

The Anesthetic Potency of Fentanyl in Terms of Its Reduction of Enflurane MAC

Michael R. Murphy, M.D.,* and Carl C. Hug, Jr., M.D., Ph.D.†

Infusion rates for fentanyl were calculated to produce stable plasma concentrations at which the ability of fentanyl to reduce enflurane MAC could be studied utilizing the tail clamp method and measurement of end-tidal enflurane. Following the determination of control enflurane MAC in each animal, an infusion of fentanyl was begun. Group 1 received continuous successive infusion rates of 0.05, 0.1, and 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with respective loading doses (given over 20 min) of 15, 15, and 30 $\mu\text{g}/\text{kg}$; Group 2 received infusions of 0.2, 0.8, and 3.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with loading doses of 30, 90, and 270 $\mu\text{g}/\text{kg}$, respectively. Group 3 was studied in the same manner except that fentanyl was omitted from the infusion solution. Enflurane MAC was determined at each infusion level and blood samples were analyzed for the concentration of fentanyl. Fentanyl concentrations in plasma were proportional to the infusion rate. Enflurane MAC was decreased significantly in proportion to fentanyl plasma concentrations up to 30 ng/ml where a reduction of MAC by 65% was evident. A threefold higher concentration produced a minimal further reduction. In Group 3 dogs, no change in enflurane MAC was seen. It was concluded that predictable, stable levels of fentanyl in plasma can be achieved, that there is a close relationship between the concentration of fentanyl in plasma and its enflurane sparing effect, and that there is a ceiling to this concentration-response relationship. (Key words: Analgesics, narcotic: fentanyl. Anesthetics, inhalational: enflurane. minimal alveolar concentration. Pharmacokinetics: infusion.)

NARCOTIC ANALGESICS are commonly used as anesthetic supplements in order to reduce the concentrations of potent inhalational anesthetics required for a given depth of anesthesia. Narcotics, especially fentanyl, also have been advocated as primary or sole anesthetic agents. Although fentanyl doses of 50–75 $\mu\text{g}/\text{kg}$ produce anesthesia in some critically ill patients, their anesthetic effects have been inadequate in physically fit subjects, and there has been a tendency to use progressively larger doses, up to 150 $\mu\text{g}/\text{kg}$ or more.¹ It is important to evaluate the anesthetic effectiveness of fentanyl, and one means of doing so is to measure its ability to substitute for a potent inhalational anesthetic such as enflurane.

The kinetics of fentanyl distribution and elimination are such that plasma and brain levels change continuously after single or intermittent intravenous doses, making it difficult to evaluate the effectiveness of a given

dose.²⁻⁴ Since there is a close relationship between the concentration of fentanyl in plasma and its effects, it should be possible to produce and to maintain a particular degree of narcotic analgesic effect by maintaining a constant plasma concentration of fentanyl.

Therefore, our objectives in performing this study were 1) to produce plasma levels of fentanyl that remained stable over a period of time during which we could determine concentration-effect relationships, and 2) to determine the ability of fentanyl to decrease the anesthetic requirement (MAC) of enflurane.

Materials and Methods

Mongrel dogs weighing 12–29 kg (mean 19 ± 1.0 SEM, $N = 18$) each were given an intravenous injection of succinylcholine chloride (0.10 ± 0.01 mg/kg) and atropine sulfate (0.10 ± 0.01 mg/kg) and anesthesia was induced immediately with 5% enflurane in oxygen, administered via a mask and a Bain anesthesia circuit. A cuffed endotracheal tube was introduced and the dog was ventilated with a Harvard® respirator to maintain a normal PaCO_2 ; blood pH was maintained in the normal range by the addition of sodium bicarbonate as needed. An intravenous catheter was placed in a foreleg vein and 5% dextrose in lactated Ringer's solution was administered at a rate of 11.4 ± 0.9 ml \cdot kg⁻¹ \cdot h⁻¹. Body temperature was maintained at $37.2^\circ \pm 0.2^\circ$ C. The electrocardiogram was monitored throughout the experimental period and a urinary catheter was inserted.

