

## Reduction of the MAC of Desflurane with Fentanyl

Peter S. Sebel, M.B., B.S., Ph.D., F.F.A.R.C.S.I.,\* Peter S. A. Glass, M.B., B.Ch., F.F.A.(S.A.),†  
James E. Fletcher, M.B., B.S., M.R.C.P., F.F.A.R.C.S.,‡ Michael R. Murphy, M.D.,\*  
Christopher Gallagher, M.D.,† Timothy Quill, M.D.†

Opioids are known to affect the MAC of inhalational anesthetics. We have determined the interaction between fentanyl and desflurane, following a bolus injection of fentanyl at induction in 134 adult patients. Five groups of patients were studied. Four groups received desflurane or isoflurane in oxygen with either fentanyl 3 or 6  $\mu\text{g}/\text{kg}$  and thiopental 2-5 mg/kg given as a bolus injection at the time of induction. An additional group received desflurane in oxygen alone. Groups were stratified by age. MAC determination, in response to the stimulus of skin incision, was made using the "up-down" method and logistic regression. The MAC of desflurane in oxygen was 6.3% (5.3-7.6%, 95% confidence interval [CI]). Fentanyl 3  $\mu\text{g}/\text{kg}$  produced a fentanyl plasma concentration of  $0.78 \pm 0.53$  ng/ml at skin incision and resulted in a MAC for desflurane of 2.6% (2.0-3.2%, 95% CI). Fentanyl 6  $\mu\text{g}/\text{kg}$  produced a fentanyl plasma concentration of  $1.72 \pm 0.76$  ng/ml at skin incision and resulted in a MAC for desflurane of 2.1% (1.5-2.6%, 95% CI). To compare recovery times to eye-opening and response to commands, patients were grouped according to the plasma fentanyl concentrations at the time of awaking. Recovery was faster in patients who received desflurane than in those who received isoflurane. The authors conclude that the MAC of desflurane is significantly reduced 25 min following a single dose of 3  $\mu\text{g}/\text{kg}$  of fentanyl and that increasing the fentanyl dose to 6  $\mu\text{g}/\text{kg}$  produces little further decrease in MAC. Desflurane is also associated with faster recovery from anesthesia than is isoflurane. (Key words: Anesthetics: recovery. Anesthetics, volatile: desflurane; isoflurane. Anesthetics, intravenous: fentanyl. Potency: minimal alveolar concentration.)

DESFLURANE is likely to be used in combination with opioids. Opioids are known to reduce the anesthetic requirement (determined by reduction of MAC) in both animals<sup>1,2</sup> and humans.<sup>3,4</sup> It is important to define the interaction of desflurane and fentanyl.

The very low solubility of desflurane in blood should reduce the time to recovery from anesthesia compared with other anesthetics. This has previously been demonstrated in rats.<sup>5</sup> It is of clinical importance to know whether or not the potential advantage of rapid recovery

from anesthesia is negated by the presence of other drugs such as opioids.

This study was designed both to compare the interaction of a bolus dose of fentanyl with desflurane or isoflurane in terms of the reduction in the MAC of these agents and to compare the speed of recovery from desflurane anesthesia with that from isoflurane anesthesia—both in the presence of fentanyl.

### Materials and Methods

After Human Investigation Committee approval had been obtained, 134 adults, ASA physical status 1 or 2 (age  $39 \pm 13$  yr, weight  $78 \pm 14.7$  kg) gave informed consent to the study. Patients were randomly allocated to five groups:

- Desflurane/oxygen
- Desflurane/oxygen/fentanyl 3  $\mu\text{g}/\text{kg}$
- Desflurane/oxygen/fentanyl 6  $\mu\text{g}/\text{kg}$
- Isoflurane/oxygen/fentanyl 3  $\mu\text{g}/\text{kg}$
- Isoflurane/oxygen/fentanyl 6  $\mu\text{g}/\text{kg}$

They were further stratified by age: 18-30 yr (the younger group) and 31-65 yr (the older group). Patients received ranitidine 150 mg and metoclopramide 10 mg orally at least 1 h prior to the scheduled time of surgery. An intravenous infusion of lactated Ringer's solution was commenced and standard monitors (automated blood pressure cuff, electrocardiogram, pulse oximeter, and precordial stethoscope) were applied. While the patients were breathing oxygen, *d*-tubocurarine 3 mg was given intravenously approximately 3 min prior to induction. One minute prior to induction, the appropriate dose of fentanyl was given over 20 s. This was followed by thiopental (2-5 mg/kg) in a dose sufficient to abolish the eyelash reflex. Succinylcholine 1.5 mg/kg was given intravenously to facilitate tracheal intubation. The concentration of anesthetic given to patients was based on previously determined MAC values. The MAC for desflurane was taken as 6.0%<sup>6</sup> in patients aged 31-65 yr and 7.25% in patients aged 18-30 yr.<sup>6</sup> The MAC for isoflurane was taken as 1.28% (age 18-30 yr), 1.15% (age 31-55 yr), and 1.05% (age 56-65 yr).<sup>7</sup>

Following induction, the patient's lungs were ventilated with 1.0 MAC (age-adjusted) end-tidal concentration of either desflurane or isoflurane in oxygen. After the onset of neuromuscular blockade, the vocal cords were sprayed with 4% lidocaine and tracheal intubation performed im-

\* Associate Professor of Anesthesiology, Emory University School of Medicine.

