Enflurane requirement for blocking adrenergic responses to incision in infants and children

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Background: **Enflurane is one of the most commonly used inhaled anesthetics in China, but its requirement to block adrenergic responses after skin incision in pediatric patients is still unknown. This study was to determine the minimum alveolar anesthetic concentration (MAC) of potent inhaled anesthetics required to blunt the adrenergic response to skin incision of enflurane (MAC_{BAR}) in infants and children.**

Methods: **Twenty-eight patients, 10 infants (6-12 months) and 18 young children (1-6 years), were studied. The 18 children were randomly assigned into two groups, with or without fentanyl. Anesthesia was induced with 3 mg/kg propofol and 0.15 mg/kg vecuronium, and maintained with enflurane in 100% oxygen. Fentanyl (3 μg/kg) was given intravenously 5 minutes before incision for the patients of fentanyl group. The "up and down" method (with 0.3 MAC as a step size and 1 MAC as the start dose) was applied to determine MAC_{BAR}. The response was considered positive if the mean arterial pressure (MAP) or heart rate (HR) increased ≥15% after incision. The MAC_{BAR} was calculated as the mean of four independent cross-over responses in each group.**

Results: **MAC_{BAR} of enflurane in children of 1-6 years old was 3.2% (95% CI, 2.8%-3.6%) and was reduced to 2.2% (95% CI, 1.8%-2.5%) by 3 μg/kg fentanyl. In infants of 6-12 months old, the MAC_{BAR} of enflurane was 3.4% (95% CI, 3.0%-3.8%).**

Conclusions: **MAC_{BAR} of enflurane in infants older than 6 months is similar to that in young children. The MAC_{BAR} of enflurane decreases with co-administration of fentanyl in the pediatric population.**

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Key words: **anesthesia; children; enflurane; infants**

Introduction

Adequate anesthesia should do more than render a patient immobile.[1-4] Even if movement is absent, surgical stimulus may cause some potential deleterious effects by inducing neuroendocrine responses.[5-7] That's why the cardiovascular responses to surgery may be an important determinant of patient morbidity.[8-11] Minimum alveolar anesthetic concentration of potent inhaled anesthetics required to blunt the adrenergic responses to skin incision (MAC_{BAR}) is an estimate of inhaled anesthetic requirement which blocks adrenergic responses to surgery. It is the minimum alveolar anesthetic concentration (MAC) that blocks cardiovascular responses to a noxious stimulus (skin incision) in 50% of a population and is greater than the minimum alveolar concentration that prevents movement in response to skin incision.[12] In children, the MAC_{BAR} of sevoflurane, as well as the effect of fentanyl in reducing sevoflurane requirement for blunting cardiovascular responses has been demonstrated recently.[12] Similar data are not available for enflurane, although it remains as one of the most commonly used inhaled anesthetics in China. We therefore set out to determine the MAC_{BAR} of enflurane in pediatric patients with or without fentanyl.

Methods

With the approval of the Fudan University Committee on Human Research, and with the informed consents from their parents or guardians, we studied 10 infants at 6 to 12 months of age (group 1) and 18 children at 1 to 6 years of age. The 18 children were randomly assigned into group 2 and 3. Patients of group 2 received 3 μg/kg fentanyl prior to skin incision but those in group 3 did not. All the subjects were scheduled for elective abdominal surgery and were classified in physical status 1 or 2 according to the American Society of Anesthesiologists (ASA). We excluded subjects with either a hematocrit lower than 30% or a hemoglobin less than 10 g/dl, with a history of cardiovascular or central nervous system diseases,

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or taking drugs with cardiovascular or central nervous system effects.