A femoral arterial cannula was utilized for continuous blood pressure recording and periodic sampling of blood for gas analysis and for the determination of unchanged fentanyl by radioimmunoassay.⁵ End-tidal enflurane was measured by a Beckman® LB-2 infrared analyzer. MAC determinations were made according to the technique of Eger *et al.*⁶ Briefly, the base of the dog's tail was shaved. At least one hour after the induction of anesthesia and with a stable end-tidal enflurane concentration maintained for a minimum of 15 min, a "sponge-stick" clamp was applied to the tail. The tail was moved continuously with the closed clamp for one min or until purposeful movement (as defined in reference 6) was elicited from the dog. MAC was determined as the point midway between the end-tidal concentrations at which the animals would or would not move. MAC was determined to the closest 0.1% end-tidal enflurane concentration maintained for at least 15 min.

* Assistant Professor of Anesthesiology.

† Professor of Anesthesiology and Pharmacology.

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Address reprint requests to Dr. Murphy.

TABLE 1. Concentrations of Fentanyl (F) in Plasma Produced by Intravenous Infusions*

F Infusion Rate		Number of Dogs	Plasma F \pm SEM (ng/ml) during MAC Determination	
Loading ($\mu\text{g}/\text{kg}$)	Maintenance ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)		Start	End
Group 1				
15	0.05	7	2.7 \pm 0.4	3.1 \pm 0.2
15	0.1	7	5.8 \pm 0.4	6.5 \pm 0.9
30	0.2	5	12 \pm 2	11 \pm 1
Group 2				
30	0.2	6	7.6 \pm 2.0	8.2 \pm 2.2
90	0.8	4	28 \pm 5	29 \pm 7
270	3.2	4	115 \pm 32	99 \pm 33

* Concentrations of fentanyl (F) in plasma produced by a loading infusion (given over 20 min) and a maintenance infusion begun at the same time are expressed as the means \pm SEM for samples taken during the last 30 min of each MAC determination.

After control measurements were made, both a loading and a maintenance infusion of fentanyl citrate (measured as the base \ddagger) were begun at the same time. Enflurane MAC was redetermined 60 min after the infusion was begun. Then, an additional loading dose was given and the continuous infusion rate was increased and maintained at the higher level for 60 min before enflurane MAC was determined again. Each dog received progressively higher fentanyl infusion rates. \S Infusion rates required for particular plasma concentrations of fentanyl were estimated by Wagner's method applied to pharmacokinetic data previously published for dogs anesthetized with enflurane.^{7,8} The continuous infusion rates for the low dose (Group 1) were 0.05, 0.1, and 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with respective loading doses (given over 20 min) of 15, 15, and 30 $\mu\text{g}/\text{kg}$. The high dose animals (Group 2) received continuous infusions of 0.2, 0.8, and 3.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with respective loading doses (over 20 min) of 30, 90, and 270 $\mu\text{g}/\text{kg}$. A third group (Group 3) of five animals were studied in exactly the same manner except fentanyl was omitted from the lactated Ringer's solution that was infused continuously over an 8-h period.

Blood samples (8 ml) were obtained every 30 min after the beginning of the infusion of fentanyl, and the plasma was analyzed for unchanged fentanyl by radioimmunoassay as described by Michiels *et al.*⁵ Values are expressed as the means \pm standard error of the mean

\ddagger Powdered fentanyl citrate was provided by Janssen Pharmaceutica, New Brunswick, New Jersey. The concentrations of the infusion solutions were expressed as fentanyl base, just as the commercially available solutions (*i.e.*, 50 μg fentanyl base/ml of Sublimase solution).

