The Effect of Fentanyl on Sevoflurane Requirements for Somatic and Sympathetic Responses to Surgical Incision

Takasumi Katoh, M.D.,* Syunji Kobayashi, M.D.,† Akira Suzuki, M.D.,† Tatsuaki Iwamoto, M.D.,‡ Hiromichi Bito, M.D.,* Kazuyuki Ikeda, M.D., F.R.C.A.§

Background: Fentanyl produces a reduction in the minimum alveolar concentration (MAC) of isoflurane and desflurane needed to blockade adrenergic response (BAR) to surgical incision in 50% of patients (MAC-BAR). MAC-BAR of sevoflurane and the reduction in MAC-BAR of sevoflurane by fentanyl have not been described previously. The purpose of this study was to determine the MAC and MAC-BAR reduction of sevoflurane by fentanyl with and without nitrous oxide (N₂O).

Methods: Two hundred twenty-six patients were randomly assigned to one of two groups: a sevoflurane group and a sevoflurane/N₂O group. Patients in each group were randomly assigned to one of five different fentanyl concentration subgroups. Patients were anesthetized with sevoflurane and fentanyl in the sevoflurane group and with sevoflurane, fentanyl, and N₂O (66 vol%) in the sevoflurane/N₂O group. Somatic and sympathetic responses to surgical incision were observed for MAC and MAC-BAR assessment at predetermined concentrations of sevoflurane.

Results: Fentanyl produced an initial steep reduction in the MAC and MAC-BAR of sevoflurane, with 3 ng/ml resulting in a 61% reduction in MAC and an 83% reduction in MAC-BAR. A ceiling effect was observed for MAC and MAC-BAR, with 6 ng/ml fentanyl providing only an additional 13% and 9% reduction in MAC and MAC-BAR, respectively. In the presence of 66 vol% N₂O, MAC and MAC-BAR of sevoflurane were reduced with increasing concentrations of fentanyl. A ceiling effect was not observed for reduction in MAC and MAC-BAR in the presence of N₂O.

Conclusions: MAC and MAC-BAR decreased similarly with increasing concentrations of fentanyl in plasma, showing an initial steep reduction followed by a ceiling effect. In the presence of N₂O, MAC and MAC-BAR decreased similarly but did not exhibit a ceiling effect. (Key words: Blood pressure; heart rate; minimum alveolar concentration; nitrous oxide.)

SOMATIC and sympathetic responses to surgical incision are clinical end points for assessing depth of anesthesia. Patient movement is easily defined and observed, and, in its absence, recall of intraoperative events by nonanesthetized patients is rare. In clinical anesthesia, however, anesthesiologists do not always use the movement/no movement end point to determine the adequacy of anesthesia. The end points used in anesthetizing surgical patients are usually hemodynamic parameters, such as mean arterial blood pressure (MAP) and heart rate. We previously reported that fentanyl reduced requirements for sevoflurane for loss of consciousness and surgical incision, but the reduction modes were not comparable in the two end points. Although fentanyl is known to decrease sympathetic responses to noxious stimuli, the reduction in the requirement for sevoflurane for blunting sympathetic responses after surgical incision by fentanyl is unknown. The reduction modes for sympathetic responses may not be comparable to those for loss of consciousness or somatic responses. This study was designed to investigate the interaction of fentanyl with the requirement for sevoflurane for loss of somatic and sympathetic responses to surgical incision, in the presence and absence of nitrous oxide (N₂O).

Materials and Methods

Subjects

After securing approval from the District Ethics Committee of Hamamatsu University Hospital and obtaining informed consent from each patient, we studied 226 patients of both sexes, all of whom were between 20 and 50 yr old, had been classified as American Society of Anesthesiologists physical status 1, and were scheduled
MAC AND MAC-BAR REDUCTION OF SEVOFLURANE BY FENTANYL

for elective surgery of the abdomen, extremities, or body surface. No patients were scheduled to receive limited incisions (e.g., laparoscopy). Exclusion criteria were history of cardiac, pulmonary, or renal disease; history of esophageal reflux or hiatal hernia; drug or alcohol abuse; significant obesity (body mass index > 30); current use of any vasoactive medications (long-term use of antihypertensive agents, vasoconstrictors, or vasodilators); current use of any medications known to affect minimum alveolar concentration (MAC) or sympathetic responses; and contraindication for inhalational induction. Local anesthetic agents and epinephrine were not used for subcutaneous infiltration before incision in any patient.