† Assistant Professor of Anesthesiology, Duke University Medical Center.

‡ Research Fellow in Anesthesiology, Emory University School of Medicine.

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Address reprint requests to Dr. Sebel: Crawford Long Hospital of Emory University, Glenn Building, 25 Prescott Street N.E., Atlanta, Georgia 30308.

mediately. Ventilation was controlled throughout the study with an end-tidal  $P_{CO_2}$  of 30–35 mmHg. Body temperature was maintained at 35.5–37.0° C. Confirmation of recovery from neuromuscular blockade was made with a peripheral nerve stimulator prior to skin incision.

After intubation, patients immediately received their predetermined end-tidal anesthetic concentration up to the time of incision. Initially, patients given fentanyl 3  $\mu\text{g}/\text{kg}$  received 0.8 MAC end-tidal concentration of the inhalational agent; patients receiving fentanyl 6  $\mu\text{g}/\text{kg}$  received 0.6 MAC end-tidal concentration of the inhalational agent; and patients receiving no fentanyl received 1.0 MAC end-tidal concentration of the inhalational agent. These concentrations were held constant until skin incision. In the 60 s following skin incision the patient was observed for movement. If the patient moved, the next patient in that treatment group received an increase of 10% MAC end-tidal anesthetic agent concentration. If the patient did not move, the next patient received a reduction of 10% MAC in end-tidal concentration of the agent.

Desflurane was vaporized using an Ohio DM 5000 anesthetic machine modified to allow for the physical properties of desflurane. Isoflurane was vaporized from an Ohmeda TEC 3 vaporizer mounted on a standard anesthetic machine. Inspired and expired anesthetic agent concentrations and carbon dioxide concentration were monitored using a PB 254 multigas anesthesia monitor (Puritan-Bennett), modified to measure desflurane concentrations also. The monitor was calibrated with a commercial reference gas source before each use after a 30-min warm-up. After skin incision, if blood pressure or heart rate increased 20% above baseline, the end-tidal anesthetic agent concentration was increased by 10–20%. If this increase provided inadequate hemodynamic control, then in the period after skin incision fentanyl 0.5–1.0  $\mu\text{g}/\text{kg}$  was administered. If blood pressure decreased by more than 30% from baseline and did not respond to fluid administration, the end-tidal anesthetic agent concentration was decreased by 10–20%. At the end of surgery, the anesthetic agent was discontinued, and the time to spontaneous eye-opening and patient response to command was measured.

In the patients who received fentanyl at induction, venous blood was drawn to measure the plasma fentanyl concentration at 20 min after fentanyl administration, at skin incision, and at the end of surgery. Plasma fentanyl concentrations were measured (at Emory University) using radioimmunoassay (Fentanyl Radioimmunoassay kit, Janssen Life Sciences).<sup>8,9</sup>

MAC was determined by two methods. Within each group the “up–down” method of Dixon was used.<sup>10</sup> MAC was determined to be that concentration midway between the stable end-tidal concentration of anesthetic agent at

which one patient moved in response to skin incision, and the succeeding patient did not move, or *vice versa*. Each pair of MAC determinations were independent; *i.e.*, a patient movement was used only in one pair of calculations.

The up–down method of Dixon only used a limited data set (pairs of crossovers) and did not allow for a display of the continuous relationship between end-expired desflurane concentration and plasma fentanyl concentration. We therefore further analyzed our data by logistic regression (see Appendix). This provided a further calculation of MAC for each study group and a display of the MAC reduction of desflurane by fentanyl concentration.

Statistical analysis was the unpaired *t* test. A value of  $P < 0.05$  was taken as significant.

## Results

### MAC DETERMINATIONS

#### *Applying the Up–Down Method to Each Group (fig. 1)*

There were between three and eight pairs of data for MAC determinations in each group. Two possible pairs of determinations were excluded from analysis: one patient moved when skin incision occurred more than 90 min after induction (more than 6 standard deviations from the mean). In another patient, in the 10 min prior to incision, we were unable to maintain a stable end-tidal desflurane concentration. The MAC determinations in the group receiving isoflurane/fentanyl 6  $\mu\text{g}/\text{kg}$  are not reported. These determinations were considered unreliable because it proved impossible to adjust the agent concentration smoothly and accurately in the 0.2% end-tidal region with a conventional vaporizer. This situation was further compounded by the fact that the PB 254 gas analyzer read to only one significant figure at this concentration, leading to large proportional swings in the displayed concentration. These factors were not a problem with desflurane because the bubble-through vaporizer was able to deliver steady low concentrations which, because of the higher MAC, were measured to two significant figures. The MAC for the younger patients receiving desflurane with no fentanyl ( $n = 3$ ) is not shown because only one value was obtained. Data from 76 patients are presented in table 1. These represent the pairs of patients whose data resulted in a MAC determination.

