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Minimum Alveolar Concentration Needed to Block Adrenergic Response of Sevoflurane with Nitrous Oxide Varies Depending on the Stimulation Sites in Adult Surgical Patients

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Abstract

Background

We examined whether minimum alveolar anesthetic concentration needed to block adrenergic response (MAC-BAR) of sevoflurane with nitrous oxide (N_2O) varies depending on body surface sites to which noxious stimuli are applied.

Methods

Seventy-seven ASA I adult patients, aged 18-50 years old, were anesthetized with sevoflurane and 66% N_2O in O_2, and their tracheas were intubated. The anesthesia was maintained with 66% N_2O in O_2 plus sevoflurane at predetermined end-tidal concentrations (0.8, 1.1, 1.4, 1.7, 2.0, 2.3, or 2.6%, n = 11 in each concentration) for at least 15 minutes. Heart rate (HR) and non-invasive blood pressure (BP) was recorded at 1-minute interval automatically. As a noxious stimulus, electrical tetanic stimulation with a 15 sec burst of 50 Hz, 0.25 msec square-wave, 55 mA electric current was applied at three different sites; forehead, abdomen, or thigh. A positive cardiovascular response was defined as an increase of either mean BP or HR by more than 15% from the prestimulation value. Logistic regression analysis was used to determine MAC-BAR.

Results

MAC-BAR of sevoflurane with 66% N_2O obtained by stimulating forehead, abdomen, and thigh were 2.01% (95% CI: 1.70-2.57%), 1.71% (1.13-2.74%), and 1.31% (0.77-1.66%), respectively. MAC-BAR on the forehead was significantly higher than that on the thigh.

Conclusion

MAC-BAR of sevoflurane with 66% N_2O varied depending on the body surface sites to which noxious stimuli were applied. These findings support our clinical impression that sensitivities to pain vary among body surface sites, and that anesthetic requirement to stabilize hemodynamic variables vary among surgical sites.

Keywords: Sevoflurane; Nitrous oxide; MAC-BAR; Body region; Tetanic stimulus

Introduction

Minimum alveolar anesthetic concentration needed to block adrenergic response to noxious stimuli (MAC-BAR) is the minimum inhaled anesthetic concentration that prevents an adrenergic response to a noxious stimulus [1], and is considered a valuable measure of the effects of an anesthetic on autonomic pathways in the spinal cord and brain stem [2]. In previous studies which determined MAC-BAR in surgical patients, the stimulated site of the body was not unified among their study protocols. That is to say, abdominal wall [3-5], extremities [4], breast [5] or other regions [6] were incised in those studies. However, from our clinical impression, the sensitivity to pain varies depending on the body surface sites, and anesthetic requirements to stabilize hemodynamic variables vary among surgical sites. Actually Lynn et al. reported that the thigh area required stronger stimulation to elicit pain sensation than the abdomen and the anterior surface of the neck [7].

Therefore, we hypothesized that MAC-BAR determined by stimulating a more sensitive region of the body may be greater than those by stimulating a less sensitive region. In the current study, we examined whether MAC-BAR of sevoflurane in the presence of 66% nitrous oxide (N_2O) varies depending on the sites of the body to which noxious stimuli were applied in adult surgical patients.

Methods and Materials

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients. We studied 77 patients (34 men and 43 women), aged 18-50 years old, who were classified as American Society of Anesthesiologists physical status I, and were scheduled for elective abdominal, gynecological or orthopedic surgeries. Patients with a history of cardiovascular or neurological disorder, those taking drugs affecting cardiovascular or central nervous systems, and those with a history of drug or alcohol abuse were excluded.

All patients fasted for at least 8 h before entering the operating room, and were premedicated with oral famotidine 20 mg 90 min before arrival in the operating room. Every patient had standard lead II of the electrocardiogram monitored (DS-5300, Fukuda Denshi, Tokyo, Japan), and heart rate (HR) was determined from average R-R intervals every 4 s from the monitor. Non-invasive blood pressure cuff (CBM 7000, Colin Co., Tokyo, Japan) and a pulse oximeter probe were applied. A 20-gauge intravenous catheter was inserted for infusion of acetated Ringer's solution during the study.

