

Pharmacokinetics, Pharmacodynamics, and Rational Opioid Selection

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Fentanyl, alfentanil, and sufentanil have important pharmacokinetic and pharmacodynamic differences. Selecting one of these opioid analgesics as an adjunct to general anesthesia requires appreciation of the relationship between the pharmacokinetic and pharmacodynamic characteristics of these drugs and the onset of and recovery from drug effect. Using a pharmacokinetic-pharmacodynamic model, the authors simulated the decrease in plasma fentanyl, alfentanil, and sufentanil concentration after intravenous administration by either bolus injection, brief infusion, or prolonged infusion. The percentage change in concentration, rather than absolute concentration, was simulated to permit comparison of the relative opioid concentration independently of drug potency. These computer simulations quantified the relationship between infusion duration and the time required for recovery after termination of the infusion. The analysis suggests that alfentanil is best used for operations longer than 6-8 h when a rapid decrease in effect site (*i.e.*, biophase) opioid concentration is desired after discontinuation of the infusion. Alfentanil may also be the most appropriate drug to provide a transient peak effect after a single bolus. Although sufentanil has longer distribution and elimination half-lives than alfentanil, recovery from sufentanil infusions may be more rapid than recovery from alfentanil infusions for operations shorter than 6-8 h. These computer simulations demonstrate that simply comparing pharmacokinetic parameters (*e.g.*, half-lives) of different drugs will not predict the relative rates of decrease in effect site concentrations after either an intravenous bolus or a continuous infusion. (Key words: Anesthetics, intravenous: alfentanil; fentanyl; infusion; sufentanil. Pharmacokinetics: computer simulation.)

ALTHOUGH EXPERIENCE, convenience, and cost are important factors in drug selection, anesthesiologists often select an opioid for use during anesthesia based on the perceived pharmacokinetic and pharmacodynamic dif-

ferences between the available drugs. Opioids with rapid elimination half-lives (*e.g.*, alfentanil) may be selected for brief procedures, whereas opioids with longer elimination half-lives (*e.g.*, fentanyl and sufentanil) may be selected for longer procedures. Clinical pharmacologists and pharmaceutical companies encourage using half-lives as a basis for opioid selection.^{1,‡} Selecting an opioid based on pharmacokinetic principles is quite logical. Although comparing half-lives is deeply entrenched in the literature and clinical thinking, simply comparing half-lives is not a rational method for selecting an opioid.

Fentanyl, alfentanil, and sufentanil are semisynthetic opioid analgesics that have become widely used to supplement general anesthesia or as primary anesthetic agents in very high doses during cardiac surgery. There are important pharmacokinetic and pharmacodynamic differences between these three drugs. As shown in table 1, alfentanil has the shortest distribution and elimination half-lives²; sufentanil has the longest half-lives³; and the half-lives for fentanyl are intermediate.² The volumes of distribution for alfentanil are smaller than those of fentanyl or sufentanil. The intercompartmental (distribution) and central (elimination) clearances of alfentanil are slower than those of fentanyl or sufentanil. A reduction in the volumes of distribution tends to decrease the time required for recovery after drug administration, whereas a reduction in clearances tends to increase the time required for recovery. Because alfentanil has smaller volumes and slower clearances than does fentanyl or sufentanil, the combined effect of these differences cannot be easily discerned from a simple comparison of the parameters presented in table 1. The major pharmacodynamic differences between these drugs are potency and rate of equilibration between the plasma and the site of drug effect (*i.e.*, biophase). The half-time of equilibration between the effect site and the plasma for fentanyl^{2,4} and sufentanil⁵ is 5-6 min, whereas half-time of equilibration for alfentanil is 1.5 min.^{2,4}

We examined the onset and offset of drug effect with computer simulations using previously published pharmacokinetics of fentanyl, alfentanil, and sufentanil. We simulated the plasma and effect site opioid concentrations after both bolus injections and continuous infusions. Physicians know from clinical experience that the time re-

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‡ Rapid-Acting Alfenta[®], Janssen Product Brochure. Janssen Pharmaceutica, Piscataway, New Jersey, January 1988.

quired for recovery increases with the duration of the infusion. The simulations quantified this relationship.

