

The Effects of Fentanyl on Sevoflurane Requirements for Loss of Consciousness and Skin Incision

Takasumi Katoh, M.D.,* Kazuyuki Ikeda, M.D., F.R.C.A.†

Background: Fentanyl produces a minimal reduction in the minimum alveolar concentration of sevoflurane to prevent response to a verbal command in 50% of patients (MAC_{awake}) at low but analgesic plasma concentrations. The reduction in MAC_{awake} , however, is still unknown at higher fentanyl concentrations. The reduction in the MAC of sevoflurane by fentanyl has not been described accurately. The purpose of this study was to determine the MAC_{awake} and MAC reduction of sevoflurane by fentanyl.

Methods: Ninety-two patients were randomly allocated to seven fentanyl concentration groups (target plasma concentrations of 0, 1, 1.5, 3, 6, 10, and 14 ng/ml). Responses to verbal command were observed for MAC_{awake} assessment at predetermined sevoflurane concentrations. Thereafter, in patients whose target fentanyl concentration was 0 to 10 ng/ml, responses to skin incision were observed for MAC assessment at new steady-state sevoflurane concentrations. The reduction in the MAC_{awake} and MAC of sevoflurane by the measured fentanyl concentration was calculated.

Results: There was an initial steep reduction in the MAC of sevoflurane by fentanyl, with 3 ng/ml resulting in a 59% MAC reduction. A ceiling effect was observed, with 10 ng/ml providing only a further 17% reduction in MAC. The initial reduction in MAC_{awake} was not as steep as that in MAC. Fentanyl reduced MAC_{awake} by approximately 24% at a plasma concentration of 3 ng/ml. Although the reduction curve of MAC_{awake} was para-

bolic, no manifest ceiling effect was observed at concentrations administered in the present study.

Conclusions: The reduction in sevoflurane requirements for loss of consciousness and skin incision by fentanyl was determined. Fentanyl reduced both requirements, but the mode of the reduction was not comparable. (Key words: Minimum alveolar concentration; opioids; potency.)

NO anesthetic drug is commonly used alone to provide all the necessary components of general anesthesia. A previous study showed that sevoflurane has a potent hypnotic action, but its analgesic potency is low.¹ The use of fentanyl, which has a potent analgesic effect, in combination with sevoflurane seems reasonable to provide two important components for clinical anesthesia: loss of consciousness and analgesia. It is important to define the interactions among the different anesthetics that may be used in combination for two clinically important endpoints, loss of consciousness and loss of response to skin incision. For the volatile anesthetics, the minimum alveolar concentration (MAC) for achieving a 50% probability of movement in response to a skin incision provides one measure of anesthetic potency. Similarly, the MAC for achieving a 50% probability of no response to a verbal command (MAC_{awake}) provides one measure of hypnotic potency. Previously we showed that the MAC_{awake} of sevoflurane is not markedly reduced by low plasma concentrations (1 ng/ml and 2 ng/ml) of fentanyl.² In contrast, fentanyl has been reported to reduce the MAC of other volatile anesthetics, such as desflurane and isoflurane, even at concentrations less than 1 ng/ml.^{3,4}

This study was designed to determine the reduction of the MAC and MAC_{awake} of sevoflurane by fentanyl.

Materials and Methods

After approval was granted from the ethics committee of our department, informed consent to participate in this study was acquired from all patients. The study

This article is accompanied by an Editorial View. Please see: Glass PSA: Anesthetic drug interactions: An insight into general anesthesia, its mechanism, and dosing strategies. ANESTHESIOLOGY 1998; 88:5-6.

* Assistant Professor.

† Professor and Chairman.

Received from the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. Submitted for publication December 2, 1996. Accepted for publication September 2, 1997.

Address reprint requests to Dr. Katoh: Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-31 Japan. Address electronic mail to: tackatoh@hama-med.ac.jp

