

Effects of Two Target-controlled Concentrations (1 and 3 ng/ml) of Remifentanyl on MAC_{BAR} of Sevoflurane

Andrea Albertin, M.D.,* Andrea Casati, M.D.,* Piercarlo Bergonzi, M.D.,† Greta Fano, M.D.,† Giorgio Torri, M.D.‡

Background: The aim of this prospective, randomized, double-blind study was to determine the effects of two different target-controlled concentrations of remifentanyl (1 and 3 ng/ml) on the sevoflurane requirement for blunting sympathetic responses after surgical incision (MAC_{BAR}).

Methods: Seventy-four patients aged 20–50 yr, with American Society of Anesthesiologists physical status I, were anesthetized with propofol, cisatracurium, and sevoflurane with a mixture of 60% nitrous oxide in oxygen. Then, patients were randomly allocated to receive no remifentanyl infusion ($n = 27$) or a target-controlled plasma concentration of 1 ng/ml ($n = 27$) or 3 ng/ml remifentanyl ($n = 20$). Sympathetic responses to surgical incision (presence or absence of an increase in either heart rate or mean arterial blood pressure of 15% or more above the mean of the values measured during the 2 min before skin incision) were determined after a 20-min period of stable end-tidal sevoflurane and target-controlled remifentanyl concentrations. Predetermined end-tidal sevoflurane concentrations and the MAC_{BAR} for each group were determined using an up-and-down sequential-allocation technique.

Results: The MAC_{BAR} of sevoflurane was higher in the group receiving no remifentanyl (2.8% [95% confidence interval: 2.5–3.0%]) as compared with patients of the groups receiving 1 ng/ml (1.1% [0.9–1.3%]; $P = 0.012$) and 3 ng/ml remifentanyl (0.2% [0.1–0.3%]; $P = 0.006$). When considering a minimum anesthetic concentration (MAC) value in this age population and the contribution of 60% nitrous oxide (0.55 MAC), the combined MAC_{BAR} values, expressed as multiples of the MAC, were 1.95 MAC, 1.1 MAC, and 0.68 MAC, in the three groups, respectively.

Conclusion: A target-controlled concentration of 1 ng/ml remifentanyl results in a 60% decrease in the MAC_{BAR} of sevoflurane combined with 60% nitrous oxide. Increasing the target concentration of remifentanyl to 3 ng/ml produces a further 30% decrease in the MAC_{BAR} values of sevoflurane.

WITH the routine use of muscle relaxants, the control of sympathetic responses induced by surgical incision represents one of the most important endpoints for assessing depth of anesthesia,¹ but no anesthetic drug is commonly used alone to provide all the necessary components of general anesthesia. It has been clearly demonstrated that opioid agents significantly reduce the minimum anesthetic concentration (MAC) of potent inhaled anesthetics required to abolish consciousness, intubate, and blunt the sympathetic response to skin incision.^{2–5} Remifentanyl is a selective μ -opioid receptor

agonist that provides intense analgesia of rapid onset and ultrashort duration⁶ and has been shown to be effective in preventing sympathetic responses induced by tracheal intubation and other surgical stimuli.^{7–9} Because of its unique pharmacokinetic–pharmacodynamic profile, remifentanyl is ideally suited for continuous intravenous infusion,^{6,7} whereas the use of a target-controlled infusion (TCI) using a computer-driven infusion device has been shown to be more effective in maintaining cardiovascular stability as compared with traditional weight-adjusted infusion.¹⁰ However, the reduction in sevoflurane requirement for blunting sympathetic responses after surgical incision (MAC_{BAR}) produced by remifentanyl is still undetermined. Therefore, we conducted this prospective, randomized, double-blind study to determine the effects of two different target-controlled plasma concentrations of remifentanyl (1 and 3 ng/ml) on the MAC_{BAR} of sevoflurane.