The fentanyl concentrations at skin incision were significantly greater in the desflurane/fentanyl 6  $\mu\text{g}/\text{kg}$  and isoflurane/fentanyl 6  $\mu\text{g}/\text{kg}$  groups than in the equivalent desflurane/fentanyl 3  $\mu\text{g}/\text{kg}$  and isoflurane/fentanyl 3  $\mu\text{g}/\text{kg}$  groups of comparable age (fig. 2). In 14 of the patients who received fentanyl, concentrations were unavailable. The time of MAC determination was not sig-

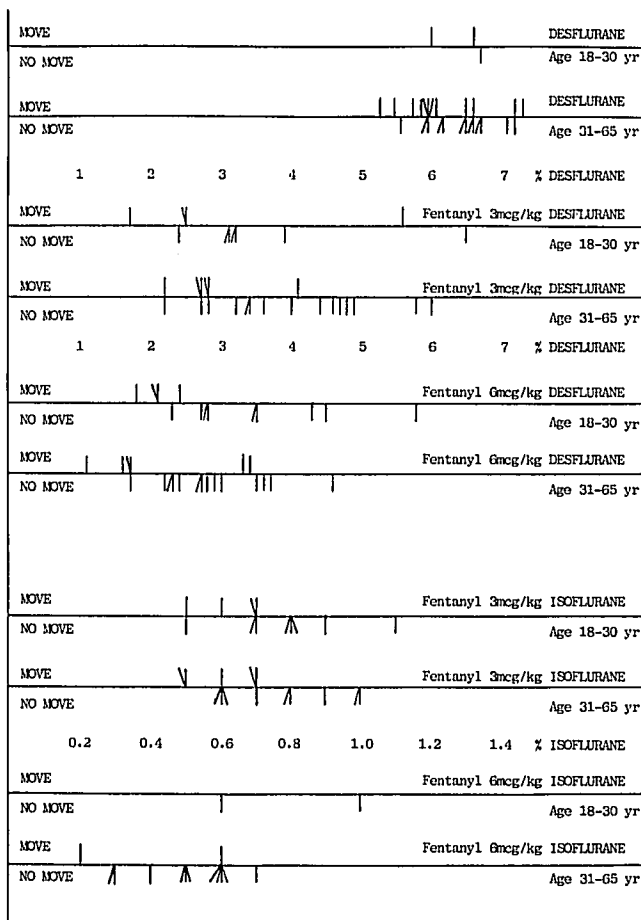


FIG. 1. The "move"/"no move" responses to skin incision of patients in each group. An upward mark represents one patient who moved, and a downward mark represents one patient who did not move. The horizontal axis shows the concentration of anesthetic gas at the time of incision, and the "move"/"no move" mark is plotted on this axis to show the concentration of anesthetic at which each skin incision was made.

nificantly different between any pair of groups who received fentanyl. However, the time to incision of the desflurane/oxygen older group ( $22.5 \pm 6.2$  min) when compared with the desflurane/fentanyl 6  $\mu\text{g}/\text{kg}$  younger group ( $29.3 \pm 8.6$  min) was different ( $P < 0.05$ ).

The MAC of desflurane in the absence of fentanyl was found to be 6.2% in the 31-65-yr age group. MAC was 3.22% (48% reduction) in the same age group following the fentanyl 3  $\mu\text{g}/\text{kg}$  bolus and further reduced to 2.25% (64% reduction) following a 6  $\mu\text{g}/\text{kg}$  bolus. In the younger age group (18-30 yr), the desflurane MAC was 2.56 and 2.35% following fentanyl 3 and 6  $\mu\text{g}/\text{kg}$ , respectively. The MAC of isoflurane, following fentanyl 3  $\mu\text{g}/\text{kg}$ , was 0.68% in the younger patients and 0.61% in the older group (table 1). Although the inclusion of a fentanyl bolus at induction resulted in a significant decrease in the MAC

of desflurane, there is no significant difference in the MAC of desflurane or isoflurane between patients who received fentanyl 3  $\mu\text{g}/\text{kg}$  and patients who received fentanyl 6  $\mu\text{g}/\text{kg}$ .

#### Analysis by Logistic Regression

Analysis by logistic regression (see Appendix) demonstrated that age was not a significant factor in the model; thus, the data from the two age groups are pooled. Using fentanyl doses as discrete categories, this analysis (fig. 3 and table 1) resulted in MAC values very similar to those obtained by the up-down method. Again, although there was a significant decrease in the MAC of desflurane by fentanyl 3  $\mu\text{g}/\text{kg}$  compared with no fentanyl, there were no significant differences between the MAC reduction obtained between the fentanyl 3 and 6  $\mu\text{g}/\text{kg}$  groups. Further analysis by logistic regression using fentanyl concentration as a continuous variable resulted in the relationship between fentanyl concentration and desflurane MAC shown in figure 4. In contrast to describing the MAC reduction of desflurane by predetermined fentanyl dose, this illustrates the MAC reduction of desflurane as a continuous function of fentanyl concentration. This uses the complete data set and actual measured fentanyl concentrations.