MAC REDUCTION OF SEVOFLURANE BY FENTANYL

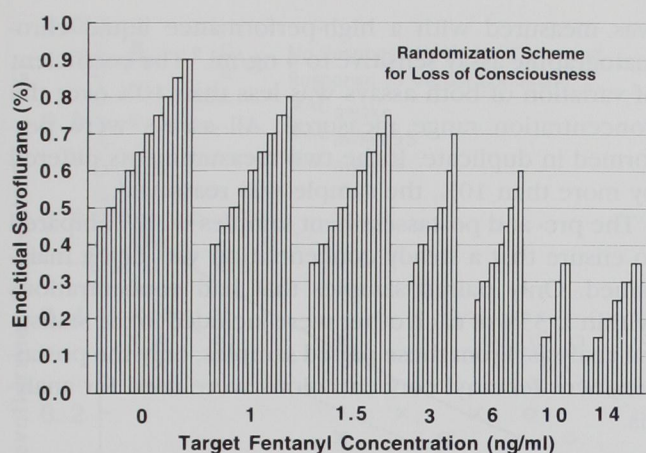


Fig. 1. Assessment of loss of response to verbal command: end-tidal sevoflurane concentrations for each patient in each of the predicted fentanyl concentration groups.

group included 92 patients of both sexes, who were classified as American Society of Anesthesiologists physical status I or II, aged 20–60 yr, and scheduled for elective surgery. The following patients were excluded from the study: (1) those in whom an inhalational induction was contraindicated; (2) those who had any significant cardiovascular respiratory, hepatic, or renal disease; (3) those who were receiving medications known to affect MAC, or MAC_{awake} , or who had a history of alcohol or drug abuse; and (4) those in whom any sudden movement may have been dangerous.

Each of the first 80 patients was initially randomly allocated into one of six different fentanyl concentration groups for MAC_{awake} measurement according to a randomization scheme (fig. 1). Group 1 received no fentanyl, whereas groups 2 to 6 each received predicted target plasma concentrations of 1, 1.5, 3, 6, and 10 ng/ml. An additional group of 12 patients was added at the conclusion of the study to more clearly define the MAC_{awake} reduction at fentanyl concentrations greater than 10 ng/ml. The target concentration of the additional group was 14 ng/ml. The patients fasted for at least 8 h before surgery and received no premedicating drugs. Before induction of anesthesia, a venous catheter was inserted into one arm for drug administration, and another venous catheter was inserted into the other arm for blood sampling. Fentanyl was administered using a pharmacokinetic model-driven, computer-controlled continuous infusion device capable of administering intravenous drugs to achieve constant target plasma concentrations. The computer-controlled continuous infusion device consisted of a NEC 9801 laptop computer

and an ATOM 1235 infusion pump (Tokyo, Japan). The pharmacokinetic parameters used in computer-controlled continuous infusion for fentanyl are based on a study by Shafer *et al.*⁵

Anesthesia was induced with sevoflurane and oxygen first during spontaneous ventilation and then during manual ventilation. Fentanyl was infused according to the predetermined randomization scheme. Vecuronium was administered at 0.02 mg/kg for precurarization. Paralysis was induced by 1.5 mg/kg succinylcholine, which was followed by tracheal intubation. During laryngoscopy, the trachea and larynx were sprayed with 2 mg/kg 4% topical lidocaine to abolish tracheal and laryngeal stimuli created by the endotracheal tube.

Measurement of MAC_{awake}

Immediately after tracheal intubation, the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to a second predetermined randomization scheme (fig. 1). These sevoflurane concentrations were chosen to provide a range that would impart both adequate and inadequate anesthesia at each fentanyl concentration, and they were based on previous data.^{2,6} End-tidal concentrations of sevoflurane and carbon dioxide were measured continuously using an infrared multigas anesthetic analyzer (Capnomac Ultima; Datex, Helsinki, Finland). Gas samples were collected *via* a Teflon catheter placed at the tracheal end of the endotracheal tube. Patients' lungs were mechanically or manually ventilated to normocapnia, and body temperature was maintained above 35.5°C.

To ensure rapid equilibration between the plasma and effect compartment, for the first 6 min the infusion was adjusted to achieve a fentanyl concentration twice the predetermined target concentration according to the half-time (k_{eo}) for equilibration between blood and the brain (6.4 min).⁷ Thereafter the target concentration of fentanyl was returned to the value to which the patient had been randomized to. After maintaining the end-tidal sevoflurane concentration for 15 min, patients were judged to be awake or asleep by having their names called loudly and being instructed to open their eyes or move their heads. If patients could open their eyes or move their heads, they were judged awake. If they did not, a return of neuromuscular function was confirmed by a peripheral nerve stimulator. The mean time from starting fentanyl infusion to verbal command was 27 min (range, 22–35 min). Blood samples were taken 5 min before and just after MAC_{awake} assessment to en-