Materials and Methods

With the approval of the institutional ethical committee (Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale San Raffaele, Vita-Salute University of Milano) and patients' written informed consent, 74 patients aged 20–50 yr, with American Society of Anesthesiologists physical status I, scheduled to undergo elective abdominal surgery requiring at least a 10-cm-long skin incision were prospectively studied. Patients undergoing laparoscopic procedures, obese patients (body mass index > 30 kg/m²), and patients with hypertension or a history of cardiac, pulmonary, or renal diseases; drug or alcohol abuse; or current use of any medications that might affect the cardiovascular system or block the adrenergic responses to surgical incision were excluded. No local anesthetic agents, atropine, epinephrine, or other vasoactive medications were used before skin incision in any case.

Patients fasted for 8 h before surgery and received no premedication. After arrival in the operating room, an 18-gauge intravenous cannula was placed in the forearm, and 10 ml/kg lactated Ringer's solution was infused. Standard monitoring was used throughout the study, including noninvasive arterial blood pressure monitoring (Dinamap 1846SX; Critikon, Tampa, FL), electrocardiography, heart rate monitoring (lead II), and pulse oximetry.

Using a computer-generated sequence of numbers, patients were randomly allocated to one of three groups, receiving no remifentanyl infusion or a TCI of remifentanyl set to maintain a plasma concentration of either 1 or 3 ng/ml.

* Staff Anesthesiologist, † Anesthesia Fellow, ‡ Professor of Anesthesiology.

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Address reprint requests to Dr. Casati: Department of Anesthesiology, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Address electronic mail to: casati.andrea@hsr.it. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

General anesthesia was induced with intravenous propofol (2 mg/kg) and a TCI of remifentanyl set at 2 ng/ml for tracheal intubation, which was facilitated with cisatracurium besilate (0.2 mg/kg). Then, the lungs were ventilated with sevoflurane and a mixture of 60% nitrous oxide (0.55 MAC) in oxygen. In patients of the no-remifentanyl group, the infusion was stopped immediately after tracheal intubation. In patients of the 1- and 3-ng/ml remifentanyl groups, the remifentanyl infusion was set at the designated target-controlled concentration. At the same time, the designated end-tidal concentration of sevoflurane was maintained stable for at least 20 min before surgical incision. According to its context sensitive half-life, this equilibration period also allowed for complete equilibration between plasma and effect site concentrations of remifentanyl.^{6,10} During this equilibration time, the patients were left unstimulated except for positioning, prepping, and draping. Respiratory gases were sampled at the Y-connector, and inspired and end-tidal oxygen, carbon dioxide, nitrous oxide, and sevoflurane concentrations were continuously monitored with an infrared gas analyzer (RGM 5250; Ohmeda, Englewood, CO) calibrated before each case according to the manufacturer's instructions. Ventilation was mechanically controlled using a Cato-Dräger anesthesia workstation (Dräger, Lubeck, Germany) set to maintain an end-tidal partial pressure of carbon dioxide ranging between 32 and 35 mmHg. Fresh gas flow was set at 10 l/min to rapidly obtain and maintain the designed end-tidal concentration of sevoflurane.

Remifentanyl was administered using a pharmacokinetic model-driven, computer-assisted, continuous infusion system allowing achievement and maintenance of constant target plasma concentrations.^{10,11} The system consisted of an Acer TravelMate 518TX computer connected to a Graseby 3500 infusion pump (Sims Graseby Limited, Waterford, Herts, United Kingdom).^{9,11} The pharmacokinetic parameters used in the computer-assisted continuous infusion for administration of remifentanyl were based on the model described by Minto *et al.*^{12,13}

Heart rate and mean arterial blood pressure (MAP), determined by an automatic oscillographic method, were recorded before induction of anesthesia, 2 and 1 min before skin incision, at skin incision, and then at 1-min intervals during the first 5 min after surgical incision. The preincision value was defined as the mean value of the 2- and 1-min measurements. If arterial blood pressure decreased before skin incision to a level that necessitated administration of a vasoactive agent (MAP < 50 mmHg), the patient was withdrawn from the study, and the same concentration of sevoflurane was repeated with the following case.