The computer simulations in the current study provide insight into the comparative pharmacokinetics of fentanyl, alfentanil, and sufentanil and can be used to select the appropriate opioid based on the length of the procedure, the desired intraoperative opioid concentration, and the desired time course of recovery.

Materials and Methods

These simulations use the fentanyl and alfentanil pharmacokinetic parameters reported by Scott and Stanski² and the sufentanil parameters reported by Hudson *et al.*³ These data sets were selected because the studies were done in patients having general anesthesia; because the rapid pharmacokinetic distribution phases were measured by frequent sampling of arterial blood; and because the samples were gathered for at least 24 h after the initial dose. We are reasonably confident in the accuracy of the fentanyl and alfentanil pharmacokinetics because we have prospectively tested these parameters in previous studies using a computer-controlled infusion pump.^{6,7} The sufentanil pharmacokinetic parameters reported by Hudson

*et al.*³ were chosen because they are based on the longest sampling period of any of the published sufentanil pharmacokinetics.

The effect site was simulated as a fourth compartment in the mamillary model with a volume 1/1,000 of that of the central compartment. Drug disposition in the effect site was modeled with the use of the rate constant of drug elimination from the effect site (k_{e0}), as described by Hull *et al.*⁸ and Sheiner *et al.*⁹ The k_{e0} s for fentanyl and alfentanil were characterized by Scott and Stanski,² whereas the k_{e0} for sufentanil is that described by Scott *et al.*⁵ Table 1 summarizes the parameters used in the simulations.

All of the simulations were performed on an 80386 computer running MS-DOS (Microsoft, Redmond, WA), using programs written in the C language by the first author (SLS). The simulations used Euler's solution to the three-compartment model¹⁰ with a step size (Δt) of 1 s.

BOLUS ADMINISTRATION

We simulated the plasma concentrations after a bolus injection. The plasma concentrations after clinically relevant doses of fentanyl, alfentanil, and sufentanil cannot be compared easily because the alfentanil concentrations will be two orders of magnitude larger than the fentanyl concentrations, which will, in turn, be an order of magnitude larger than the sufentanil concentrations. However, if the concentrations are divided by the initial concentration and the curves are superimposed, then the rates of decline from 100% of the initial concentration can be compared. Because the pharmacokinetics are assumed to be first order (*i.e.*, "linear"), it does not matter whether the initial dose is small or large; the time required for a given *percentage* decrease will not change.

The concentration of drug at the effect site, not the plasma concentration, governs the drug effect. Because a single bolus of drug usually is given to achieve an intended peak effect, and to allow visual comparison of the curves, we normalized the effect site opioid concentration curves to the peak effect site opioid concentration. Because the pharmacokinetics at the effect site are also assumed to be linear, it does not matter whether the initial dose is small or large, and the time required for a given *percentage* decrease in effect site concentration will not change.

BRIEF INFUSIONS

The infusion regimen was designed to maintain the peak effect site concentration for 10 min after the bolus.

LONG INFUSIONS

We simulated the relationship between infusion duration and the time required for recovery. Recovery was

TABLE 1. Opioid Pharmacokinetic Parameters

	Fentanyl ²	Alfentanil ²	Sufentanil ³
Fractional coefficients (%)			
A	90	83	84
B	8	12	15
C	2	5	1
Hybrid rate constants (min ⁻¹)			
α	0.67	1.03	0.48
β	0.037	0.052	0.030
γ	0.0015	0.0062	0.0012
Half-lives (min)			
α	1.0	0.67	1.4
β	19	13	23
γ	475	111	562
Volumes (l)			
Central	13	2.2	18*
Peripheral			
Rapid	50	6.7	47*
Slow	295	15	476*
Steady state	358	23	541*
Clearances (l·min ⁻¹)			
Central	0.62	0.20	1.2*
Intercompartmental			
Rapid	4.8	1.4	4.8*
Slow	2.3	0.25	1.3*
Micro rate constants (min ⁻¹)			
k_{10}	0.0492	0.0910	0.0653
k_{12}	0.380	0.656	0.272
k_{13}	0.179	0.113	0.0723
k_{21}	0.0960	0.214	0.102
k_{31}	0.0077	0.017	0.0027
Effect site rate constant (min ⁻¹)			
k_{e0}	0.147 ²	0.77 ²	0.227 ⁵