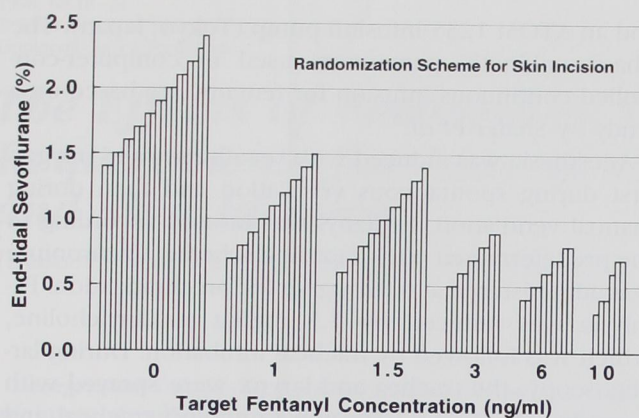


Fig. 2. Assessment of response to skin incision: end-tidal sevoflurane concentrations for each patient in each of the predicted fentanyl concentration groups.

sure that steady plasma fentanyl concentration were being maintained.

Measurement of Minimum Alveolar Concentration

After the above assessment, the end-tidal sevoflurane concentration was either maintained or changed to the predetermined concentration according to the scheme for skin incision (fig. 2). These sevoflurane concentrations were chosen to provide a range that would impart both adequate and inadequate anesthesia at each fentanyl concentration, and they were based on data from previous MAC reduction studies.^{3,4} After maintaining the end-tidal concentration constant for more than 15 min, blood samples were taken 5 min before and just after skin incision. The mean time from starting fentanyl infusion to skin incision was 50 min (range, 45–75 min). The average time lag between the MAC_{awake} and MAC determinations was 23 min (range, 20–45 min). Patients were observed for gross purposeful movement for 60 s after skin incision. Coughing, chewing, or swallowing was not considered purposeful movement.

Blood Sample Analysis

Blood samples were allowed to clot for 15 min, and the serum was separated and frozen at -70°C until assay. The fentanyl concentration was determined using a previously described radioimmunoassay technique.⁸ The assay was linear over the concentrations measured, with a lower limit of detection of 0.13 ng/ml and a coefficient of variation of less than 10%. Plasma lidocaine concentration at the time of MAC_{awake} assessment

was measured with a high-performance liquid chromatographic assay sensitive to 4 ng/ml.⁹ The coefficient of variation of both assays was less than 10% over the concentration range measured. All assays were performed in duplicate. If the two measurements differed by more than 10%, the sample was reassayed.

The pre- and postassessment samples were compared to ensure that a steady concentration was being maintained. Only paired samples that had concentrations within $\pm 35\%$ of each other were included in the statistical analysis. From these paired samples, only the postassessment fentanyl concentrations were used for analysis.

Statistical Analysis

The technique used to determine the MAC_{awake} and MAC of sevoflurane in the absence of fentanyl was adapted from the method described by Waud.¹⁰ We estimated the reduction of sevoflurane MAC_{awake} and MAC by fentanyl using a multiple independent variable logistic regression model with the natural log of the drug concentration as predictor variables.⁴ In addition, the product of the log of the drug concentrations was included in the model to determine an interaction (deviation from linearity) effect. The concentration of sevoflurane required to prevent response to skin incision in 95% of patients (MAC₉₅) and the concentrations required to prevent response to verbal command in 5% and 95% (MAC_{awake95} and MAC_{awake5}, respectively) were also determined.

Results

Ninety-two patients (39 men, 53 women) were enrolled in the study. Their average age was 42.9 ± 10.6 (SD) yr (range, 21–60 yr); their average weight was 58.6 ± 12.1 (SD) kg (range, 40–78 kg). Postassessment fentanyl concentrations, which were used in the statistical analyses, ranged from 0 to 15.8 ng/ml.

MAC_{awake} Determination

Eight patients were excluded from the MAC_{awake} analysis because pre- and postassessment paired samples did not have concentrations within $\pm 35\%$ of each other. In addition, four patients were excluded because of uncontrollable severe movement during maintaining steady-state concentration of sevoflurane. Thus the results of 80 patients are analyzed. Of 80 patients, 18 did not receive fentanyl.