Similar to previous investigations,^{3,14} the MAC_{BAR} of sevoflurane was determined using an up-and-down sequential-allocation technique.¹⁵ The response of a patient determined the concentration of sevoflurane given

to the following patients in each group. We arbitrarily started in each group with an end-tidal concentration of sevoflurane of 3% (corresponding to 1.5 MAC according to the age of the studied population¹⁶). If the response of a patient in that group was positive (an increase of either heart rate or MAP \geq 15% above the mean of the values measured during the 2 min before skin incision), the end-tidal concentration given to the next patient was increased by 0.5% (0.25 MAC). If the response was negative (neither heart rate nor MAP increased \geq 15% above the mean of the values measured during the 2 min before skin incision), the end-tidal concentration of sevoflurane given to the next patient was decreased by the same amount.

To increase the precision of the final estimator, we used a modified up-and-down method, based on altering the test space.¹⁷ In this modified method, the up-and-down sequence is formed by two stages: the first stage consists of an original up-and-down sequence on the predetermined equally spaced test levels until three changes of response type are observed. The second stage consists of reducing the initial test space, restarting the up-and-down sequence at the nearest level to the average, and continuing the experiment at the next higher or the next lower level according to the response type on the reduced test space. According to this modified up-and-down method, the initial test space was reduced to 0.2% (0.125 MAC) for an *a priori* number of independent negative-positive up-and-down deflections of four with the new reduced test space. Reducing the test space at a certain space increases the precision of the final estimator, reducing the mean squared error under normal tolerance distribution, and has been shown to be substantially better than the original method when the initial test space is relatively wide and the initial dose is away from the final median lethal dose.^{18,19} The mean (with 95% confidence interval) of the MAC_{BAR} of sevoflurane was then calculated from the midpoints of pairs of concentrations from consecutive patients in which a negative response was followed by a positive one after the initial test space was reduced according to the modified up-and-down method.^{3,14-19} We predetermined that 27 patients should be enrolled in each group to achieve the minimum required number of positive-negative crossovers.

The day after surgery, all of the studied patients were interviewed to evaluate the presence of explicit recall of any intraoperative event. The anesthesiologist recording cardiovascular parameters and determining the positive-negative response to surgical incision was blinded to patient grouping. The data were also analyzed using a logistic regression model to estimate the effective sevoflurane concentration needed for blockade of cardiovascular responses in 50% and 95% of patients (ED₅₀ and ED₉₅, respectively).

Statistical analysis was performed using the program Statistica 5.1 (StatSoft Italia, Vigonza, Padova, Italy). In-

Table 1. Comparisons during the 2 Min before Skin Incision among Groups Receiving No Remifentanil Infusion or a 1-ng/ml or 3-ng/ml Target-controlled Concentration of Remifentanil

	No Remifentanil (n = 27)	1 ng/ml Remifentanil (n = 27)	3 ng/ml Remifentanil (n = 22)
Age, yr	36 ± 7	38 ± 7	36 ± 8
Weight, kg	62 ± 10	61 ± 10	60 ± 10
Height, cm	164 ± 10	162 ± 9	164 ± 8
Sex (M/F)	7/20	3/24	4/16
Preoperative, HR beats/min	75 ± 8	74 ± 7	76 ± 7
Preoperative systolic blood pressure, mmHg	117 ± 8	116 ± 9	115 ± 10
Preoperative diastolic blood pressure, mmHg	71 ± 7	73 ± 8	69 ± 8
Mean MAP before skin incision, mmHg	99.5 ± 13	95.7 ± 13	97 ± 15

HR = heart rate; MAP = mean arterial blood pressure.

tergroup comparisons were performed using analysis of variance and a Student *t* test with the Bonferroni correction for multiple comparisons. A *P* value of 0.05 or less was considered statistically significant. Data are presented as mean ± SD and 95% confidence intervals.

Results

A total of seventy-six patients completed the study. Two patients in the 3-ng/ml remifentanil group were excluded from the investigation because of a significant reduction in MAP (< 50 mmHg) before skin incision necessitating administration of vasoconstrictors. No differences in patient characteristics, preoperative heart rate and MAP, or mean MAP during the 2 min before skin incision were reported among the three groups (table 1). Heart rate and MAP decreased significantly after induction of general anesthesia in each group; however, no differences were reported among the three groups. At the postoperative visit 24 h after surgery, no patient reported explicit recall of any intraoperative event.