* Per 70 kg. (Only the sufentanil volumes and clearances were weight adjusted in the original research.)

expressed as the percentage decrease from 100% of the intraoperative concentration to allow application of these curves to diverse clinical situations and to compensate for the different potencies of these opioids.

The infusions used to create these curves were simulated to maintain a constant effect site opioid concentration, based on the work of Krüger-Thiemer¹¹ and Schwilden¹² and implemented in computer-controlled infusion pumps.¹⁰ The infusion regimens were modified slightly to target the effect site rather than the plasma. Although this infusion regimen is possible only with a computer-controlled infusion pump, use of this infusion regimen preserved the concept of expressing the decline in terms of a decrease from 100% of the maintained concentration.

Results

BOLUS ADMINISTRATION

Figures 1A–C show the relative plasma opioid concentrations after bolus injections of fentanyl, alfentanil, and sufentanil. In the first 90 min after the simulated bolus injection (fig. 1A), the decrease in relative plasma opioid concentration is indistinguishable for fentanyl, alfentanil, and sufentanil, despite the differences in half-lives reported in table 1. From 90 to 180 min (fig. 1B) the relative plasma sufentanil concentrations are approximately half those of the relative plasma fentanyl and alfentanil concentrations. The relative plasma alfentanil concentration decreases below the relative plasma fentanyl concentration at 135 min. Despite the significantly faster distribution and elimination half-lives of alfentanil compared with sufentanil, the relative plasma sufentanil concentrations remain lower than the relative plasma alfentanil concentrations until 5 h after the bolus is injected (fig. 1C), at which time the relative plasma alfentanil concentration finally decreases to less than the relative plasma sufentanil concentration.

Figure 2A shows the plasma concentration for fentanyl during the first 10 min after bolus injection. Superimposed is the effect site fentanyl concentration, based on an equilibration half-time of 4.7 min.² The fentanyl concentration in the effect site peaks 3.6 min after the bolus injection at an apparent concentration that is 17% of the initial plasma concentration. Figures 2B and C show similar curves for alfentanil and sufentanil. The rapid plasma-effect site equilibration for alfentanil produces at 1.4 min a peak apparent effect site concentration (fig. 2B) that is 37% of the initial plasma alfentanil concentration. The effect site sufentanil concentration peaks at 5.6 min (fig. 2C) at an apparent concentration that is 20% of the initial plasma sufentanil concentration. Although the simulation predicts a later peak for sufentanil, the slope of the curve is very flat near the peak, and thus the relative effect site