Study Design

Patients initially were randomly assigned to one of two groups: a sevoflurane group (n = 96) or a sevoflurane/N₂O group (n = 86). Each group was further divided into five fentanyl concentration subgroups according to a randomization scheme (figs. 1A and 1B). Subgroup 1 received no fentanyl, whereas subgroups 2, 3, 4, and 5 received predicted target concentrations in plasma of 1.0, 2.0, 4.0, and 8.0 ng/ml, respectively. An additional 44 patients were added at the conclusion of the study to define more clearly the MAC of sevoflurane needed to blockade adrenergic response (BAR) to surgical incision in 50% of patients (MAC-BAR) reduction at concentrations of fentanyl of 0 (n = 22), 4 (n = 10), and 8 (n = 4) ng/ml in the sevoflurane group and 0 ng/ml (n = 8) in the sevoflurane/N₂O group. Patients were anesthetized with sevoflurane and fentanyl in the sevoflurane group and with sevoflurane, fentanyl, and 66 vol% N₂O in the sevoflurane/N₂O group. During surgical incision, each patient was monitored for somatic and sympathetic response. All patients were monitored for somatic response for 60 s after surgical incision; coughing, chewing, or swallowing was not considered positive purposeful movement. A positive sympathetic response was defined as a more than 15% increase in heart rate or MAP over the preincision value. Heart rate and MAP determined by oscillometry (CBM 7000; Colin Co., Tokyo, Japan) were recorded 2 and 1 min before incision, at incision, and at 1-min intervals over the first 5 min after incision. The preincision value was defined as the mean value of the 2- and 1-min measurements.

Infusion of Fentanyl

Before induction of anesthesia, a venous catheter was inserted into one arm for administration of drug, and another venous catheter was inserted into the other arm for blood sampling. Fentanyl was administered using a pharmacokinetic model-driven computer-assisted continuous infusion device capable of administering intravenous drugs to achieve constant target concentrations in plasma. The device consisted of an NEC 9801 laptop computer (Tokyo, Japan) and an ATOM 1235 Infusion Pump (ATOM, Tokyo, Japan). The pharmacokinetic parameters used in computer-assisted continuous infusion for administration of fentanyl were based on a study by Shafer et al.6 To ensure rapid equilibration between the plasma and effect compartment, infusion was adjusted for the first 6 min to achieve a concentration of fentanyl twice the predetermined target concentration according to the half-time (kₑₑₑ) for equilibration between blood and brain (6.6 min).7 Thereafter, the target concentration of fentanyl was returned to the value for the patient's subgroup.

Fig. 1. End-tidal concentrations of sevoflurane for each patient in each of the predicted fentanyl concentration groups in the sevoflurane group (A) and the sevoflurane/nitrous oxide group (B).
Management of Anesthesia

Patients fasted for approximately 8 h before surgery, were routinely monitored, and received no premedication. Anesthesia was induced with sevoflurane and oxygen, first during spontaneous ventilation and then during manual ventilation. In the sevoflurane/N₂O group, N₂O also was used for induction of anesthesia. Fentanyl was infused according to the predetermined concentration for the patient’s subgroup. Vecuronium was administered at 0.02 mg/kg for precurarization. Paralysis was then induced by succinylcholine (1.5 mg/kg), followed by tracheal intubation. Immediately after tracheal intubation, the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to the predetermined randomization scheme (figs. 1A and 1B). In the sevoflurane/N₂O group, N₂O was administered at an end-tidal concentration of 66 vol%. End-tidal concentrations of sevoflurane, N₂O, and carbon dioxide were measured continuously using an infrared multigas 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 catheter placed at the tracheal end of the endotracheal tube. Patients’ lungs were mechanically ventilated to normocapnia, and body temperature was maintained at more than 35.5°C (range, 36.2 to 35.5°C). After maintaining the end-tidal concentration constant for more than 20 min, blood samples were taken 5 min before and within 30 s after incision to measure the concentration of fentanyl in plasma. The mean time from starting infusion of fentanyl to surgical incision was 50 min (range, 45 to 75 min). If hypotension occurred (< 50 mmHg in MAP), the patient’s blood pressure was restored by a combination of fluid administration and ephedrine, and the patient was excluded from the analysis. We confirmed that patients could not respond to verbal command just before surgical incision. When a patient responded to the command, blood was taken as a postincision sample, and the concentration of sevoflurane was increased so the patient could not respond to the verbal command. Such patients were excluded from the data analysis. If patients did not move in response to incision, residual neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the train-of-four ratio returned to almost 1.0 and that the first-twitch height at skin incision was not different from that recorded before administration of a muscle relaxant. More than 40 min elapsed between the administration of a muscle relaxant and the skin incision. All patients were judged to have recovered from the paralysis.