Anesthesia was induced with 66% N_2O in O_2 plus increasing concentrations of sevoflurane starting with 0.5% up to 5% with a total fresh gas flow of 6 L/min via a face mask. After endotracheal intubation with the aid of intravenous vecuronium 0.1 mg/kg, sevoflurane concentration was decreased to maintain "end-tidal (ET)" concentrations at the predetermined concentration. ET-sevoflurane concentrations studied were 0.8, 1.1, 1.4, 1.7, 2.0, 2.3, or 2.6 in the presence of 66% N_2O in O_2. We used the sealed envelope system to determine the predetermined ET-sevoflurane concentration or stimulation site in each patient. A randomly generated predetermined ET-sevoflurane concentration was indicated on a paper within sealed opaque envelopes. Once a patient has consented to enter a trial an envelope was opened and the patient was then offered the allocated ET-sevoflurane concentration. In each patient, one of randomly predetermined ET-sevoflurane concentration was maintained for at least 15 min before noxious stimuli were applied. ET and inspired concentrations of sevoflurane and N_2O were measured continuously using an infrared multi-gas anesthetic analyzer (Capnomac Ultima, Datex, Helsinki, Finland), which was calibrated before anesthesia for each patient using a standard gas mixture. Gas samples were collected via a Teflon catheter placed at the Y-connector. Ventilation was mechanically controlled to maintain ET partial pressure of carbon dioxide at 35-40 mmHg. Bladder temperature was measured and maintained at more than 36.5°C.

As a noxious stimulus, electrical tetanic stimulation with a 15 sec burst of 50 Hz, 0.25 msec square-wave, 55 mA electric current from a peripheral nerve stimulator (NS-3A, Life-Tech, Inc, Houston, TX, USA) was applied. The electrodes for stimulation were metal bars with the globular heads 2.5 cm apart each other, and were touched to the skin at three different sites of the body; forehead (just above the eyebrow of either one), abdomen (the midpoint of the xiphoid process and the umbilicus), or thigh (the midpoint of the front thigh). The order of stimulation at three different sites was also determined by the sealed envelope system. After a stable hemodynamic state was obtained following 15-min equilibration period, pre-stimulation systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were recorded. Then, a tetanic stimulus was applied to one of the stimulation sites described above. SBP/DBP and HR were recorded at 1-min intervals over the first 3 min after the stimulation. Maximum values of SBP/DBP and HR after the stimulation within 2 min were recorded. Mean blood pressure (MBP) was calculated using SBP and DBP values with the following formula: MBP = DBP + (SBP – DBP)/3. A positive cardiovascular response to a noxious stimulus was defined as an increase of either MBP or HR by more than 15% compared with the prestimulation values. The next stimulus was applied to one of other sites at least 5 min after the adjacent stimulation with confirming both SBP and HR returned to prestimulation values ± 3%, and the same measurements were repeated up to three times for three stimulation sites in each patient. When we did not have much time for the second or third stimulation because of clinical situation, the measurement ended with the first or second stimulation.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). To determine MAC-BAR for each stimulation site, logistic regression curve was obtained from probability of negative responses for each ET-sevoflurane concentration (JMP 8.0.1, SAS Institute Inc, Cary, NC, USA). MAC-BAR was determined as the effective dose 50 (ED50: the dose required for desired effect in 50% of the population exposed to it). We also calculated the effective dose 95 (ED95: the dose required for desired effect in 95% of the population exposed to it).