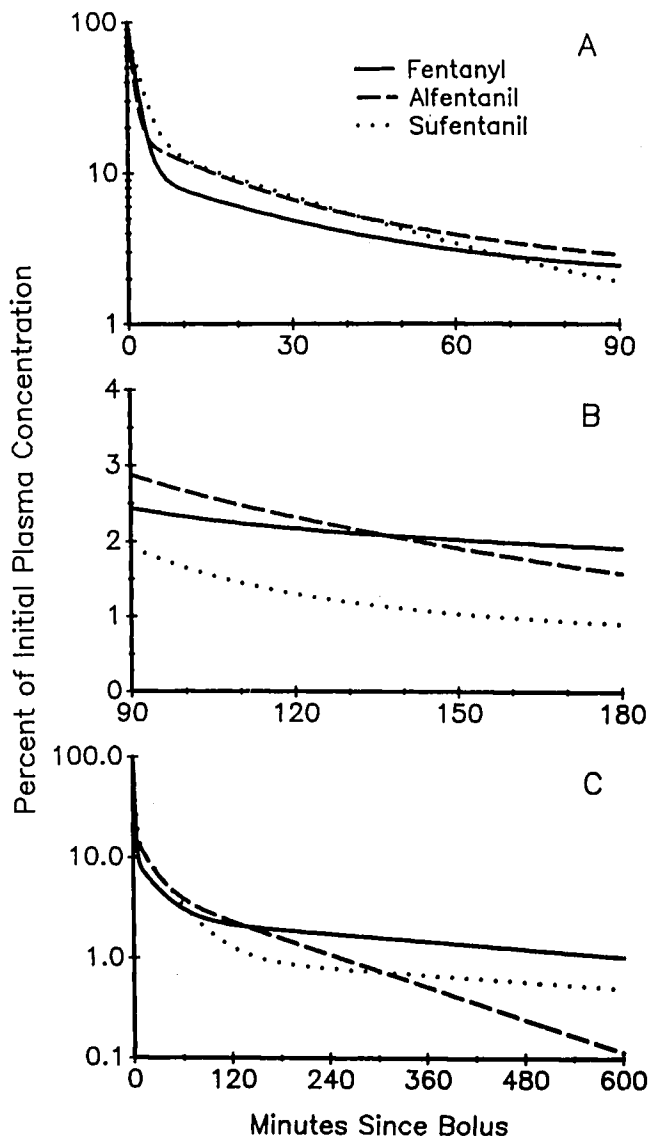


FIG. 1. Plasma opioid concentrations over time after a bolus injection, as a percentage of the initial plasma concentration.

concentrations of fentanyl and sufentanil after bolus injection are nearly indistinguishable.

Because the effect site opioid concentration peaks at a relatively greater level after an injection of alfentanil bolus than after a bolus of fentanyl or sufentanil (fig. 2B), it takes relatively less alfentanil to reach the same peak effect. When normalized for peak effect (figs. 3A and B), this results in a more rapid recovery over the first 10 min for alfentanil (fig. 3A), which persists over many hours (fig. 3B).

BRIEF INFUSIONS

When the peak effect site concentration is maintained for 10 min (figs. 4A and B), alfentanil no longer demon-