Analysis of Blood Sample

Blood samples were allowed to clot for 15 min, and then the serum was separated and frozen at –70°C until assayed. The concentration of fentanyl was determined using a previously described radioimmunoassay technique.** The assay was linear over the concentrations measured with a lower detection limit of 0.13 ng/ml and a coefficient of variation of < 10%.

The pre- and postincision concentrations of fentanyl were compared to ensure that a steady concentration was being maintained. Only paired samples that had concentrations within ± 35% of each other were included in the statistical analysis. Actual differences in concentrations of fentanyl between preincision and postincision samples used for data analysis ranged from –23.0% to +29.7%. From these paired samples, only the postincision concentrations of fentanyl were used for analysis.

Statistical Analysis

The technique used to determine MAC-BAR and MAC of sevoflurane in the absence of fentanyl was adapted from the method described by Waud.** We estimated the reduction of sevoflurane MAC-BAR and MAC by fentanyl using a multiple independent variable, logistic regression model with the natural logs of the drug concentration as predictor variables.** In addition, the product of the log of the drug concentrations was included in the model to determine an interaction effect (deviation from linearity). The concentration of sevoflurane required to prevent response to surgical incision in 95% of patients (MAC₉₅) and the concentrations required to prevent sympathetic responses to surgical incision in 95% of patients (MAC-BAR₉₅) also were determined.

Results

Of the 132 patients in the sevoflurane group who enrolled in this study, 2 were excluded because their concentrations of fentanyl in plasma measured 5 min before incision were not within ± 35% of the sample obtained just after the incision. Eight patients who required ephedrine because of hypotension also were excluded. In addition, four patients were excluded because they were judged as being awake just before skin incision. The concentrations of sevoflurane and fentanyl
MAC AND MAC-BAR REDUCTION OF SEVOFLURANE BY FENTANYL

Fig. 2. (A) Reduction by increasing concentrations of fentanyl of the concentration of sevoflurane at which 50% or 95% of patients did not move at skin incision (MAC or MAC\textsubscript{95}, respectively). (B) Reduction of concentration of sevoflurane by increasing concentrations of fentanyl at which 50% or 95% of patients did not show sympathetic responses (an increase in heart rate or mean arterial pressure >15%) at skin incision (MAC-BAR or MAC-BAR\textsubscript{95}, respectively).

measured in these patients are illustrated in figure 2A. Thus, the results of 118 patients (53 men and 65 women) were analyzed. Their average ± SD (range) age was 41.6 ± 9.4 yr (20 to 50 yr), and weight was 55.0 ± 12.4 kg (42 to 84 kg). Of the 94 patients in the sevoflurane/N\textsubscript{2}O group who enrolled in this study, 2 were excluded because their concentrations of fentanyl in plasma measured 5 min before incision were not within ±35% of the sample obtained just after the incision. One patient who required ephedrine because of hypotension also was excluded. Thus, the results of 91 patients (42 men and 49 women) were analyzed. Their average ± SD (range) age was 42.7 ± 10.7 yr (20 to 50 yr), and average weight was 57.2 ± 14.2 kg (43 to 76 kg). There was no difference in age or body weight of the patients between the two groups. The postincision concentrations of fentanyl, which were used in the statistical analyses, ranged from 0.00 to 9.66 ng/ml. No patients recalled any event occurring during this study at the postoperative interview.