\S One dog in Group 1 and two dogs in Group 2 received different infusion rates for the second and third infusions in preliminary studies; the data for these infusion rates are not shown.

unless designated otherwise. Significant differences were determined by analysis of variance and paired *t* tests with $p < 0.05$ as the minimal limit of significance. Fentanyl doses and concentrations are calculated and expressed as the base.

Results

Fentanyl concentrations in plasma were proportional to the infusion rates and were maintained in a narrow range ($\pm 19\%$) during the period of enflurane MAC determinations (table 1). The values in table 1 are the concentrations of fentanyl in plasma at the beginning and end of the last 30-min period of each MAC determination, and this corresponded to the 90- to 120-min interval of each continuous infusion rate in all but three animals in which the MAC determination required an additional 30 min. In Group 1, doubling the loading dose (on a cumulative basis) and maintenance infusion rate resulted in an approximate doubling of the plasma concentration in each instance. In Group 2, quadrupling the loading dose (on a cumulative basis) and the continuous infusion rate approximately quadrupled the plasma concentrations in plasma. It is apparent that the concentration of fentanyl in plasma for the third dose in Group 1 is higher than the first dose in Group 2, even though the infusion rates (both maintenance and loading) were the same. This discrepancy can be explained by the accumulation of fentanyl from the preceding doses administered to the animals of Group 1. At the time of MAC determinations, the concentration of fentanyl in plasma was approaching but had not yet attained the predicted steady-state level.

In order to demonstrate the stability of enflurane MAC during the 8-h experimental period, five dogs were given infusions of lactated Ringer's solution containing no fentanyl (placebo infusions) and enflurane MAC determinations were repeated over an 8-h period in a sequence similar to that employed in the animals receiving fentanyl. The initial enflurane MAC was 2.26 \pm 0.02%, and it remained unchanged during the three placebo infusions; MAC was 2.23 \pm 0.06, 2.19 \pm 0.10, and 2.19 \pm 0.10% at 4, 6, and 8 h, respectively.

Figure 1 shows the reduction of enflurane MAC as a function of the log concentration of fentanyl in plasma. Enflurane MAC was decreased significantly in proportion to fentanyl plasma concentrations up to approximately 30 ng/ml where the reduction appeared to plateau at a 65% reduction from control (table 2). Essentially the same reductions in enflurane MAC were evident at approximately the same plasma concentrations of fentanyl whether the concentrations were achieved in the first hour (Group 2) or the seventh hour (Group 1) of exposure to fentanyl (table 2 and fig. 1).

Discussion

The idea of continuously infusing drugs is not new, but it is becoming increasingly important to the anesthesiologist. For many years, it has been recognized that there is a particular range of drug levels in plasma that are therapeutic; higher concentrations often produce toxicity or side effects, and lower concentrations are ineffective. Common examples are lidocaine infusion for treatment of dysrhythmias,⁹ procaine infusion to produce general anesthesia,¹⁰ or succinylcholine infusion for muscular relaxation.¹¹ For the infusion of a drug to be useful, there must be a reasonably close relationship between the concentration of the drug in plasma and its desired effect. Also, a reliable method for achieving and maintaining the desired drug concentration is required.

Single bolus doses of intravenous anesthetics produce a continuously changing (usually decreasing) level of anesthesia. For this reason, small bolus doses often have been repeated to maintain reasonable levels of anesthesia; the closer together the doses are given, the more stable the effect. An infusion is the ultimate of repeating many small bolus doses at short intervals. The concentration of the drug in plasma will tend to remain relatively constant and a stable level of anesthesia is more properly maintained.

Infusion of intravenous agents is analogous to the inhalation of volatile anesthetics. The therapeutic range, or MAC, for various inhalational agents is known and is produced by "infusion" of the agent through the lungs, generally starting with a higher concentration (loading dose) and decreasing to a lower but stable level for the duration of the anesthetic (maintenance dose).