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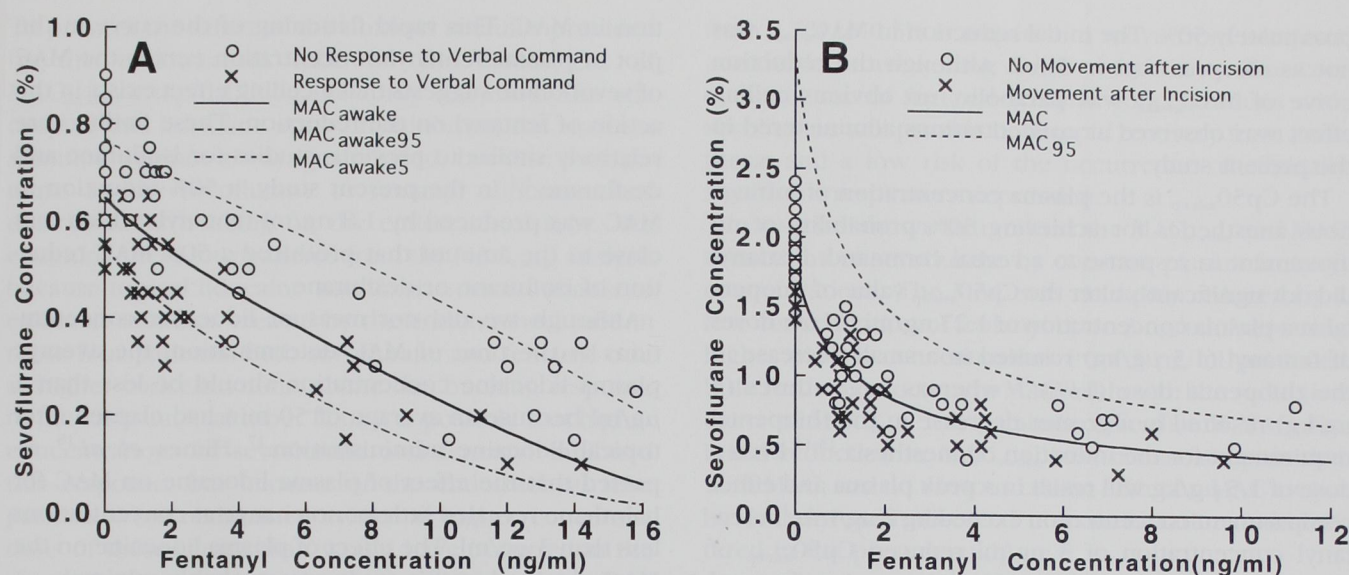


Fig. 3. (A) Reduction by increasing concentrations of fentanyl of sevoflurane at which 50%, 5%, or 95% of patients were awake (MAC_{awake}, MAC_{awake5}, or MAC_{awake95}, respectively). (B) Reduction by increasing concentrations of fentanyl of sevoflurane at which 50% or 95% of patients did not move at skin incision (MAC or MAC₉₅, respectively).

The MAC_{awake} determined from the patients not receiving fentanyl was $0.62 \pm 0.03\%$ (SE). The MAC_{awake5} was 0.71%. Based on the model that included both patients receiving and not receiving fentanyl, the predicted MAC_{awake} for sevoflurane alone was 0.65%. The MAC_{awake} was reduced with increasing plasma fentanyl concentrations. The reduction of MAC_{awake} was approximately 10%, or 24% at fentanyl concentrations of 1 or 3 ng/ml, respectively. A 50% reduction in MAC_{awake} was produced by 7.3 ng/ml fentanyl (fig. 3A).

Plasma lidocaine concentration at the time of MAC_{awake} assessment was $1.4 \pm 0.24\%$ (SD) $\mu\text{g/ml}$.

Minimum Alveolar Concentration Determination

Two patients were excluded from the MAC analysis because pre- and postassessment paired samples did not have concentrations within $\pm 35\%$ of each other. Thus the results of 78 patients were analyzed. Of 78 patients, 20 did not receive fentanyl. The MAC determined from the patients not receiving fentanyl was $1.84 \pm 0.08\%$ (SE). The MAC₉₅ was 2.21%. Based on the model that included patients both receiving and not receiving fentanyl, the predicted MAC for sevoflurane alone was 1.77%. The MAC was markedly reduced with increasing fentanyl concentration. The reduction of MAC was approximately 38%, or 59% at fentanyl concentrations of 1 or 3 ng/ml, respectively. A 50% reduction in MAC_{awake}

was produced by 1.8 ng/ml fentanyl. A ceiling effect was observed, with 10 ng/ml providing only a further 17% reduction in MAC (fig. 3B).