Of the 132 patients in the sevoflurane group, 48 did not receive fentanyl. The MAC determined from the patients not receiving fentanyl was 1.85 vol% (95% confidence interval [CI], 1.67–2.03). MAC\textsubscript{95} was 2.28 vol%. The MAC for sevoflurane alone determined from patients receiving and those not receiving fentanyl was 1.76 vol%. The MAC was markedly reduced by increasing concentrations of fentanyl. The reduction of MAC was approximately 37% and 61% at concentrations of fentanyl of 1 and 3 ng/ml, respectively. A ceiling effect was observed, with 6 ng/ml providing only a 13% further reduction in MAC. A 50% reduction in MAC was produced by 1.8 ng/ml fentanyl (fig. 2A).

MAC-BAR determined from the patients not receiving fentanyl was 4.15 vol% (95% CI, 3.40–4.89 vol%) or 2.24 MAC. MAC-BAR\textsubscript{95} was 6.26 vol%. The MAC-BAR for sevoflurane alone determined from patients receiving and those not receiving fentanyl was 4.12 vol%. MAC-BAR was markedly reduced with increasing concentrations of fentanyl. The reduction of MAC-BAR was approximately 57% and 83% at concentrations of fentanyl of 1 and 3 ng/ml, respectively. A 50% reduction in MAC-BAR was produced by 0.78 ng/ml fentanyl, and a ceiling effect was observed, with 6 ng/ml providing only a 9% further reduction in MAC-BAR (fig. 2B). Although MAC-BAR was 2.30 vol% higher than MAC in the absence of fentanyl, the difference decreased rapidly with increasing concentrations of fentanyl. Beyond 3.1 ng/ml, MAC-BAR was lower than MAC with a small difference: less than 0.2 vol%.

In the presence of 66 vol% N\textsubscript{2}O, the MAC determined from the patients not receiving fentanyl was 0.79 vol% (95% CI, 0.64–0.93). MAC\textsubscript{95} was 1.10 vol%. The reduction in MAC of sevoflurane by fentanyl in the presence of 66 vol% N\textsubscript{2}O is presented in figure 3A. The concentration of fentanyl in plasma capable of reducing MAC of sevoflurane by 99% was 3.9 ng/ml. In the presence of 66 vol% N\textsubscript{2}O, the MAC-BAR determined from the patients not receiving fentanyl was 2.52 vol% (95% CI, 2.30–2.74), or 1.32 MAC. MAC\textsubscript{95} was 2.98 vol%. The MAC-BAR for sevoflurane with N\textsubscript{2}O determined from patients receiving and those not receiving fentanyl was 2.45 vol%. The reduction in the MAC-BAR of sevoflurane by fenta-
which was the highest concentration administered in the current study, change in blood pressure or heart rate in response to skin incision were not suppressed in all patients. We did not administer higher concentrations of sevoflurane, which could suppress blood pressure and heart rate responses in all patients, because of the risk of excessive hypotension. At concentrations higher than 3.6 vol%, 7 of 21 patients required ephedrine because of hypotension. Similar hemodynamic instability at high anesthetic concentrations in the absence of surgical stimulation has been reported during sevoflurane- and isoflurane-induced anesthesia. In the determination of MAC-BAR, elimination of patients with hypotension may have constituted a bias in the current study. It is possible that this subgroup of patients would have a greater or lesser response than the remainder of the population. In previous human and animal studies, isoflurane did not prevent cardiovascular responses at clinical concentrations (1 to 2 MAC) when given as a sole agent, a finding that agrees with that of the current study. MAC-BAR determined in goats when isoflurane was administered alone was 2.65 MAC, which is in agreement with our finding for sevoflurane. The clinical implication of these findings is that sevoflurane would be safer and more effective when used with another agent rather than as a sole agent.