#### RECOVERY

The median fentanyl concentration, at the end of surgery, of both the desflurane and isoflurane patients was 0.61 ng/ml. Using this figure as the dividing line between "low" and "high" fentanyl concentrations allowed both the desflurane and isoflurane patients to be divided into two equally sized groups. Patients were allocated into "low" and "high" groups. Recovery, measured as the time taken for the patients to open their eyes and obey a command ("squeeze my hand") from discontinuing anesthesia, was always faster in patients who received desflurane than in those who received isoflurane within the high or low fentanyl concentration group (table 2). There was no significant intergroup difference in the length of surgery.

#### Discussion

##### MAC REDUCTION

MAC determinations for volatile anesthetics usually involve an inhalational induction followed by a period of time at a stable end-tidal concentration for equilibration between the brain and the blood to occur. Such methods have been applied both to humans<sup>7</sup> and to animals.<sup>1</sup> Although some human studies of the effect of opioids on MAC have been performed, these used a relatively small dose of opioid (morphine 8-15 mg<sup>3,4</sup> or 8-15 mg<sup>3</sup> pen-

TABLE 1. MAC Determinations

	Desflurane	Desflurane	Desflurane	Desflurane	Desflurane	Isoflurane	Isoflurane
Number of patients	16	6	10	8	10	6	8
Fentanyl dose ( $\mu\text{g}/\text{kg}$ )	0	3	3	6	6	3	3
Age (yr)	31-65	18-30	31-65	18-30	31-65*	18-30	31-65
Fentanyl concentration at 20 min (ng/ml)	—	0.66 $\pm$ 0.35	0.82 $\pm$ 0.37	1.93 $\pm$ 0.66*	1.71 $\pm$ 0.68	0.99 $\pm$ 0.34	0.73 $\pm$ 0.37
Fentanyl concentration at incision (ng/ml)	—	0.60 $\pm$ 0.50	0.82 $\pm$ 0.59	1.65 $\pm$ 0.84*	1.64 $\pm$ 0.69*	0.95 $\pm$ 0.63	0.72 $\pm$ 0.35
Time of incision (min after induction)	22.5 $\pm$ 6.2†	29.3 $\pm$ 15.9	25.8 $\pm$ 10.2	29.3 $\pm$ 8.6	24.1 $\pm$ 9.4	25.1 $\pm$ 9.7	24.1 $\pm$ 9.0
MAC by Dixon <sup>10</sup> method	6.2 $\pm$ 0.3	2.56 $\pm$ 0.45‡	3.22 $\pm$ 0.71‡	2.35 $\pm$ 0.28‡	2.25 $\pm$ 0.96‡	0.68 $\pm$ 0.08	0.61 $\pm$ 0.09
MAC by logistic regression	6.3	2.6		2.0		0.61	
95% confidence interval for MAC by logistic regression	5.3-7.6	2.0-3.2		1.5-2.5		0.31-0.81	

MAC determinations and fentanyl concentrations in each group. Data are mean  $\pm$  SD.

\*  $P < 0.05$  compared with desflurane/fentanyl 3  $\mu\text{g}/\text{kg}$  and isoflurane/fentanyl 3  $\mu\text{g}/\text{kg}$ .

†  $P < 0.05$  compared with age 18-30 yr desflurane/fentanyl 6  $\mu\text{g}/\text{kg}$ .

‡  $P < 0.05$  compared to desflurane with no fentanyl.

tazocine 0.2 mg/kg<sup>11</sup>). The interaction between larger doses of opioids and anesthetic MAC has generally been studied in animals.<sup>1,2,12,13</sup> In animals, it is possible to produce varying but stable plasma concentrations of opioid that will allow study of concentration-effect relationships. It is also possible to conduct multiple MAC determinations on the same animal under different conditions, a procedure not possible in humans. Using these techniques, Murphy and Hug have shown that fentanyl induces dose-related MAC reductions of enflurane in the dog.<sup>1</sup> This MAC reduction showed a ceiling effect at 64-66%, and this was observed with a plasma fentanyl concentration of 28-97 ng/ml. However, a MAC reduction of 33% was achieved with a fentanyl concentration of only 3.0 ng/ml and a steep dose-response effect was shown between 3 and 6 ng/ml, which then flattened at higher concentrations. A MAC reduction of 85% of the maximum observed was achieved with a fentanyl concentration of 6.5 ng/ml.<sup>1</sup> This implies that the concentration response (MAC reduction in dogs) is initially steep but becomes fairly flat at higher fentanyl concentrations.