Figures 1–3 show individual responses to skin incision according to the up-and-down sequence. The MAC_{BAR} value of sevoflurane was 2.8% (95% confidence interval: 2.5–3.0%) in patients not receiving remifentanil, compared with 1.1% (0.9–1.3%) in patients with a target-controlled concentration of 1 ng/ml remifentanil (*P* = 0.012) and 0.2% (0.1–0.3%) in patients with a target-controlled concentration of 3 ng/ml remifentanil (*P* = 0.006). Based on the MAC of sevoflurane described in the age range of the study population¹⁰ and the concomitant use of 60% nitrous oxide, the combined MAC_{BAR} of sevoflurane expressed as a multiple of the MAC was 1.95 (1.8–2.1) MAC in group not receiving remifentanil, 1.1 (1.0–1.2) MAC in the group receiving 1 ng/ml remifentanil, and 0.68 (0.6–0.75) MAC in the group receiving 3 ng/ml remifentanil.

The ED₅₀ and ED₉₅ for blockade of cardiovascular responses to skin incision obtained from logistic regression analysis were 2.8 ± 0.4 and 3.3 ± 0.5% in the group not receiving remifentanil (1.95 and 2.2 MAC, respectively), 1.57 ± 0.2 and 1.98 ± 0.3% in the group receiving

1 ng/ml remifentanil (1.33 and 1.54 MAC, respectively), and 0.27 ± 0.05 and 0.29 ± 0.2% in the group receiving 3 ng/ml remifentanil (0.68 and 0.7 MAC, respectively) (values include the contribution of 60% nitrous oxide). The ED₅₀ values did not differ significantly from the MAC_{BAR} values obtained with the Dixon method.

Discussion

The main finding of this prospective, randomized, double-blind study is that achieving and maintaining a target-controlled plasma concentration of 1 ng/ml remifentanil reduces the MAC_{BAR} of sevoflurane combined with 60% nitrous oxide by 60%. Increasing the target-controlled concentration of remifentanil up to 3 ng/ml results in a further 30% reduction in the MAC_{BAR} of sevoflurane.

The MAC_{BAR} of sevoflurane reported in the current investigation in patients who did not receive remifentanil at skin incision is similar to that reported in previous investigations with sevoflurane itself or other potent inhalation anesthetics. Daniel *et al.*³ reported MAC_{BAR} values of 1.85 ± 0.18 MAC for isoflurane and 1.85 ± 0.34

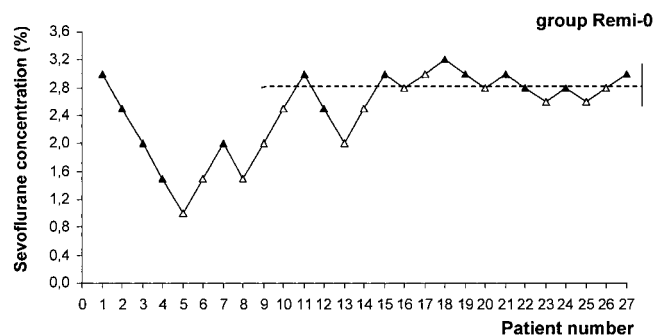


Fig. 1. Individual responses to skin incision according to the up-and-down sequence in patients receiving no remifentanil infusion. When a patient showed an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration of sevoflurane given to the next patient was increased (positive response [open symbols]), whereas in the absence of an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration given to the next patient was decreased (negative response [filled symbols]).

