Title : EFFECTS OF VOLATILE ANESTHETICS AND AGE ON THE DOSE REQUIREMENT AND DURATION OF NEUROMUSCULAR BLOCKADE WITH PIPECURONIUM

Authors : E. Tassonyi, M.D., J.F. Pittet, M.D., J.C. Rouge, M.D., G. Gemperle, M.D., M. Richter, M.D., D.R. Morel, M.D.

Affiliation : Departments of Anesthesiology and Surgery, Hôpital Cantonal Universitaire 1211 Geneva, Switzerland

Introduction: Pipecuronium (PIP) is a new long acting non-depolarizing bisquaternary muscle relaxant which has been found to have a neuromuscular (NM) blocking action similar to pancuronium in young and middle aged patients (1). It appears that the ED_{50} and ED_{90} of PIP is similar in the young and the geriatric population during fentanyl-N_2O anesthesia (2). Comparative data between children and adults are lacking, as well as data on the influence of inhaled anesthetic agents on PIP-induced NM block. Therefore, the purpose of the present study was to examine the dose-response of PIP in adults and children during fentanyl-N_2O, halothane-N_2O, and isoflurane-N_2O anesthesia, to determine the interactions between inhaled agents and PIP on NM blockade, and finally to compare NM variables between the two age groups.

Methods: We obtained approval from the local ethic committee on human research and informed consent to study 58 ASA I or II patients undergoing elective surgery. Two groups of patients were investigated: group A included 30 adult patients, age 25 ± 12 years (mean ± SD), weight 62 ± 12 kg; group B included 28 children: age 4.9 ± 2.5 years, weight 18.9 ± 6.4 kg. In both groups, the patients were randomly assigned to one of the following anesthesia groups: fentanyl-N_2O (F), halothane (H), and isoflurane (I). Each group included 10 patients except for H group in children, in which only 8 patients were investigated. After premedication with diazepam p.o. 0.15 mg/kg in group A or 0.3 mg/kg rectal in group B, anesthesia was induced with thiopental 4-5 mg/kg and fentanyl 2-6 ug/kg i.v. N_2O and O_2 were administered by face mask in a 60:40 ratio and 1 to 2% halothane or isoflurane were administered according to the treatment group. The trachea was intubated using topical anesthesia, without muscle relaxant. A Datex Capnomac gas analyzer was connected to the endotracheal tube for measuring continuously end-tidal CO_2, O_2, N_2O, and halothane or isoflurane concentrations. The end-tidal concentration of the volatile anesthetics was adjusted to 1.35 MAC, which included the 0.6 MAC contribution from N_2O. The resulting end-tidal concentration was 0.5% for halothane, and 0.9% for isoflurane. Ventilation was controlled to keep end-tidal CO_2 between 4.3 to 4.8 vol%. NM transmission was measured by electromyography (Relaxograph, Datex), at the left ulnar nerve-hypotenar muscle, using transcutaneous electrodes. This device delivered supramaximal stimuli of train-of-four at 2 Hz in every 20 sec. The first of the four evoked responses was considered as the twitch height, and the maximum percentage of this response was referred to as peak effect. Every patient was his own control. After end-tidal anesthetic concentration was stable for 30 min., incremental i.v. doses of PIP were given. After each dose, the twitch response was observed until stable, as judged by recording three consecutive twitches of equal height, before the next incremental dose was given. In this manner, the dose necessary to reach a fixed end-point response, 95 ± 2% suppression of the twitch, was carefully titrated (3). The time from this point to 25% recovery of twitch is referred to as duration 25% (D_{25}), and the time from 25% to 75% recovery of twitch is referred to as recovery index (RI). Using linear regression analysis, we determined the dose-response relationship (peak effect *vs* log dose) for PIP in each group. To compare the potency of PIP between anesthetic groups, we calculated the ED_{50} and ED_{95} (doses causing 50% and 95% depression of twitch, respectively) from the linear regression analysis. Using a one-way analysis of variance followed by a Duncan's test, we compared ED_{50}, ED_{95}, D_{25}, and RI within both age groups. Using an unpaired Student's t-test, we compared the same variables between the corresponding anesthesia groups of adults and children, with differences considered as significant when $P<0.05$.

Results: Results are summarized in Table 1 and illustrated in Fig. 1. Comparing the three anesthetic techniques, ED_{50} and ED_{95} were significantly decreased in both age groups during isoflurane and halothane anesthesia, compared to the fentanyl-N_2O group. In contrast, D_{25} was not significantly affected by the anesthetic techniques. RI was significantly prolonged in children during both isoflurane- and halothane-, compared to fentanyl-N_2O anesthesia, whereas in adults no significant differences in RI were found. Comparing the two age groups, ED_{50} and ED_{95} were significantly lower in adults than in children during fentanyl-N_2O anesthesia, but not during either of the inhalation anesthesia.

Discussion: This study demonstrates that similarly to other non-depolarizing relaxants (4), the NM potency of pipecuronium is increased by isoflurane and halothane, and this, both in adults and in children. During fentanyl-N_2O anesthesia, the requirement of pipecuronium is increased in children as compared to adults, but this age-related difference is no more evident with the use of halothane or isoflurane. However, halothane and isoflurane slowed down the recovery rate of pipecuronium-induced NM blockade in children, resulting in a prolonged residual effect of pipecuronium.

References: 1. Foldes FF, et al. *Anesthesiology* 65: A116, 1986
2. Azad S, et al. *Anesthesiology* 67: A370, 1987
3. Donlon JV Jr, et al. *Anesth Analg* 53: 934-9, 1974
4. Rupp SM, et al. *Anesthesiology* 63: 16-9, 1985

Table 1: The potency and duration of PIP blockade in adults and children during fentanyl (F), halothane (H), and isoflurane (I) anesthesia

Variables	Adults			Children		
	F	H	I	F	H	I
ED_{50} (ug/kg)	29.5 ± 3.6	24.4 ± 2.3	18.4* ± 2.3	42.5** ± 4.9	29.5* ± 1.9	22.2* ± 2.0
ED_{95} (ug/kg)	55.7 ± 4.5	45.5 ± 3.2	40.9 ± 2.6	74.2** ± 7.6	54.3* ± 5.9	45.7* ± 2.4
D_{25} (min)	41.4 ± 5.0	38.6 ± 4.1	41.6 ± 4.2	38.7 ± 5.9	26.6** ± 2.1	52.8 ± 3.3
RI (min)	32.8 ± 5.2	24.1 ± 3.0	32.3 ± 3.7	23.1 ± 1.4	30.8* ± 3.4	42.9* ± 4.3
n	10	10	10	10	8	10

mean ± SE, * significantly different from fentanyl, ** significantly different from adults ($P < 0.05$)

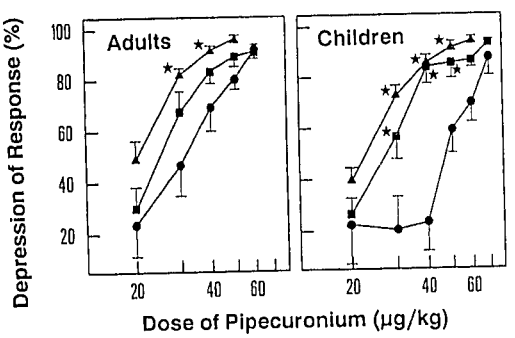

FIGURE 1: Dose response of pipecuronium in adults and children during isoflurane (▲), halothane (■), and fentanyl (●) anesthesia.
* $P<0.05$ different from fentanyl group; $\bar{x}$ ± SE, n = 10.