In the current study, we demonstrated that fentanyl produces a steep decrease in the MAC-BAR of sevoflurane in the absence of N₂O. This decrease then reaches a plateau with minimal further reductions. This rapid flattening of the curve in the plot of concentration of fentanyl in plasma versus MAC-BAR of sevoflurane suggests that a ceiling effect exists in the action of fentanyl in preventing sympathetic responses at a sevoflurane concentration less than 0.4 vol%. We could not test somatic and sympathetic responses to incision at concentrations of sevoflurane less than 0.3 vol% because of awareness. Even if these three patients showed all positive or all negative sympathetic responses, the MAC-BAR reduction curve would not change shape sufficiently to affect the conclusions of the current study.

The MAC of sevoflurane in the presence of 66 vol% N₂O was 0.74 vol%, which was similar to the MAC of sevoflurane determined in our previous study. In the current study, we demonstrated that MAC was reduced less parabolically by the addition of fentanyl in the presence of N₂O than by its addition in the absence of N₂O. When N₂O was present, fentanyl plus N₂O could prevent movement in 50% of patients. Using the current model, we were not able to calculate the concentration

Discussion

The MAC of sevoflurane and the reduction in MAC by fentanyl noted in this study agree with previous studies of sevoflurane, isoflurane, and desflurane. MAC-BAR was determined in patients who did not receive fentanyl as 4.15 vol%. Even at 4.2 vol% sevoflurane,
of fentanyl in plasma that would reduce MAC of sevoflurane by 100%, therefore, we determined the concentration in plasma that would reduce the MAC of sevoflurane by 99% as a substitute for the concentration of drug in plasma for preventing motor response to surgical incision in 50% of patients (Cp₅₀). The predicted Cp₅₀ value (3.9 ng/ml) was close to that determined by Glass et al. (3.26 ml/ml).¹⁶

MAC-BAR determined for sevoflurane in the presence of 66 vol% N₂O in the current study (1.32 MAC) was close to those values determined for desflurane (1.3 MAC) and isoflurane (1.3 MAC) by Daniel et al.⁵ and appeared to be greater than those determined for halothane (0.88 MAC) and enfurane (1.03 MAC) by Roizen et al.¹⁷ The conditions and criteria for the determination of MAC-BAR used in the current study were similar to those used by Daniel et al. but differed from those used by Roizen et al. It is unclear what could account for the difference in MAC-BAR/MAC between these anesthetic agents, but the ratio of MAC-BAR/MAC among volatile anesthetic agents may not be uniform, like the MAC-awake/MAC ratio.¹⁸

MAC-BAR was reduced less parabolically by fentanyl in the presence of N₂O than in the absence of N₂O, and no ceiling effect was observed. Because 66 vol% N₂O provides a significant amount of anesthesia in humans, adding fentanyl would blunt hemodynamic responses (thereby achieving MAC-BAR without any other concomitant anesthetic agent).¹⁶ These effects could account for the difference in the MAC-BAR reduction curve between the sevoflurane and sevoflurane/N₂O groups. This observation does not agree with Daniel et al., who showed that fentanyl given at 1.5 μg/kg decreases MAC-BAR for isoflurane and desflurane with no further decrease produced by 3 μg/kg fentanyl. They administered 1.5 and 3.0 μg/kg fentanyl by a bolus injection 5 min before incision, whereas we maintained a constant concentration in plasma for 45 min or more before incision. Although they did not measure concentrations of fentanyl in plasma 5 min after 3.0 μg/kg fentanyl was administered, the effect-site concentration of fentanyl calculated with the pharmacokinetic parameters used by Shafer et al. would be approximately 3.5 ng/ml.⁶ The difference in results might have been a result of this difference in administration. We determined the concentration of fentanyl in plasma that would reduce MAC-BAR of sevoflurane by 99% as a substitute for Cp₅₀-BAR. The predicted Cp₅₀-BAR value (4.4 ng/ml) was similar to that determined by Glass et al. (4.17 ng/ml).¹⁶

With a concentration of fentanyl of 1.5 ng/ml, i.e., a normal analgesic concentration not associated with respiratory depression, and 66 vol% N₂O, the MAC-BAR concentration of sevoflurane is almost equal to its MAC-awake concentration. Thus, anesthesia that inhibits autonomic and somatic responses is achieved with concentrations of sevoflurane and fentanyl that are associated with rapid awakening and yet adequate analgesia during discontinuation of the N₂O. In the absence of N₂O with sevoflurane, the concentration of sevoflurane would have to be doubled (fig. 4), thus significantly increasing recovery time at the end of surgery.