For an infusion to be useful, there must be a demonstrable relationship between the concentration of the drug in the blood and its effect. A very close relationship between the concentration of fentanyl in plasma and its respiratory depressant effects, following the rapid equilibration of fentanyl between plasma and the central nervous system, has been shown previously.^{2,4} This study also demonstrates a relationship between the concentration of fentanyl in plasma and its effectiveness in decreasing the MAC of enflurane.

Wagner has described a method for calculating loading and maintenance infusion rates as well as for estimating the peak and stable concentrations likely to result from the infusions.⁷ His method was described for drugs fitting a two-compartment pharmacokinetic model. We applied his method to pharmacokinetic data previously reported for fentanyl in dogs anesthetized with enflurane.⁸ The same method should be applicable to the clinical use of fentanyl, since the needed pharmacokinetic parameters in humans are available, and in

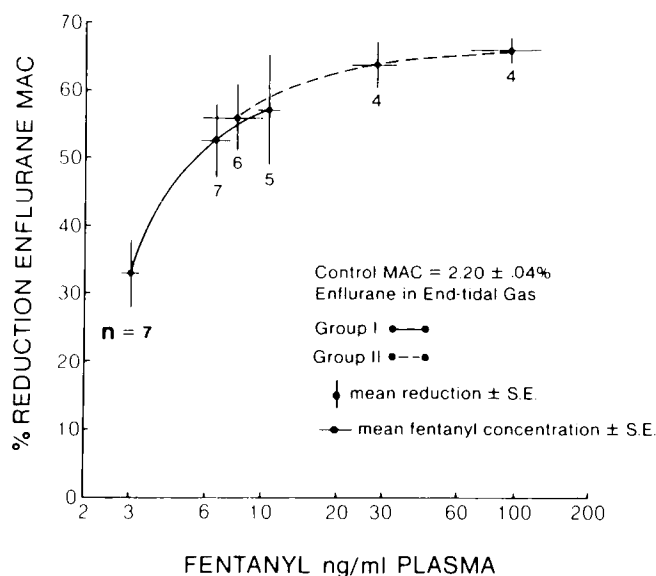


FIG. 1. Per cent reduction of enflurane MAC as a function of the logarithm of the plasma fentanyl concentration. Each point represents the mean concentration (\pm SEM) of fentanyl in plasma and the average per cent (\pm SEM) reduction of enflurane MAC in the number of dogs indicated below the vertical standard error bar. The control MAC for Groups 1 and 2 are shown in table 2.

fact, fentanyl infusion techniques are being utilized.^{12,13} However, the variables likely to affect plasma levels of fentanyl in patients have not yet been evaluated. Furthermore, the concentrations of fentanyl in plasma needed for particular clinical situations have not been defined. The maintenance of stable plasma levels of fen-

TABLE 2. Reduction of Enflurane MAC at Different Concentrations of Fentanyl in Plasma*

Fentanyl Loading/ Maintenance ($\mu\text{g}/\text{kg}/\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Enflurane MAC (Mean % ET \pm SEM)	Per Cent Reduction mean % \pm SEM	Plasma Concentration ng/ml mean \pm SEM
Group 1			
Control n = 7	2.25 \pm 0.08	0	0
15/0.05 7	1.51 \pm 0.12	33 \pm 5	3.0 \pm 0.3
15/0.1 7	1.06 \pm 0.13	53 \pm 6	6.5 \pm 0.9
30/0.2 5	0.93 \pm 0.19	57 \pm 8	10.5 \pm 1.2
Group 2			
Control n = 6	2.06 \pm 0.06	0	0
30/0.2 6	0.90 \pm 0.10	56 \pm 5	7.8 \pm 2.1
90/0.8 4	0.75 \pm 0.09	64 \pm 4	28.2 \pm 5.9
270/3.2 4	0.70 \pm 0.07	66 \pm 2	97.0 \pm 31.8

* The reductions of enflurane MAC in both groups are significant ($P < 0.01$) by analysis of variance (AOV). Also, two-way AOV shows that the results in Group 1 differ significantly ($P < 0.05$) from those in Group 2. Statistically significant differences ($P < 0.05$, Student's *t* test) include the MAC reductions at the following fentanyl concentrations: control vs. 3.0 ng/ml; 3.0 ng/ml vs. 6.5 ng/ml; 6.5 ng/ml vs. 97.0 ng/ml.

tanyl should be useful in solving both problems—variables affecting fentanyl levels and the drug-concentration-response relationships.