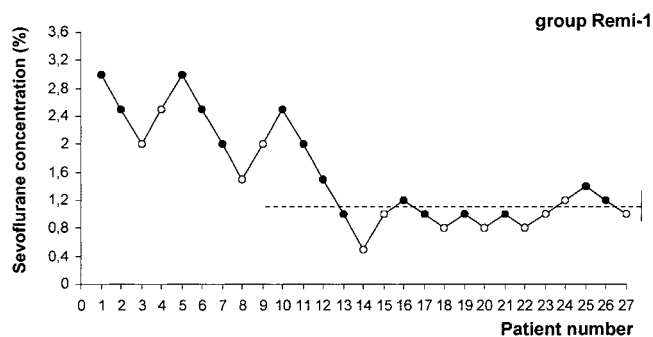


Fig. 2. Individual responses to skin incision according to the up-and-down sequence in patients receiving a 1-ng/ml target-controlled concentration of remifentanyl. When a patient showed an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration of sevoflurane given to the next patient was increased (positive response [open symbols]), whereas in the absence of an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration given to the next patient was decreased (negative response [filled symbols]).

MAC for desflurane with the contribution of 60% nitrous oxide, and Katoh *et al.*⁴ reported that in the presence of 66% nitrous oxide, the MAC_{BAR} of sevoflurane determined from patients not receiving opioids was 2.5% (2.3–2.7%) (or 1.95 MAC if one takes into account the concomitant use of nitrous oxide) and seemed to be greater than those determined for halothane (0.8 MAC) and enflurane (1.03 MAC).²⁰ Nakata *et al.*,¹⁴ evaluating the effects of two different concentrations of xenon (0.7 and 1 MAC) as compared with 0.7 MAC of nitrous oxide on the MAC_{BAR} of sevoflurane, reported a MAC_{BAR} value as high as 2.5 MAC. Although these differences in the MAC_{BAR}:MAC ratio could be related to differences in the experimental methodology, Nakata *et al.*¹⁴ suggested that sevoflurane might have a less potent cardiovascular-suppressive effect compared with other inhalational agents.

Katoh *et al.*⁴ also evaluated the effects of different fentanyl concentrations on the MAC_{BAR} of sevoflurane and demonstrated that the concentration of fentanyl reducing the MAC_{BAR} of sevoflurane by 99% was 4.4 ng/ml. In the current investigation, we observed a 92% reduction in the MAC_{BAR} of sevoflurane when maintaining a target-controlled concentration of 3 ng/ml remifentanyl. Considering the 1:1.2 potency ratio between fentanyl and remifentanyl, this finding is in agreement with the study of Katoh *et al.*⁴ and similar to the reduction in MAC_{BAR} reported with other potent inhalational agents.^{3,21}

The MAC_{BAR} of sevoflurane determined in those patients who received 3 ng/ml remifentanyl was really low, much lower than the MAC_{awake}.² These results are in agreement with those reported with similar concentrations of fentanyl⁴ and could potentially result in an inadequate level of hypnosis in these patients. Despite the use of very low concentrations of sevoflurane at skin incision in patients who received 3 ng/ml remifentanyl,

none of the considered patients reported any explicit recall at the postoperative follow-up visit. This can be reasonably explained by the concomitant administration of 60% nitrous oxide²¹; nonetheless, to minimize the risks of awareness in these patients, we stopped patient enrollment in the 3-ng/ml group before enrolling the scheduled 27 patients because we already had an adequate number of negative–positive crossovers. However, it must be pointed out that even with small doses of opioids, patients can be aware of intraoperative events despite the lack of changes in cardiovascular parameters, potentially leading to intraoperative awareness.²²

Induction of anesthesia was obtained with intravenous administration of propofol and remifentanyl also in the patients of the no-remifentanyl group to provide adequate protection from the stress response induced by tracheal intubation. This could represent a potential shortcoming of the study. However, the remifentanyl infusion was stopped immediately after tracheal intubation, while the time of equilibration of the target concentration of sevoflurane before skin incision (at least 20 min) allowed a complete washout of both intravenous agents according to their pharmacokinetics properties.^{23,24} In fact, although plasma concentrations of remifentanyl were not directly determined, the plasma concentration of remifentanyl calculated before skin incision was zero in all of the patients in the no-remifentanyl group after the 20-min equilibration period, and this is indirectly confirmed by the fact that the MAC_{BAR} of sevoflurane calculated in patients of the no-remifentanyl group was similar to that reported by other authors in absence of opioid administration.⁴

