2	38.7 ± 5.9	32.8 ± 3.3	25.7 ± 2.0*†
RI (min)	33.0 ± 5.3	32.3 ± 3.7	24.1 ± 3.0	23.1 ± 1.4	42.9 ± 4.3*	28.6 ± 3.1
D_{75} (min)	78.0 ± 9.1	73.9 ± 7.1	62.6 ± 6.4	61.8 ± 7.8	75.7 ± 7.1	54.3 ± 4.6

Mean ± SE of 10 patients in each group.
CD: clinical duration; RI: recovery index; D_{75}: duration to 75% recovery (see text for details).

* Significantly different from fentanyl ($P < 0.05$).
† Significantly different from the same anesthetic technique in adults ($P < 0.05$).

In adults, mean time necessary to obtain maximal NM blockade was 12.5 ± 0.3 min in the fentanyl group (range: 7–14 min), 10.2 ± 0.3 min in the isoflurane group (range: 7–12 min), and 11.1 ± 0.3 min in the halothane group (range: 7–13 min). In children, this time was 11.0 ± 0.4 min in the fentanyl group (range: 6–18 min), 10.1 ± 0.3 min in the isoflurane group (range: 7–12 min) and 13.3 ± 0.2 min in the halothane group (range: 10–14 min). The time necessary to obtain maximal NM blockade was not statistically different between the groups. In adults, CD was 45.0 ± 5.0 min during fentanyl-N_2O/O_2 anesthesia, and was not significantly affected by isoflurane or by halothane. In children, CD was 38.7 ± 5.9 min during fentanyl-N_2O/O_2 anesthesia and was not significantly affected by isoflurane. In contrast, CD was significantly shorter during halothane compared to fentanyl-N_2O/O_2 anesthesia (25.7 ± 2.0 min *vs.* 38.7 ± 5.9 min, $P < 0.05$). CD was also significantly shorter during halothane anesthesia in children than in adults (25.7 ± 2.0 min *vs.* 38.5 ± 4.2 min, $P < 0.05$). In adults, RI did not significantly change with the different anesthetic agents, whereas in children, RI was significantly prolonged during isoflurane compared to fentanyl-N_2O/O_2 anesthesia (42.9 ± 4.3 min *vs.* 23.1 ± 1.4 min, $P < 0.05$). D_{75} was not significantly different between anesthetic subgroups in any of the age group.

There were no significant differences within the age groups in body weight, age, rectal temperature, dose of thiopental, or end-tidal P_{CO_2} between the three anesthetics. Cardiovascular variables of both groups of patients were stable during the entire investigation.

Discussion

The results of this study show that, when compared to fentanyl-N_2O/O_2 anesthesia, isoflurane but not halothane enhances the NM blocking effect of pipecuronium, and this both in adults and children. However, despite the significant 30% reduction of ED_{95} of pipecuronium by isoflurane, the time necessary to obtain a 75% recovery of twitch height was not reduced in adults or in children. Finally, there was no significant difference in total dose requirement of pipecuronium between children and adults.

To determine the potency of pipecuronium in the two age groups with different anesthetic agents, we used the cumulative dose-response technique, as described by Donlon *et al.*[5] Such a technique may be employed if the dose increments of muscle relaxant are given within a brief period (10–12 min) relative to the duration of action of the muscle relaxant.[5,6] In each patient, the time necessary to construct the dose-response relationship was not greater than 14 min, except in one child of the fentanyl group where it was 18 min, and similar to the one reported by Donlon for d-tubocurarine and pancuronium.[5] ED_{95} of pipecuronium in adults during fentanyl-N_2O/O_2 anesthesia was 59.4 ± 5.4 μg/kg body weight, slightly higher than the one reported with the bolus technique by Boros (54 μg/kg),[7] and Tassonyi (50 μg/kg),[6] using a mechanomyographic method during benzodiazepine-induced fentanyl-N_2O/O_2 anesthesia. Furthermore, Tassonyi found close values of ED_{95} of pipecuronium with both cumulative and bolus doses (55 and 50 μg/kg, respectively).[6] However, Chae *et al.*[8] and Stanley *et al.*[9] reported lower ED_{95} (33 μg/kg and 45 μg/kg, respectively) also using the bolus technique and mechanomyography. Therefore, it is unlikely that the reported variations in ED_{95} are related only to differences in the method of NM measurement and technique of constructing dose-response curves. These variations could rather be explained by geographic disparity and slight differences in anesthetic protocol.

The enhancement of the potency of pipecuronium by isoflurane found in the present study is similar to that observed with atracurium,[10,11] or vecuronium,[12] despite the differences in end-tidal concentration of volatile agents and methodology of measurement of the NM blockade used in these different studies. Miller *et al.* have reported that isoflurane is twofold more effective than halothane in increasing the potency of d-tubocurarine and pancuronium.[13] It has recently been described that volatile an-

esthetics and nondepolarizing muscle relaxants may have synergistic prejunctional actions at the neuromuscular junction.[14] Although all muscle relaxants produce pre- and postjunctional receptor blockade, they may differ in their relative rates of interaction with pre- and postjunctional sites.[15] This fact may explain the variability of the potentiation of muscle relaxants by different volatile anesthetics.

In children, ED_{50} and ED_{95} of pipecuronium were not significantly different than in adults with all anesthetic agents, except ED_{50} during fentanyl-N_2O/O_2 anesthesia which was increased in children. Similar results have been published with vecuronium.[16] However, difference in dose requirement of muscle relaxants related to age have been reported with other muscle relaxants, such as pancuronium,[17] atracurium,[18] or doxacurium.[19] Age-related differences may be explained by an increased volume of distribution of these muscle relaxants in children relative to adults. Indeed, in a study where administration of muscle relaxant was based on body surface area to compensate for the changes in extracellular fluid volume with the age, Cook did not find any difference in d-tubocurarine dose requirement between adults and children.[20] Brandom obtained identical results with atracurium.[18]

To report CD is important for the clinician, since it expresses the duration of the pipecuronium-induced surgical relaxation. However, we have considered in this paragraph D_{75} (*i.e.*, CD and RI together) to better understand the effect of different anesthetic agents on the twitch height recovery. During isoflurane anesthesia, despite a significant 30% reduction of ED_{95} of pipecuronium, D_{75} was not reduced in adults or in children, as compared to fentanyl-N_2O/O_2 anesthesia. This effect of isoflurane could be attributed to the modification of the kinetic properties of the acetylcholine receptor channel at the NM synapse by isoflurane, modification similar to that produced by local anesthetics.[21]

In conclusion, this study demonstrates that isoflurane, in contrast to halothane, increases the neuromuscular potency of pipecuronium, both in adults and children. Dose requirement for pipecuronium is not different between children and adults with any of the anesthetics used. Finally, isoflurane and halothane do not change the duration of the pipecuronium-induced neuromuscular blockade in adults or in children.

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