The operating theater was warmed to approximately 25°C-30°C before arrival of each patient. Patients were fasted 6 hours prior to anesthesia. No patients were pre-medicated but EMLA cream was applied to the planned venous cannulation sites. All patients were monitored with electrocardiogram (ECG) and pulse oximeter (Datex-Ohmeda Cardiocap II CH_2S, Helsinki, Finland) on arrival. After venous cannulation with a 24 guage cannula, an infusion of warmed lactated Ringer's solution was started at a rate of 10 ml/kg per hour. Anesthesia was induced with 3 mg/kg intravenous propofol, and tracheal intubation was facilitated with 0.15 mg/kg intravenous vecuronium. After induction, a 24 guage cannula was placed in the radial artery for arterial blood pressure measurement. Esophageal temperature probes were placed after tracheal intubation. Temperature was maintained at 36.5°C with a warming blanket. All patients were maintained with enflurane in 100% oxygen. The children allocated to the fentanyl group received intravenous 3 μg/kg fentanyl 5 minutes before incision. The same Dräger SA2 anesthetic machine, equipped with a Dräger Vapor 19.3 enflurane vaporizer and a pediatric circle circuit, was used for all subjects. Fresh gas flow was adjusted to 4 L/min. The subjects were ventilated to maintain an end tidal CO_2 concentration from 34 to 36 mmHg. Inspiratory and expiratory carbon dioxide partial pressure, oxygen and enflurane concentration were measured continuously by an infrared spectrometer (Datex-Engstrom Capnomac Ultima, Helsinki, Finland). The gas analyzer was calibrated with a commercial standard (Datex-Engstrom Quick Cal™ Calibration Gas, Helsinki, Finland). Gases were sampled at a rate of 200 ml/min through a 22-gauge needle inserted into the end of the endotracheal tube as close to the patient as possible, and the needle was connected to the spectrometer by a 1-meter length of the narrow-bore nylon tube. Target end tidal enflurane concentrations were maintained for 15 minutes prior to skin incision. Incision was not made until 45 minutes after induction of anesthesia. Heart rate (HR) and mean arterial pressure (MAP), determined by ECG and invasive pressure transducer, were recorded immediately before and after skin incision. The maximal HR and MAP in the first 3 minutes following skin incision were recorded.

Similar to previous investigations,[12-15] the MAC_{BAR} was determined using an "up and down" sequential-allocation technique. In each group, the end tidal enflurane concentration given to the first patient was 1 MAC of his age group based on published data (2.2% for 6-12 months old infants and 2.0% for 1-6 years old children).[16] Then, the response of the preceding patient determined the concentration given to the succeeding one. If the response of the preceding patient was positive (an increase of either HR or MAP ≥15% above the value just before incision during the first 3-minute period after incision), the end tidal concentration given to the next patient was increased by 0.3 MAC. If the response was negative (neither HR nor MAP increased by ≥15% above the value just before incision during the first 3-minute period following incision), the end tidal concentration given to the next patient was decreased by 0.3 MAC. The mean of four independent crossovers of response provided the MAC_{BAR} for each group.

The data of the two groups were analyzed by variance analysis or the Chi-square test. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Version 10.0 statistical software.

Results

The demographic data for each group are listed in the Table. The mean age and weight were significantly different ($P<0.05$) between the infant group and the child groups. There was no significant difference in age or weight between the two child groups. The mean arterial pressure before incision in all groups was not

Table. MAC_{BAR} and clinical characteristics of the patients

	Group 1	Group 2	Group 3
Number of patients	10	8	10
Age	9.0±2.3 mon*	3.5±1.6 y	3.7±1.4 y
Weight (kg)	9.5±1.6*	15.3±1.4	16.6±4.2
Sex ratio (female/male)	6/4	3/5	4/6
Start concentration (%)	2.2	2.0	2.0
Fentanyl dose (μg/kg)	0	3	0
MAP before incision (mmHg)	53±7	54±10	58±6
HR before incision (bpm)	132±7	111±6*	120±9
MAC_{BAR}	3.4%±0.5% (1.5MAC±0.2MAC)	2.2%±0.4% (1.1MAC±0.2MAC)*	3.2%±0.5% (1.6MAC±0.3MAC)
95% CI of MAC_{BAR} (%)	3.0-3.8 (1.4-1.7MAC)	1.8-2.5 (0.9-1.3MAC)*	2.8-3.6 (1.4-1.8MAC)

*: $P<0.05$ compared to other two groups. MAP: mean arterial pressure; HR: heart rate.