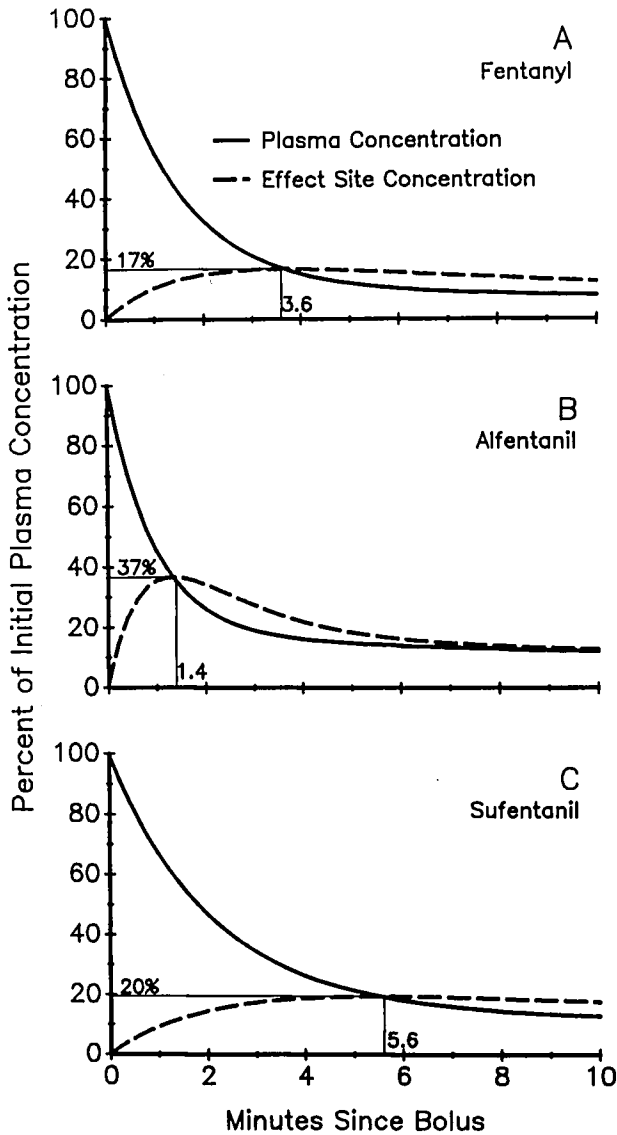


FIG. 2. Plasma and effect site opioid concentrations over the first 10 min after a bolus injection, as a percentage of the initial plasma concentration.

strates more rapid recovery. In the first 60 min, the rates of decrease in effect site fentanyl, alfentanil, and sufentanil concentrations are indistinguishable (fig. 4A). After 300 min, the relative effect site alfentanil concentration decreases below the relative effect site sufentanil concentration after a bolus plus a brief infusion (fig. 4B).

LONG INFUSIONS

Figures 5A-C show the time for recovery as a function of the duration of the infusion for fentanyl, alfentanil, and sufentanil, respectively. For each drug, if only a small decrease in effect site opioid concentration is required at the conclusion of the anesthetic, recovery will be prompt

once the infusion is terminated. Conversely, if the intraoperative effect site concentration is maintained at levels several-fold greater than those desired at emergence (or on discharge from the recovery room), then long recovery times may result, even from brief infusions.

Figures 6A-C show the combined curves for fentanyl, alfentanil, and sufentanil for a 20, 50, and 80% decrease in effect site concentration, respectively. Figure 6A demonstrates that the effect site alfentanil or sufentanil concentration should decrease 20% within 10-15 min, regardless of the duration of the anesthetic. After a 4-h infusion, a 20% decrease requires twice as long for fentanyl, compared with alfentanil and sufentanil. After a 10-h infusion, a 20% decrease in effect site fentanyl concentration requires 45 min, almost four times longer than required for sufentanil and alfentanil.

Figure 6B demonstrates that the time required for a 50% decrease in effect site opioid concentration is indistinguishable among fentanyl, alfentanil, and sufentanil for infusions of 30 min or less. For infusions longer than 30 min, the fentanyl curve begins to increase sharply. For infusions shorter than 8 h, the effect site concentration will decrease by 50% more rapidly after a sufentanil infusion than after an alfentanil infusion. For infusions lasting longer than 8 h, the effect site concentration will de-

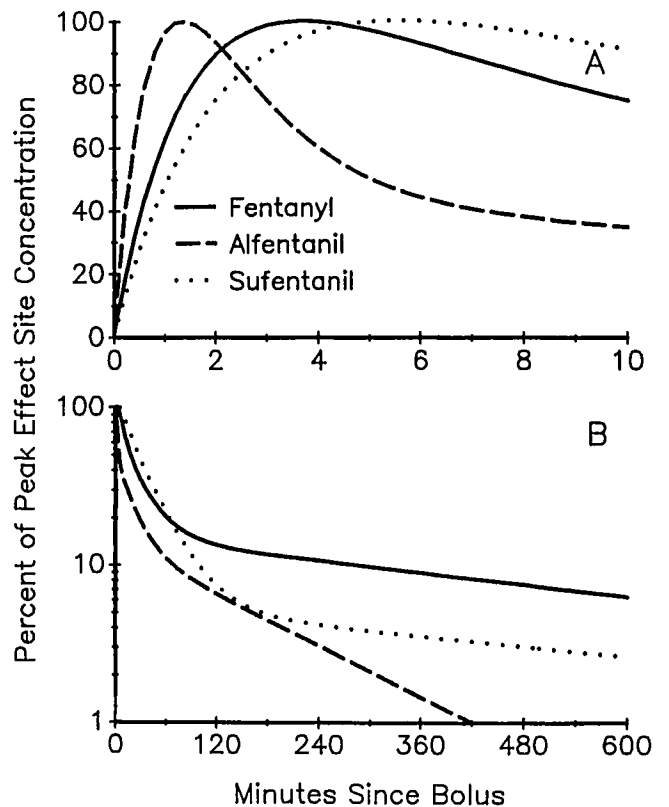


FIG. 3. Effect site opioid concentrations over time after a bolus injection, as a percentage of the peak effect site concentration.