We used the up-down method of determining MAC. With this method, the chance of a patient moving in response to skin incision is increased if the previous patient did not move, because the end-tidal anesthetic concentration is reduced, and similarly the chance of movement decreased if the previous patient did move, because the anesthetic concentration is increased. This tends to focus the anesthetic concentration to which patients are exposed around a single value (MAC). In patients who received fentanyl, a relatively high concentration of anesthetic was initially administered. This resulted in many patients not moving while gradually the anesthetic concentrations were reduced. Because there were eight groups of patients who received fentanyl, data from a large number of our pa-

tients did not contribute to a MAC determination and were used only to reduce the anesthetic concentration to near MAC. Furthermore, with the up-down method, if two consecutive patients do not move, followed by two consecutive patients who do move, then only one MAC determination can be made, even though all four patients are responding (or not) around MAC and represent the normal variation of sensitivity to anesthesia seen in patients. For these two methodological reasons, we made fewer MAC determinations than initially planned. The

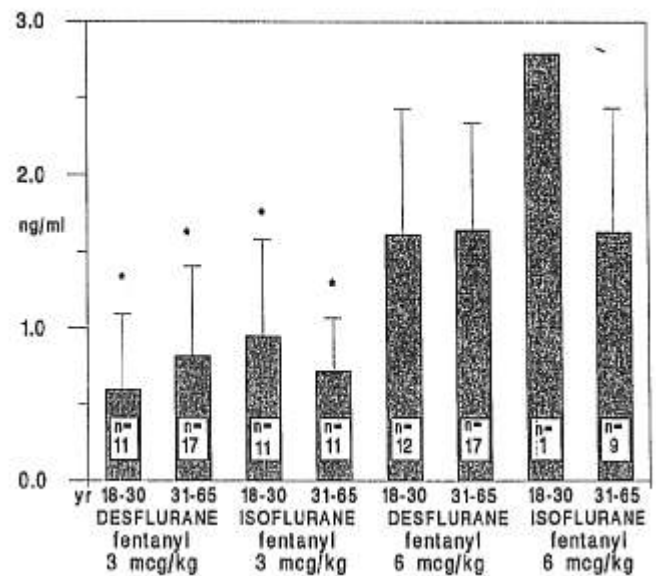


FIG. 2. Plasma fentanyl concentration at the time of incision in each group. The number of patients (n) who had a fentanyl concentration measured is superimposed on the bar. Patients in the first two groups are not shown because they had received no fentanyl. Data are mean  $\pm$  SD. \* $P < 0.05$  compared to patients receiving fentanyl 6  $\mu\text{g}/\text{kg}$ .

patient population that we randomly included in the study contained relatively few patients in the 18–30-yr age group, as demonstrated in table 1. Thus, more emphasis can be placed on the data from the 31–65-yr old patients.

The logistic regression analysis was used to determine MAC for several reasons. The up-down method, by its nature, does not use the full data set. Further, it requires an adequate number of crossovers in each group. The up-down method does not allow modeling using a continuous variable such as plasma fentanyl concentration. Thus, logistic regression may be more applicable in de-

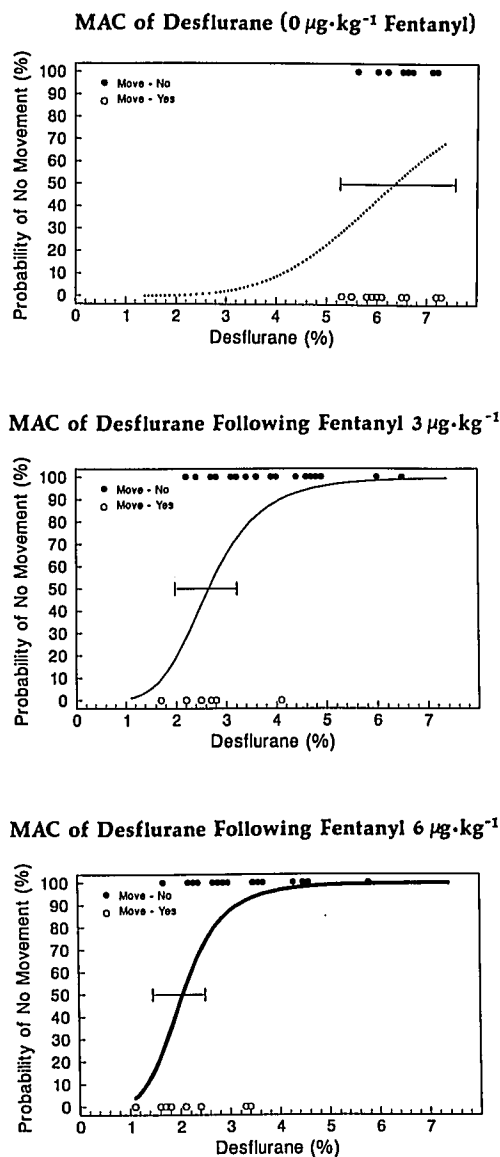


FIG. 3. Logistic regression of probability of movement fitted for desflurane concentration against no fentanyl, fentanyl 3  $\mu\text{g}/\text{kg}$ , or fentanyl 6  $\mu\text{g}/\text{kg}$ . The MAC (50% probability of no movement) and its 95% confidence interval (horizontal line) are shown on each graph, and the numerical values are given in table 1.