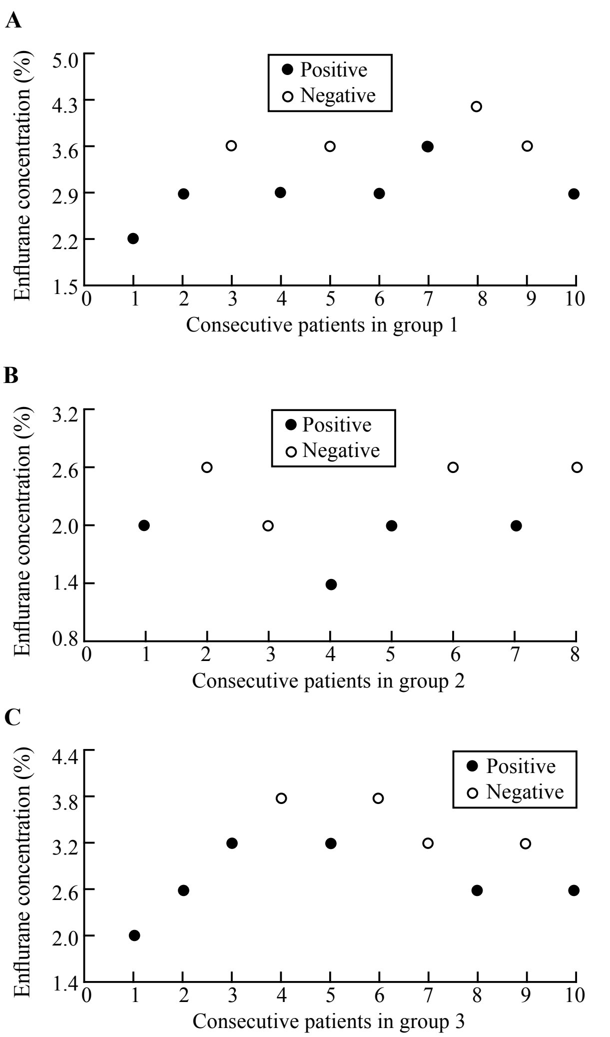

Fig. Cardiovascular responses and consecutive enflurane concentrations in groups 1, 2 and 3.

significantly different.

The MAC_{BAR} is also shown in the Table. For subjects not receiving fentanyl, the MAC_{BAR} was not significantly different in infants compared with children. MAC_{BAR} was significantly less in children receiving fentanyl than in those not receiving fentanyl.

Cardiovascular responses and consecutive enflurane concentrations of the patients are shown in Fig. A-C.

Discussion

We determined the MAC_{BAR} of enflurane in pediatric patients with and without fentanyl. The MAC_{BAR} of enflurane for infants older than 6 months was similar to that of young children. With the analgesic effects of opioid medications as expected, MAC_{BAR} of enflurane decreased with co-administration of fentanyl in pediatric patients.

The results of this study were consistent with those of other studies on some other volatile anesthetics, such as sevoflurane, halothane and isoflurane,[12-14] if we calculated the contribution of nitrous oxide to their MAC_{BAR}. That is to say, the MAC_{BAR} values of different volatile anesthetics are almost the same, or 1.5 times as much as the classic MAC (age-adjusted value) values and 3 μg/kg fentanyl will reduce them significantly.

Roizen and his colleagues[17] could not find a relationship between the higher dose of enflurane and less cardiovascular response after incision in adults. But we did find the relationship in pediatric patients. Although 60% nitrous oxide (0.57 MAC) was added to oxygen when their patients were ventilated, they reported the doses of "enflurane" including contribution of 0.57 MAC of nitrous oxide. According to the Meyer-Overton rule, 0.57 MAC nitrous oxide was as potent as 0.57 MAC of enflurane.[18] Possibly different study populations can partially explain the difference, but important differences existed between the two studies with respect to the design of the studies. Firstly, they used heart rate-blood pressure product (multiple of heart rate multiplied by systolic blood pressure) to measure cardiovascular changes. What we applied was either heart rate or blood pressure. Comparing to heart rate or blood pressure, heart rate-blood pressure product was less sensitive to a given cardiovascular change because of the baroreflex. Secondly, they used thiopental for induction, but we used propofol. Because thiopental acted longer than propofol did, the hemodynamic status altered by the induction agent might be more profound in their study. More vitally, they recorded the cardiovascular changes during a period of 3-10 minutes after incision. What we did was to record the greatest value within the first 3 minutes after incision. According to our observation, the greatest response usually occurred within 3 minutes after incision in the pediatric population. In other words, Roizen and his colleagues probably missed the greatest cardiovascular response to the incision.

Our measurement of enflurane concentration was based on a clinically available technique, namely end-tidal gas analysis. To minimize any inaccuracies caused by the end-tidal technique, we delayed the incision to at least 45 minutes after induction and to at least 15 minutes after steady concentrations of enflurane were achieved. The latter guaranteed at least 95% equilibration between arterial and brain tensions for enflurane according to Eger's assuming.[19] In addition, we sampled end tidal gas from the breathing circuit as close to the patient as possible according to the technique of Badgwell.[20] We excluded not only infants younger than 6 months but also those with cardiopulmonary diseases owing to the limitations of the end-tidal technique in these populations. Derived from clinically available measurement, our data may be more relevant to clinicians at the bedside.

In conclusion, MAC_{BAR} of enflurane for infants older than 6 months is similar to that of young children. The MAC_{BAR} of enflurane decreases with co-administration of fentanyl in the pediatric population.

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Ethical approval: This study was approved by the data inspectorate of China and by the regional committee for medical research ethics.

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