Narcotic analgesics have been utilized as primary anesthetic agents (along with muscle relaxants) for several years, and fentanyl is especially popular at present because of its minor effects on myocardial performance. Some investigators have attempted to overcome some of the shortcomings of fentanyl anesthesia (*e.g.*, awareness, sympathetic responses to noxious stimulation) by increasing the dose, up to and exceeding 150 $\mu\text{g}/\text{kg}$.¹ To the extent that fentanyl's reduction of enflurane MAC in dogs is equivalent to anesthetic depth in humans, the results of the present study indicate that there is a ceiling to the effectiveness of fentanyl as an anesthetic. In dogs, the concentrations of fentanyl in plasma greater than 30 ng/ml did not produce more than a 65% reduction in enflurane MAC.

Enflurane has been shown to increase central nervous system activity on the electroencephalogram. It is possible that stimulant activity of *low* concentrations of enflurane contributed to the responsiveness of these dogs even in the presence of very high concentrations of fentanyl. This possibility will have to be tested by further studies utilizing another inhalational anesthetic agent. However, it should be noted that the EEG and motor changes indicative of CNS stimulation occur at *high* concentrations of enflurane, especially in the presence of hypocarbia (not evident in our dogs).¹⁴ Also, there was no motor evidence of seizure-like activity in our animals, even in response to clamping their tails.

In patients, the concomitant use of muscle relaxants with narcotic analgesics may decrease the input to the reticular activating system and facilitate the loss of consciousness.¹⁵ The dogs utilized in this study were paralyzed only transiently by succinylcholine administered long before the first determination of enflurane MAC.

The concentrations of fentanyl in this study ranged from less than 3 ng/ml of fentanyl in plasma to over 170 ng/ml after doses as high as 270 $\mu\text{g}/\text{kg}$ given over 20 min with an infusion of 3.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. These compare to concentrations of 10 to 100 ng/ml of plasma in surgical patients given 2.4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over 20 min as a loading dose, along with 0.15 to 0.3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for maintenance.¹² In the dog, concentrations beyond 30 ng/ml had no further effect in reducing enflurane MAC. Since the dog has been shown to be less sensitive to narcotics than humans, it is probable that the higher doses used in clinical situations may already be producing a maximal effect.

Quasha *et al.*¹⁶ reviewed factors that alter MAC. They noted that although halothane MAC was constant for more than 8 h in dogs, both acute and chronic tolerance to nitrous-oxide-induced analgesia had been demonstrated. In this study, no tolerance to enflurane anesthesia was noted over the eight-hour period during

which enflurane was administered to the Group 3 animals for control. Also, no tolerance to fentanyl was apparent since the same reduction of enflurane MAC was found for comparable levels of fentanyl in plasma, whether that level was attained within the first 1.5 h of exposure to fentanyl as in Group 2 or in the seventh or eighth hour as in Group 1 (fig. 1). Other factors which may have altered the MAC of enflurane, such as temperature, *pH*, PaCO_2 , were maintained within normal ranges (or within ranges shown not to alter MAC).

In summary, by utilizing available pharmacokinetic data, predictable plasma levels of fentanyl could be achieved and maintained for extended periods. There is a close relationship between fentanyl concentrations in plasma and its enflurane (anesthesia) sparing effects. Factors that may alter the individuals' sensitivity to a given concentration of fentanyl remain to be evaluated. The infusion techniques utilized in this study should facilitate the identification and quantitation of the most important factors.

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