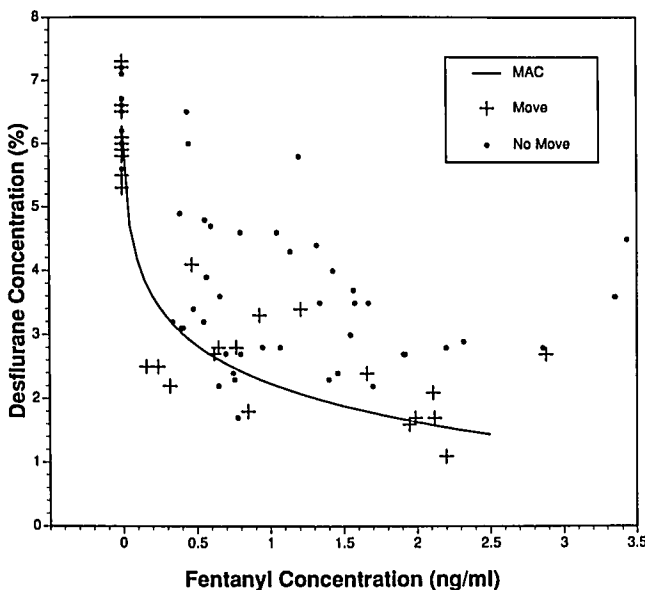


FIG. 4. MAC reduction of desflurane by fentanyl. Logistic regression of desflurane concentration and fentanyl concentration showing the 50% probability of no movement (MAC) for the combination.

scribing the interaction of two drugs. When considering fentanyl dose as a categorical variable, both methods of analysis gave essentially the same results (Table 1). Therefore, both methods appear valid. In addition, logistic regression allowed us to relate the actual fentanyl concentration to the 50% probability of movement for desflurane. Figure 4 gives the MAC of desflurane for fentanyl concentrations below 2.5 ng/ml. It can be seen from this relationship that the MAC reduction of desflurane is steep between 0 and 1 ng/ml fentanyl concentration but flattens at higher concentrations. These data are consistent with the MAC reduction by fentanyl in dogs.<sup>1</sup> Fentanyl 3  $\mu\text{g}/\text{kg}$  resulted in a plasma concentration at incision of  $0.78 \pm 0.53$  ng/ml, whereas fentanyl 6  $\mu\text{g}/\text{kg}$  resulted in  $1.72 \pm 0.76$  ng/ml. These concentrations are on the flatter part of the curve, and it is not surprising that we were unable to determine statistically significantly different MAC reductions between these two groups.

In our study, we chose to use a single dose of fentanyl rather than a continuous infusion. This was because we wished to determine the MAC reduction resulting from a measured plasma concentration produced by a bolus dose of fentanyl in a manner akin to common clinical usage. It is important to note, however, that the MAC reduction resulting from a measured plasma concentration produced by a bolus dose of fentanyl can be considerably different from the MAC reduction produced by the same fentanyl concentration obtained by a continuous infusion. We cannot measure fentanyl concentration at the effector site, the brain, but there is good evidence physiologically that hysteresis exists between the plasma

TABLE 2. Time (minutes) to Open Eyes and Respond to Command (Hand-squeeze) after Discontinuing Anesthesia

	Desflurane "low"	Isoflurane "low"	Desflurane "high"	Isoflurane "high"
Concentration of fentanyl (ng/ml)	0.386 ± 0.162*	0.412 ± 0.124*	1.018 ± 0.465	1.041 ± 0.395
Duration of anesthesia (min)	125 ± 67.8	127 ± 51.3	161 ± 97.2	123 ± 45.6
Open eyes (min)	5.13 ± 2.02†	7.83 ± 5.62	5.83 ± 3.67†	9.50 ± 4.98
Obey command (min)	5.66 ± 2.13†	8.97 ± 5.11	6.24 ± 3.53†	10.11 ± 4.82
Number of patients	31	18	30	17

Data are mean ± SD.

\*  $P < 0.001$  compared to high concentration fentanyl.

†  $P < 0.02$  compared to isoflurane at same fentanyl concentration range.

and effector site concentration.<sup>14</sup> Because of hysteresis, there is an initial lag between increase in plasma concentration and the effector compartment concentration. Similarly, as the plasma concentration decreases, there is a lag between the decrease in the effector site and the plasma. Thus, the plasma concentration measured after a bolus dose is not necessarily reflective of its concentration within the brain. Scott *et al.*, using the EEG, has calculated the rate constant between plasma and effector site for fentanyl ( $K_{EO}$ ) to be 6.4 min.<sup>14</sup> Using this  $K_{EO}$  value, computer simulations§ predict that after a single bolus dose of fentanyl (3 or 6  $\mu\text{g}/\text{kg}$ ), the plasma concentration would be approximately 70% of the effector site concentration at 25 min. The average plasma concentration of fentanyl measured at skin incision after 3 and 6  $\mu\text{g}/\text{kg}$  was  $0.78 \pm 0.53$  and  $1.72 \pm 0.76$  ng/ml, respectively. Thus, the estimated effect site concentration would be considerably higher from the measured plasma concentration at skin incision. Therefore, if we account for hysteresis, the MAC reduction observed in our study (1.1–2.2 ng/ml concentration in the effector compartment producing 47–65% MAC reduction) is not too dissimilar to the 50% MAC reduction observed with isoflurane under steady-state conditions of 2.1 ng/ml in dogs.¶