Discussion

Our purpose was to determine the reduction of end-tidal sevoflurane concentrations at two different endpoints: loss of response to a verbal command and loss of response to skin incision by fentanyl administered using a pharmacokinetic model-driven computer-controlled continuous infusion. The MAC_{awake} of sevoflurane obtained in this study was 0.62%. This is similar to the determined sevoflurane MAC_{awake} in our previous study.² In that investigation, we showed that fentanyl significantly reduced the MAC_{awake} of sevoflurane at a plasma concentration of 2 ng/ml. However, this reduction was much smaller than that reported for the MAC reduction of other volatile anesthetics by fentanyl. The interaction of sevoflurane along a continuum of fentanyl concentration is accurately calculated using logistic regression analysis. An initial steep reduction, which was observed in the MAC reduction of volatile anesthetics by fentanyl, was not observed in the MAC_{awake} reduction. The results correspond with our previous findings for MAC_{awake}. The MAC_{awake} reduction by 2 ng/ml of fentanyl was approximately 15%, whereas the MAC reduction by the same fentanyl concentration was ap-

proximately 50%. The initial reduction in MAC_{awake} was not as steep as that in MAC. Although the reduction curve of MAC_{awake} was parabolic, no obvious ceiling effect was observed at concentrations administered in the present study.

The $Cp50_{asleep}$ is the plasma concentration of intravenous anesthetics for achieving 50% probability of no movement in response to a verbal command. Fentanyl did not significantly alter the $Cp50_{asleep}$ value of thiopental at a plasma concentration of 1.27 ng/ml.¹¹ Low doses of fentanyl (1.5 μ g/kg) resulted in a small decrease in the thiopental dose (13%),¹² whereas larger doses (4 μ g/kg) resulted in a greater decrease in the thiopental requirement for the induction of anesthesia.^{13,14} Even a dose of 1.5 μ g/kg will result in a peak plasma and effect compartment concentration exceeding 2 ng/ml.¹¹ A fentanyl concentration of 3 ng/ml reduced $Cp50_{asleep}$ of propofol by approximately 40%.¹⁵ Increasing fentanyl concentration beyond 3 ng/ml produced a small further reduction in propofol $Cp50_{asleep}$.¹⁵ This ceiling phenomenon in the propofol study was not consistent with that observed in the present sevoflurane study. Both thiopental and propofol have a potent hypnotic action, but their analgesic potency is low, similar to that with sevoflurane. The magnitude of the reduction in $Cp50_{asleep}$ or MAC_{awake} of these potent hypnotics by 2 ng/ml fentanyl was similar at approximately 15–20%. Streisand *et al.*⁶ suggested that intravenous fentanyl produced unconsciousness, even when administered without other concomitant anesthetics. At an estimated effect site fentanyl concentration of 9.7 ng/ml, 50% of patients did not respond to command in their study. The results of the present study suggest that at a fentanyl concentration of 9.7 ng/ml, more than 50% of patients would respond to verbal command. Streisand *et al.* administered fentanyl in a single bolus, whereas we used the computer-controlled continuous infusion technique. This methodologic difference may explain the discrepancy. Plasma lidocaine was reported not to decrease the MAC_{awake} of isoflurane at the plasma concentration of 2.09 μ g/ml.¹⁶ Because the mean plasma lidocaine concentration at the MAC_{awake} assessment was 1.4 μ g/ml, the effect of plasma lidocaine on the MAC_{awake} obtained in this study was probably minimal.

Fentanyl produces an initial steep decrease in the MAC of sevoflurane. This decrease then reaches a plateau with minimal further reduction in the MAC of sevoflurane at a fentanyl concentration greater than 3 ng/ml of fentanyl. Doubling the plasma concentration from 3 ng/ml to 6 ng/ml only produces a further 11% reduc-

tion in MAC. This rapid flattening of the curve in the plot of plasma fentanyl concentration *versus* the MAC of sevoflurane suggests that a ceiling effect exists in the action of fentanyl on the reduction. These findings are relatively similar to previous studies for isoflurane and desflurane.^{3,4} In the present study, a 50% reduction in MAC was produced by 1.8 ng/ml fentanyl, which was close to the amount that produced a 50% MAC reduction of isoflurane or desflurane.