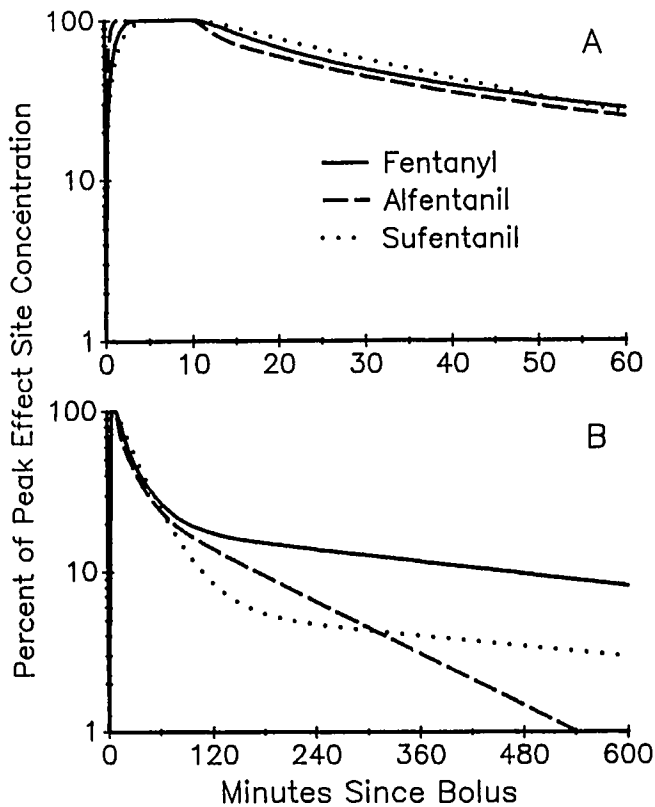


FIG. 4. Effect site opioid concentrations (as a percentage of the peak effect site concentration) over time after a bolus injection plus an infusion designed to maintain the peak effect site concentration until 10 min.

crease by 50% more rapidly after an alfentanil infusion. Several hours will be required for the effect site concentration to decrease by 80% after an infusion of any of these opioids (fig. 6C), particularly for fentanyl. For infusions shorter than 3 h, the effect site concentration will decrease by 80% more rapidly after a sufentanil infusion than after an alfentanil infusion. If the infusion lasts longer than 3 h, then the effect site concentration will decrease by 80% most rapidly after an alfentanil infusion.

Discussion

CLINICAL INTERPRETATION OF THE SIMULATIONS

Interpretation of these simulations requires an understanding of the opioid concentrations necessary during anesthesia. Table 2 shows the opioid concentrations that provide hemodynamic stability for various anesthetic techniques, based on a review of the published literature describing fentanyl, alfentanil, and sufentanil use in general anesthesia. The concentration ranges shown in table 2 are consistent with all of the references located by a computerized literature search. In our review of the lit-

erature, we found that several investigators did not measure the plasma opioid concentrations in an otherwise valuable study. In these cases we simulated the effect site opioid concentrations from the doses published by the investigators, using the pharmacokinetic parameters shown in table 1. These results are indicated in table 2 by a dagger. A few of the concentrations in table 2 could not be documented in the literature. In these cases, we simulated the effect site concentrations that would result from the pharmaceutical company's recommended dose. These results are indicated in table 2 with an asterisk.