In previous studies of the potency of inhalational anesthetics, it has generally been found that MAC decreases as age increases.<sup>7</sup> We were unable to obtain a significant effect of age on MAC reduction in this study. This may be due in part to the way in which patients were entered into our study group. Each patient was assigned to the next appropriately randomized group, regardless of age. They were then subdivided by age. With our relatively older patient group included in this study, it may be that we had an insufficient number of young patients to obtain a statistically significant difference between the two groups. Previous studies have generally used one volatile anesthetic and then investigated the effects of altering

age on the MAC of that anesthetic. In the present study, we added an additional confounding variable, that of a varying fentanyl concentration. It may be that introducing the second variable (which was not held constant throughout the study) will increase the variance of MAC, such that the age effect is not apparent. Indeed, this is the case from our analysis both by the Dixon<sup>10</sup> method and by logistic regression.

Although MAC determinations are usually carried out using an inhalational induction, we chose to use an intravenous induction for this study, as has been performed elsewhere.<sup>15</sup> Inhalational induction, particularly using isoflurane, would be unacceptable to many of our patients. Because the MAC determination was carried out approximately 25 min after thiopental, the effect of the induction agent was believed likely to be minimal. The MAC determination of 6.2% in patients who received thiopental/desflurane/oxygen (age 31–65 yr) is, in fact, very similar to the previously described MAC of 6.0% using an inhalational induction.<sup>6</sup>

Our protocol included lidocaine spray (160 mg) to anesthetize the larynx at the time of intubation. This was performed in order to reduce the possibility of laryngeal irritation interfering with the stabilization of anesthetic gas concentrations due to coughing and to avoid adding to the stimulus of skin incision. It is possible that the central nervous system effects of absorbed lidocaine may have contributed to a deepening of anesthesia and resulted in the determination of a lower MAC value. Local anesthesia of the larynx has, however, been used in previous studies in humans of MAC reduction with opioids.<sup>3,4</sup>

The data from this study suggest that 25 min after a dose of fentanyl 3–6  $\mu\text{g}/\text{kg}$ , a reduction in the MAC of desflurane between 48 and 68% may be anticipated and that after fentanyl 3  $\mu\text{g}/\text{kg}$ , using our methodology, the MAC of isoflurane is found to be 0.61–0.68%. Using historical control data,<sup>7</sup> this represents a decrease in the MAC of isoflurane of 47% similar to the reduction of MAC of desflurane. However, these historical controls received only isoflurane, unlike our patients who also received other drugs, and may not be directly comparable with the patients in our study.

§ Jacobs J: Personal communication.

¶ Murphy MR, Hug CC: Efficacy of fentanyl in reducing isoflurane MAC: antagonism by naloxone and nalbuphine (abstract). ANESTHESIOLOGY 59:A338, 1983.

## RECOVERY

Grouping of patients by fentanyl concentration at the end of surgery is more logical than by the dose given at induction because many patients (especially those not receiving 6  $\mu\text{g}/\text{kg}$  fentanyl) required extra fentanyl during surgery. Although clinical criteria dictated the administration of fentanyl, it was not our normal practice to give fentanyl in the last 45 min of surgery. Thus, large changes in the plasma and brain concentrations over time were unlikely to be occurring (in contrast to after induction). The recovery data from our study show that patients who are anesthetized with desflurane have more rapid return of consciousness than patients anesthetized with isoflurane, confirming previous animal<sup>5</sup> and human<sup>16</sup> data. The use of fentanyl did not prevent a difference in times to awakening.

In conclusion, fentanyl 3  $\mu\text{g}/\text{kg}$  given as an intravenous bolus at induction resulted in a marked reduction in the MAC of desflurane. Increasing this dose to 6  $\mu\text{g}/\text{kg}$  results in only a small further decrease in the MAC of desflurane. We also observed a more rapid awakening at the end of surgery in patients who were anesthetized with desflurane as compared to those anesthetized with isoflurane when their plasma fentanyl concentrations were similar.

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## Appendix

Estimates of MAC were derived from the data through the use of logistic regression. Such analyses model the probability of a dichotomous (*i.e.*, yes or no response) outcome as a linear function of the exponential part of logit of the logistic function. In the logit we may fit a number of different regressors (*i.e.*, age, weight, and drug treatment), either continuous or discrete in distribution. If the outcome is D (0 = response, 1 = no response) and  $X_1, X_2, \dots, X_n$  consists of n regressors, then the fitted probability of a positive outcome as a function of the  $X_i$  is

Logistic probability  $[D = 1 | (X_1, X_2, \dots, X_n)]$

$$= (1 + \exp[-\text{logit}])^{-1} = (1 + \exp - [A + \Sigma(B_i X_i)])^{-1}$$

The  $X_i$ ,  $i = 1$  to  $n$ , represent  $n$  variables in the model. These variables were the concentration of desflurane (for which a MAC is desired), measured plasma concentration of fentanyl, or indicator variables to represent discrete doses of administered fentanyl, age, or other variables that might influence the likelihood of response.  $A$  is an intercept, and the  $B_i$  are the fitted regression coefficients of the respective variables. The fit of the model to the data is accomplished using an iterative maximum likelihood technique. The predicted probability of no response for any combination of variables in a patient will then lie between 0 and 1. Calculation of the MAC is then accomplished by setting the predicted probability of no response to 0.5 and solving the function for the concentration of desflurane.