Although we did not measure lidocaine concentrations at the time of MAC determination, the average plasma lidocaine concentration should be less than 1 μ g/ml because an average of 50 min had elapsed after topical lidocaine administration.¹⁷ Himes *et al.*¹⁸ reported that the effect of plasma lidocaine on MAC for halothane revealed little or no change at concentrations less than 3 μ g/ml. The effect of plasma lidocaine on the MAC obtained in this study was probably minimal.

Our data show that fentanyl reduced the sevoflurane requirements for loss of response to both verbal command and skin incision. The mode of reduction was, however, different between the two endpoints. Some observations suggest that motor responses to a noxious stimulus may be primarily mediated by subcortical structures, including the spinal cord in lower animals.^{19,20} In contrast, purposeful responsiveness to a verbal command apparently needs intact cortex function. Fentanyl, therefore, probably acts at different sites in producing its effect on the MAC and MAC_{awake} reductions. The difference in sites of action may explain the difference in the mode of reduction by fentanyl between the MAC and MAC_{awake} .

The method used to measure MAC_{awake} was initially defined and validated by Stoelting *et al.*²¹ They measured MAC_{awake} after operation in patients with tracheas intubated. We chose MAC_{awake} as one measurement of hypnotic potency for the purpose of assessing interaction in hypnosis between sevoflurane and fentanyl. The MAC_{awake} defined by Stoelting *et al.* may not reflect a pure hypnotic potency of a volatile anesthetic because they measured MAC_{awake} in intubated patients without trying to remove any stimuli created by an endotracheal tube. Therefore, the MAC_{awake} defined by Stoelting *et al.* indicates not only hypnotic potency but also antitussive potency of a volatile anesthetic and may not be comparable to the MAC_{awake} we determined here.

We could not determine the MAC_{awake} in the absence of an endotracheal tube because of rigidity caused by high concentrations of fentanyl. Thus an endotracheal tube was placed in all patients to facilitate ventilation.

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To prevent the effect of the noxious stimulus provided by the endotracheal tube on the assessment of MAC_{awake} , a topical lidocaine spray was used. The efficacy of this lidocaine spray in inhibiting the noxious stimulus was not always guaranteed, because four patients at low sevoflurane or fentanyl concentrations demonstrated bucking on the endotracheal tube. We excluded these four patients from the MAC_{awake} analysis because topical lidocaine anesthesia seemed unable to eliminate stimulus created by the endotracheal tube in these four patients. Both sevoflurane and fentanyl can, at higher concentrations, ablate this bucking response to the endotracheal tube. Thus it is possible that higher concentrations of sevoflurane and fentanyl inhibited this response, but because of the endotracheal tube patients were maintained awake at higher concentrations of these agents than would have occurred in the absence of potent stimulus such as the endotracheal tube. Therefore the data may overestimate the true MAC_{awake} concentration, but the presence of an endotracheal tube and topical lidocaine spray is unlikely to have affected the shape of the interaction curve for MAC_{awake} .

To ensure adequate anesthesia to all patients, most clinicians will administer an anesthetic to achieve a sevoflurane and fentanyl concentration at which 95% of patients do not respond to skin incision. For awakening, the sevoflurane concentration must decrease to the MAC_{awake} concentration. Thus awakening times can be estimated from the time it takes for the sevoflurane concentration to decrease from the MAC_{95} value of any combination to the $MAC_{awake95}$ value for any combination. Based on this, the time to awakening will occur most rapidly when a fentanyl concentration of 3.6 ng/ml is used. Adequate recovery, however, depends on return of consciousness and on adequate spontaneous ventilation. Fentanyl concentrations greater than 2–3 ng/ml have a high likelihood of producing clinically significant respiratory depression.²² Thus the fentanyl concentration will need to decrease from 3.6 ng/ml to less than 2 ng/ml (approximately 50%). The time for fentanyl to decrease by 50% varies according to the duration of its infusion and can be estimated from its context-sensitive half-time²³ but is invariably longer than the time for the sevoflurane concentration to decrease from the MAC_{95} value to the $MAC_{awake95}$ value (approximately 5–10 min). Nearly maximal MAC reduction has already occurred using concentrations of fentanyl between 1–2 ng/ml without clinically significant MAC_{awake} reduction; that is, a decrease in sevoflurane

from 1.5% to 0.5% is required to move from adequate anesthesia to awakening in 95% of patients. The concomitant use of fentanyl at these concentrations with sevoflurane will provide both rapid recovery from anesthesia and a low risk of the occurrence of clinically significant respiratory depression.