Results

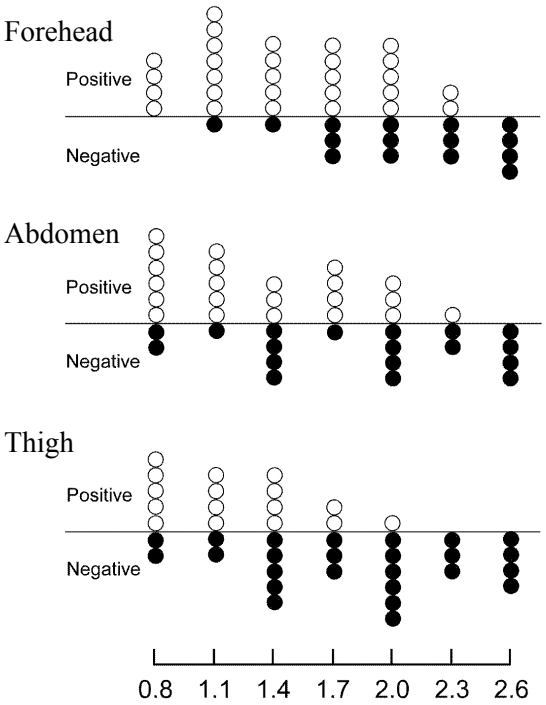
The average age, height, and weight were 32 ± 10 years, 159 ± 5 cm, and 55 ± 6 kg, respectively. The numbers of the enrolled patients for each ET-sevoflurane concentration were 11. The numbers of the enrolled patients for each stimulation site were 43 for forehead, 40 for abdomen, and 41 for thigh, respectively. Figure 1 shows each patient's response to noxious stimuli in each stimulation site.

The logistic regression curves were shown in Figure 2. MAC-BAR of sevoflurane in the presence of 66% N_2O on the forehead, abdomen, and thigh were 2.01% (95% confidence intervals: 1.70-2.57%), 1.71% (1.13-2.74%), and 1.31% (0.77-1.66%), respectively. Based on the fact that 95% confidence intervals were not overlapping each other, MAC-BAR on the forehead was significantly larger than MAC-BAR on the thigh. There was no significant difference between the MAC-BAR on the forehead and on the abdomen. ED95 on the forehead, abdomen and thigh obtained from the logistic regression curves were 3.11% (95% confidence intervals: 2.56-5.71%), 3.52% (2.59-12.2%), and 2.48% (1.98-4.96%), respectively. There was no significant difference in ED95 among the three stimulation sites.

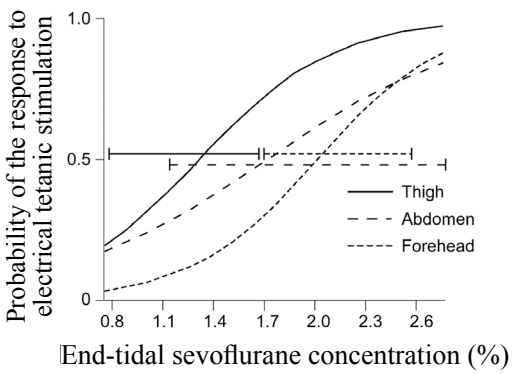
Discussion

The main finding of the current study is that MAC-BAR of sevoflurane in the presence of 66% N_2O varied depending on the body surface sites to which noxious stimuli were applied in adult surgical patients. MAC-BAR on the forehead was significantly higher than that on the thigh. In other words, the result revealed that forehead was more sensitive to electrical tetanic stimulation than thigh under sevoflurane-N_2O anesthesia.

Our current results are clinically important since the results support our empirical impression that sensitivity to pain varies according to body surface sites, and that anesthetic requirement to stabilize hemodynamic variables vary among surgical sites. As stated before, Lynn et al. reported that the thigh was less sensitive for heat, cold, and sharp prick pain than the anterior surface of the neck and the abdomen [7]. Furthermore, there is a report that the face area had a greater sensitivity to heat and cold pain compared to leg and dorsum of the foot [8]. Our current results are consistent with these previous studies. From our current results, due to the MAC-BAR of sevoflurane on the forehead is higher than that on the thigh, in order to obtain a stable hemodynamics, a higher sevoflurane concentration is needed to depress adrenergic response when surgery is performed in the area of forehead compared to in the thigh.