Our initial analyses quantified fentanyl dose through the use of indicator variables to represent the three doses: 0, 3, and 6  $\mu\text{g}/\text{kg}$ . By using an indicator variable, no assumption about the functional form or shape of the fentanyl dose or response relationship was made except that desflurane acts similarly at each level of fentanyl.  $C$  levels of a categorical variable may be represented in this way by  $C - 1$  dichotomous variables, each of which takes on a value of 1 if the patient is in that category, and otherwise is equal to 0. One category is used as a comparand

level; when a patient is in that category all C - 1 indicator variables are set equal to 0. We used the dose of 0 µg/kg as our comparand level and thus had two indicator variables in the model: F3 represented a dose of 3 µg/kg, and F6 represented a dose of 6 µg/kg. In addition, we fitted the measured end-tidal concentration of the natural log of desflurane as a variable L. The natural log of desflurane was used to ensure that neither the calculated values for MAC nor their confidence limits would be less than 0. Also, the fit of response or no response to the natural log of desflurane end-tidal concentration was superior to that in its original scale. Thus, we had the following model:

$$\text{Logistic probability } [D = 1 | (F_3, F_6, L)] = (1 + \exp[-\text{logit}])^{-1} \\ = (1 + \exp - (A + B_1 \cdot F_3 + B_2 \cdot F_6 + B_3 \cdot L))^{-1}$$

If we set the probability equal to 0.5, then

$$(1 + \exp[-\text{logit}])^{-1} = 0.5 = 1/2 \\ (1 + \exp[-\text{logit}]) = 2 \\ \exp(-\text{logit}) = 1$$

and

$$\text{logit} = 0$$

Thus we solve the following relationship for desflurane end-tidal concentration L:

$$\text{logit} = A + B_1 \cdot F_3 + B_2 \cdot F_6 + B_3 \cdot L = 0$$

leading to

$$L_m = \text{Ln}(\text{MAC}) = -(A + B_1 \cdot F_3 + B_2 \cdot F_6)/B_3$$

and

$$\text{MAC} = \exp[-(A + B_1 \cdot F_3 + B_2 \cdot F_6)/B_3]$$

TABLE A1. Fitted Values for the Coefficients of the Model Using Discrete Doses of Fentanyl

	A	B <sub>1</sub>	B <sub>2</sub>	B <sub>3</sub>
Coefficient	9.3975	4.4405	5.7233	5.0925
Standard error	2.7119	1.2900	1.5525	1.4544

TABLE A2. Fitted Values for the Coefficients of the Model Using Measured Fentanyl Plasma Concentration as a Continuous Variable

	A	B <sub>1</sub>	B <sub>2</sub>
Coefficient	2.8424	1.1059	1.2642
Standard error	1.0759	0.3072	0.3732
Probability	0.0082	0.0003	0.0007

The fitted values of the coefficients in this model are shown in table A1. The MAC is calculated by solving for the desflurane end-tidal concentration at a specific dose of fentanyl: *i.e.*, 0, 3, or 6 µg/kg.

For the measured fentanyl plasma concentration, the data had to be converted to a continuous function. Thus, in an additional analysis we fitted the natural logarithm of the fentanyl plasma concentration (fentanyl concentration + 0.01; because some values of fentanyl were 0, a small constant was added, since Ln(0) is undefined) (F), with coefficient B<sub>1</sub>. In this model desflurane end-tidal concentration, L, was fitted in its original scale, with coefficient B<sub>2</sub>.

The fitted values of the coefficients in this model are shown in table A2.

Thus we solve the following relationship for desflurane end-tidal concentration L:

$$\text{Logit} = A + B_1 \cdot F_3 + B_2 \cdot L = 0$$

leading to

$$L_m = \text{MAC} = -(A + B_1 \cdot F)/B_2$$

$$= -(2.842 + 1.1059 \cdot F)/1.2642 = 2.2484 - 0.8748 \cdot F$$

a linear, decreasing function of the natural log of the fentanyl plasma concentration. This is displayed in figure 4.

The tests of significance of each coefficient in these regression models (that is, tests of the assumption that they were 0 or that their respective variables had no significant relationship to outcome) led to probabilities always much less than 0.01. When age was also included as an additional covariate in such models, the significance level of its relationship was never as small as 0.05 and, in fact, was usually greater than 0.50, indicating that in this sample of patients with this study design, no relationship of response to age was noted.