Increases in MAP and heart rate in response to surgical incision usually are considered to be indicators of inadequate anesthesia, but there is not always a good correlation between somatic and hemodynamic responses.¹⁹,²⁰ In the current study, an increase of approximately 15% over the mean preincision values for heart rate or MAP was considered to be a significant sympathetic response. When sevoflurane was administered alone, sympathetic responses were always positive in patients whose somatic responses were positive but were not always negative in patients whose somatic responses were negative. When fentanyl was administered concomitant with sevoflurane, particularly at high concentrations of fentanyl, sympathetic responses were not always positive in patients whose somatic responses were positive and were not always negative in patients whose somatic responses were negative. The absence of a sympathetic response could not be relied on as a good indicator of a lack of somatic response. Sebel et al. reported a similar observation in a multicenter study.²¹
Hug provided that, with the use of opioids, some patients may be completely awake and aware of intraoperative events at times when there is absolutely no change in hemodynamics or any manifestation of increased sympathetic activity; similarly, reflex somatic responses do not necessarily correlate with awakening. Clinicians may use the lack of movement or the lack of hemodynamic response to a surgical stimulus as an indication that anesthetic concentration is sufficient to indicate loss of consciousness. We demonstrated that the difference between MAC and MAC-BAR decreased rapidly with increasing concentrations of fentanyl in plasma in the current study and that MAC-awake did not decrease with increasing concentrations of fentanyl as did MAC or MAC-BAR in the previous study (Fig. 4). These results should alert clinicians to the possibility that the signs commonly used for adequate anesthesia in the absence of an opioid may not persist if even small doses of an opioid are administered, and clinicians need to use the lack of movement and the lack of hemodynamic response to a surgical stimulus as indicators that the anesthetic concentration is sufficient to provide loss of consciousness.

Some animal studies have shown that lack of movement in response to noxious stimuli appears to result from anesthetic action in the spinal cord. The spinal cord also influences the cardiovascular system, e.g., significant cardiovascular responses develop in brain-dead humans subjected to noxious stimuli. A recent study suggests that cardiovascular responses to noxious stimuli may be primarily mediated by subcortical structures, at least in goats. These studies suggest that subcortical structures, including the spinal cord, are important as sites of anesthetic action to prevent motor and cardiovascular response to noxious stimuli, which may partly explain the similarity in shape of MAC and MAC-BAR reduction curves by fentanyl. The initial reduction of MAC-BAR, however, appears to be steeper than that of MAC. This implies that the site of anesthetic blocking action for each may not be the same. Blocking of motor response occurs mainly in the spinal cord rather than in the periphery. Suppression of cardiovascular responses to a noxious stimuli also may occur in the periphery (e.g., heart, sympathetic nerves, blood vessels).

We determined the MAC and MAC-BAR reduction of sevoflurane by constant concentrations of fentanyl in plasma. MAC and MAC-BAR were markedly reduced by low concentrations of fentanyl up to 3 ng/ml. Increasingly higher concentrations in plasma, more than 3 ng/ml, produced little further reduction in MAC and MAC-BAR. Although the reduction curve of MAC-BAR was similar to that of MAC, the initial reduction appears to be steeper in MAC-BAR than in MAC. N2O (66 vol%) reduced MAC and MAC-BAR effectively at any concentration of fentanyl in plasma. Even without sevoflurane, N2O combined with fentanyl suppressed somatic and sympathetic response after skin incision.

The authors thank the staff at Hamamatsu University Hospital for their support and Dr. Shibuani at New York Medical College for encouragement and numerous suggestions.

References

14. Zbinden AM, Petersen FS, Thomson DA. Anesthetic depth de-
MAC AND MAC-BAR REDUCTION OF SEVOFLURANE BY FENTANYL

25. Rampil JJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. ANESTHESIOLOGY 1994; 80:606–10
27. Antognini JF, Kien ND. Potency (minimum alveolar anesthetic concentration) of isoflurane is independent of peripheral anesthetic effects. Anesth Analg 1995; 81:69–72