Individual patient's responses to electrical tetanic stimulation at each end-tidal sevoflurane concentration in each stimulation site. Open circles represent each patient who showed the positive responses (an increase of either mean blood pressure or heart rate by more than 15%) to stimulation, whereas closed circles represent each patient who showed the negative responses.



Logistic regression curves derived from end-tidal sevoflurane concentrations and probabilities of no response to electrical tetanic stimulation at three different stimulation sites. Horizontal bars represent 95% confidence intervals of ED50 (Effective Dose 50, MAC-BAR) in each stimulation sites. MAC-BAR on the forehead was significantly higher than that on the thigh.

MAC-BAR of sevoflurane with N_2O has been reported previously. MAC-BAR of sevoflurane were 2.58% with 60% N_2O (skin incision on abdomen) [3], 2.52% with 66% N_2O (skin incision on abdomen, extremities, or other body surface) [4], 2.58 MAC with 0.7 MAC N_2O (skin incision on abdomen or breast) [5], and they were considerably greater than the MAC-BAR on the forehead in our study. Such discrepancy is likely to be due to the difference in types of noxious stimulus. A skin incision was used in these previous studies instead of electrical tetanic stimulation. Electrical tetanic stimulation has already been used to determine MAC of inhaled anesthetics [9-13]. Advantages of electrical tetanic stimulation were ease of performance, repeatability, harmlessness, and reproducibility [14], though an electrical tetanic stimulation may be less intense than a skin incision [15]. We used electrical tetanic stimulation in order to apply noxious stimulus more than once to the same patients. To confirm our empirical impression regarding the differences in pain sensitivity and anesthetic requirement among body sites in a more clinical settings, and to reveal more practical MAC-BARs at each body surface sites, it's worthwhile to determine the MAC-BARs using skin incision as a noxious stimulus in the future.

In the current study, any opioid was not administered during the study period. It is well known that opioid, such as fentanyl, decreases MAC and MAC-BAR of inhaled anesthetics [4]. Therefore, opioid may have decreased MAC-BAR to a large extent if we used in this study. Because our primary goal of this study was to investigate whether MAC-BAR varies depending on the stimulation sites, we avoided using opioid so as to clearly demonstrate difference in MAC-BAR among the stimulation sites. However, because there may be some who argue that there is an ethical issue, we should have considered the use of opioid.

In studies using Dixon's method, about 7-8 patients were the most in each concentration to get 6 to 7 independent crossovers of response (positive-negative) [16]. We could not use Dixon's up-down methods because multiple stimuli were applied to each patient. Therefore, we enrolled 11 patients to include much enough patients in each concentration even if we cannot apply tetanic stimulus to 1 or 2 of 3 stimulation sites (forehead, abdomen, or thigh) in limited time of clinical situation.

There are several limitations in the current study. First, an adaptation to stimulation may have elicited smaller hemodynamic responses to second or thereafter tetanic stimulations. However, we believe that the effect of an adaptation must be minimal, because tetanic stimulation to each site was done in random order in every patient. Second, we should have measured the sevoflurane concentration by gas chromatograph instead of an infrared multi-gas anesthetic analyzer to maximize the accuracy of sevoflurane concentration. However, it was impossible because of the limitations of facilities in our hospital.

In conclusion, the current study demonstrated that MAC-BAR of sevoflurane in the presence of 66% N_2O varied depending on the body surface sites to which noxious stimuli were applied. According to our results, a higher sevoflurane concentration is needed to depress adrenergic response when surgery is performed in the area of forehead compared to in the area of thigh in order to obtain a stable hemodynamics. These findings support our clinical impression that sensitivities to pain vary among body surface sites, and that anesthetic requirement to stabilize hemodynamic variables vary among surgical sites.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Acknowledgements

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