In conclusion, we determined the MAC_{awake} and MAC reductions of sevoflurane by constant plasma fentanyl concentrations. The MAC was markedly reduced by a low concentration of fentanyl up to 3 ng/ml. Increasing higher plasma concentrations from 3 ng/ml produced little further reduction in MAC. Although the reduction curve of MAC_{awake} was parabolic, like that of MAC, the initial reduction in MAC_{awake} was not as steep as that with MAC, and no obvious ceiling effect on MAC awake by fentanyl was observed at concentrations administered in the present study.

The authors thank Dr. Shibutani at New York Medical College for his encouragement and numerous suggestions.

References

1. Tomi K, Mashimo T, Tashiro C, Yagi M, Pak M, Nishimura S, Nishimura M, Yoshiya I: Alternations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; 70:684–6
2. Katoh T, Uchiyama T, Ikeda K: Effect of fentanyl on awakening concentration of sevoflurane. *Br J Anaesth* 1994; 73:322–5
3. Sebel PS, Glass PSA, Fletcher JE, Murphy MR, Gallagher C, Quill T: Reduction of the MAC of desflurane with fentanyl. *ANESTHESIOLOGY* 1992; 76:52–9
4. McEwan AI, Smith C, Dyar O, Goodman D, Smith LR, Glass PSA: Isoflurane minimum alveolar concentration reduction by fentanyl. *ANESTHESIOLOGY* 1993; 78:864–9
5. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *ANESTHESIOLOGY* 1990; 73:1091–102
6. Streisand JB, Bailey PL, LeMaire L, Ashburn MA, Tarver SD, Varvel J, Stanley TH: Fentanyl-induced rigidity and unconsciousness in human volunteers. Incidence, duration, and plasma concentrations. *ANESTHESIOLOGY* 1993; 78:629–34
7. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioide effect: the comparative pharmacodynamics of fentanyl and alfentanil. *ANESTHESIOLOGY* 1991; 74:34–42
8. Michiels M, Hendricks R, Heykants J: A sensitive radioimmunoassay for fentanyl: Plasma levels in dogs and man. *Eur J Clin Pharmacology* 1977; 12:153–8
9. Klein J, Fernandes D, Gazarian M, Kent G, Koren G: Simultaneous determination of lidocaine, prilocaine and the prilocaine metabolite o-toluidine in plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Appl* 1994; 655:83–8
10. Waud DR: On biological assays involving quantal response. *J Pharmacol Exper Therap* 1972; 183:577–607
11. Telford RJ, Glass PSA, Goodman D, Jacobs JR: Fentanyl does

not alter the "sleep" plasma concentration of thiopental. *Anesth Analg* 1992; 75:523-9

12. Splinger WM, Cervenka F: Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: Effects of fentanyl, lidocaine and thiopental. *Can J Anaesth* 1989; 36:370-6

13. Kissin I, Mason JO, Bradley EL: Morphine and fentanyl hypnotic interactions with thiopental. *ANESTHESIOLOGY* 1987; 67:331-5

14. Bowdle TA, Ward RJ: Induction of anesthesia with small doses of sufentanyl or fentanyl: Dose versus EEG response, speed of onset, and thiopental requirements. *ANESTHESIOLOGY* 1989; 70:26-30

15. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PAS: The interaction of fentanyl on the CP_{50} of propofol for loss of consciousness and skin incision. *ANESTHESIOLOGY* 1994; 81:820-8

16. Inagaki Y, Mashino T, Kuzukawa A, Tsuda Y, Yoshiya I: Epidural lidocaine delays arousal from isoflurane anesthesia. *Anesth Analg* 1994; 79:368-72

17. Yusa T, Taira Y, Sasara T, Yoza K: Effects of intratracheal lidocaine spray on circulatory responses to endotracheal intubation in (Japanese). *Masui* 1990; 39:1325-32

18. Himes RS Jr, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *ANESTHESIOLOGY* 1977; 47:437-40

19. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. *ANESTHESIOLOGY* 1993; 78:707-12

20. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. *ANESTHESIOLOGY* 1993; 79:1244-9

21. Stoelting RK, Longnecker DE, Eger EI II: Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC_{awake} . *ANESTHESIOLOGY* 1970; 33:5-9

22. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. *Anesth Analg* 1983; 62:966-74

23. Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *ANESTHESIOLOGY* 1992; 76:334-41