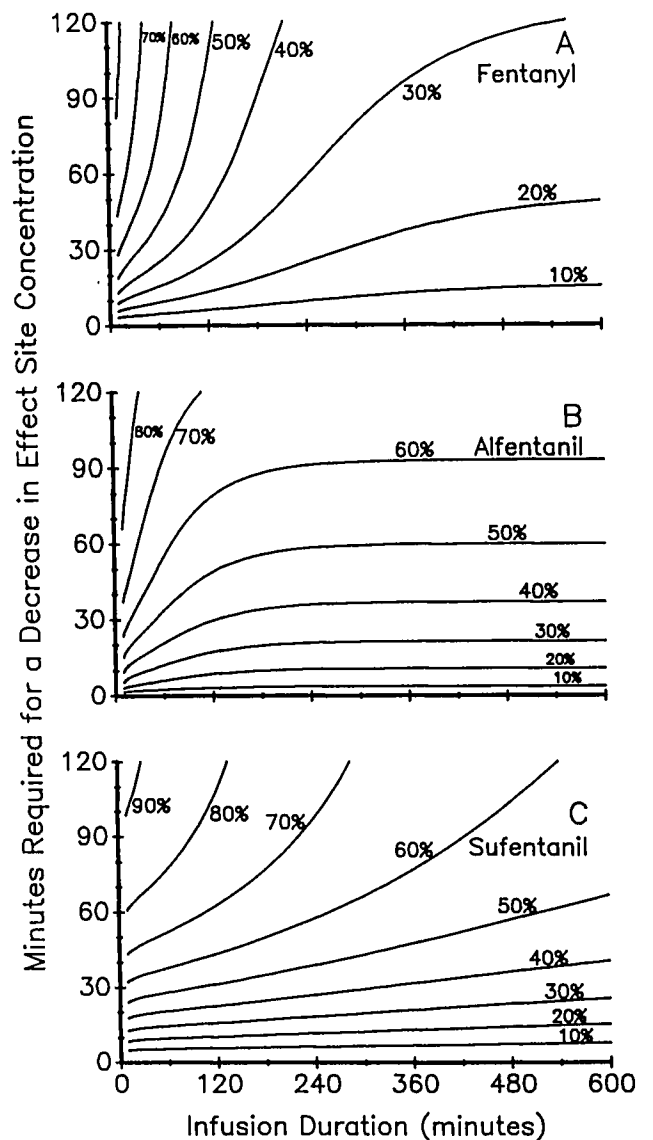


FIG. 5. Recovery curves for fentanyl, alfentanil, and sufentanil showing the time required for decreases of a given percentage (labeled for each curve) from the maintained intraoperative effect site concentration after termination of the infusion.