The lack of direct determination of plasma concentrations of remifentanyl can be considered another important shortcoming of the study. However, the pharmacokinetic model we used to achieve and maintain a stable

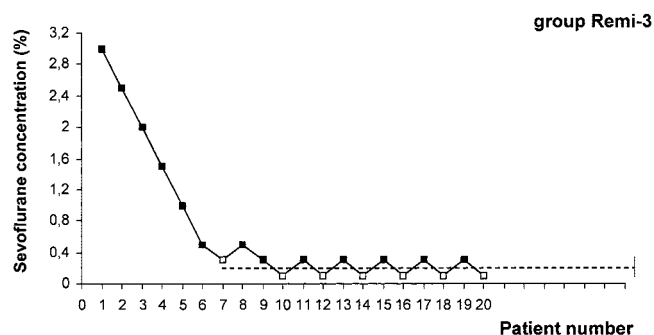


Fig. 3. Individual responses to skin incision according to the up-and-down sequence in patients receiving a 3-ng/ml target-controlled concentration of remifentanyl. When a patient showed an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration of sevoflurane given to the next patient was increased (positive response [open symbols]), whereas in the absence of an increase in either heart rate or mean arterial blood pressure of 15% or more from the preincision value, the end-tidal concentration given to the next patient was decreased (negative response [filled symbols]).

plasma concentration of remifentanil has been shown to be adequately accurate in predicting plasma and effect site concentrations of remifentanil.^{10,12,13} Evaluating the predictive performance of computer-assisted TCI of remifentanil using five different remifentanil parameters sets, Mertens *et al.*²⁵ recently reported that the pharmacokinetic parameter set described by Minto *et al.*^{12,13} resulted in an overprediction of the measured remifentanil concentration, with a median performance error of 15%. However, the population studied by Mertens *et al.* was constituted by a selected group of patients; Mertens *et al.* concluded that the use of a population pharmacokinetic parameter set, like that of Minto *et al.*, could be applied with acceptable accuracy in a heterogeneous groups of patients.

The statistical model we used to calculate the MAC_{BAR} of sevoflurane is not free from its own flaws, because calculations are made on a relatively small number of observations as compared with the multiple-dosing approach; however, this method is widely used in basic and clinical pharmacologic research,^{3,14} providing the relevant advantage of minimizing the number of patients with a “negative” response over the traditional random group-assignment design, thus reducing the ethical concerns about determining a dose-response curve in human patients.²⁶ Moreover, it has also been shown that the up-and-down method can be more efficient than a fixed-sample method to estimate the ED₅₀ of a dose-effect relation when a yes/no answer can be identified, because the fixed-sample method necessitates up to three times as many observations as does the up-and-down method to have the same mean squared error.^{27,28} However, the ED₅₀ calculated with the logistic regression analysis from data set obtained in each group with the up-and-down sequence was similar to the MAC_{BAR} values obtained by crossover points.

In the current investigation, we used a computer-assisted TCI to achieve and maintain stable plasma concentrations of remifentanil.¹¹ TCI of remifentanil has been shown to allow an easy and rapid adaptation of intraoperative analgesia, improving cardiovascular stability as compared with continuous weight-adjusted infusion^{10,11}; however, it also requires complex and expensive infusion devices, including a computer to control the infusion pump. For practical purposes, when using conventional weight-adjusted administration, similar results can be achieved in daily practice with infusing a 1- $\mu\text{g}/\text{kg}$ bolus during a 60-s period followed by a continuous infusion of either 0.03 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the 1-ng/ml concentration or 0.12 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the 3-ng/ml concentration.

In conclusion, this prospective, randomized study showed that a target-controlled concentration of 1 ng/ml remifentanil reduces the MAC_{BAR} of sevoflurane by 60%, whereas increasing the target concentration of remifentanil up to 3 ng/ml further reduces the MAC_{BAR} of sevoflurane by 30%.

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