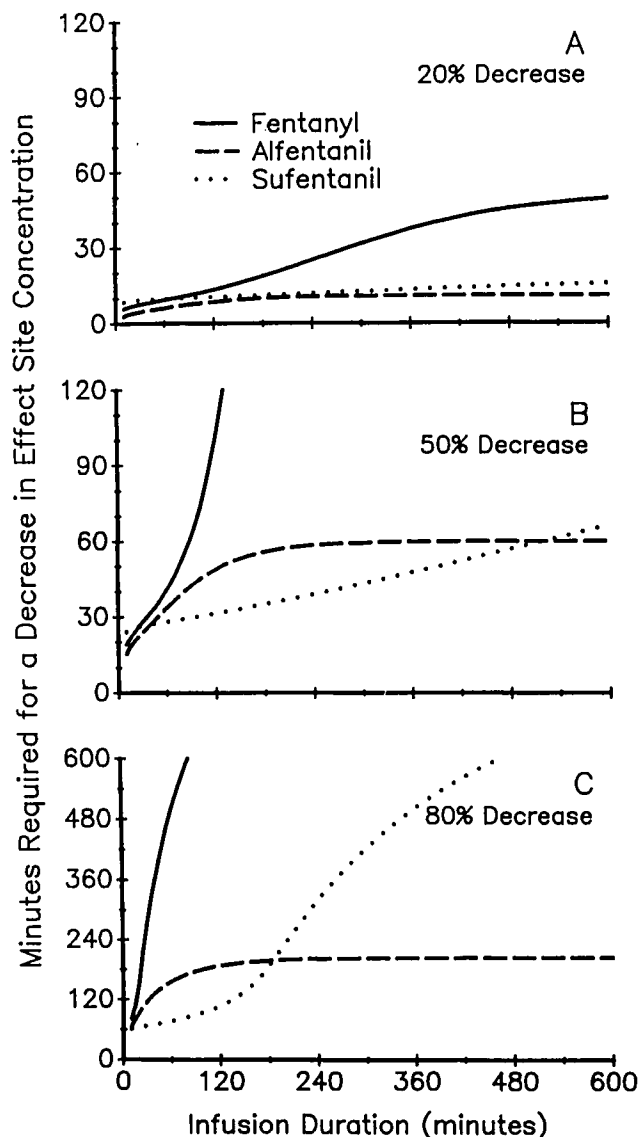


FIG. 6. Overlay of the fentanyl, alfentanil, and sufentanil recovery curves describing the time required for decreases of 20, 50, and 80% from the maintained intraoperative effect site concentration after termination of the infusion.

Table 2 also shows the maximum steady-state opioid concentrations desirable at the emergence of anesthesia to provide analgesia with minimal respiratory depression.

Table 2 suggests that the relative potencies of fentanyl, alfentanil, and sufentanil are approximately 1:1/70:9. This potency ratio is roughly preserved throughout the concentration-response range shown in table 2. The striking exception is the report by some investigators¹³ of a relatively higher sufentanil requirement during cardiac surgery (sufentanil-oxygen technique). This may reflect the difficulty in obtaining complete anesthesia with an opioid-oxygen technique, where small changes in the dose of

preanesthetic medication may produce large changes in intraoperative opioid requirement.¹⁴⁻¹⁶ It may also reflect the difficulty of obtaining complete anesthesia with an opioid, as recently documented by Philbin *et al.*¹⁷ With this exception, it would appear that the relative opioid concentrations associated with respiratory depression, anesthesia with a potent agent and nitrous oxide, anesthesia with nitrous oxide alone, and anesthesia (or near anesthesia) with only oxygen are similar for fentanyl, alfentanil, and sufentanil.

Fentanyl, alfentanil, and sufentanil produce the same EEG response to an infusion.^{2,4,5,18-21} The EEG changes from the high-frequency, low-voltage pattern of wakefulness to the low-frequency, high-voltage pattern associated with profound opioid drug effect. The IC_{50} is the apparent effect site opioid concentration (*i.e.*, plasma concentration at steady state) associated with 50% of the observed maximal drug effect and can be used as a measure of relative drug potency. Table 3 shows the pharmacodynamic parameters obtained from EEG studies using fentanyl, alfentanil, and sufentanil. The IC_{50} values again suggest a potency ratio of 1:1/70:9 for fentanyl, alfentanil, and sufentanil. The γ parameter shown in table 3 is the steepness of the concentration-EEG effect relationship. The γ values for all three opioids are quite similar, again suggesting that the potency ratio remains consistent throughout the range of the concentration-response relationship. Recently, Ebling *et al.* demonstrated the use of pharmacodynamic parameters derived from the EEG to compare the onset and offset of fentanyl and alfentanil drug effect.²²

Bolus Administration

The different potencies of fentanyl, alfentanil, and sufentanil complicate pharmacokinetic comparison of these drugs. Fortunately, both clinical studies and pharmacodynamic models based on EEG analysis suggest that the relative potencies are consistent over the clinically relevant concentration range. This justifies the scaling used in analyzing the pharmacokinetics after bolus administration (figs. 1-3).

When normalized to peak effect site concentration (fig. 3), the recovery from an alfentanil bolus will be faster than the recovery from a bolus of fentanyl or sufentanil. Thus, if only a single peak effect is desired, such as might be needed to blunt the response to intubation during a very brief procedure, then alfentanil is the drug of choice. This is not because alfentanil has more rapid elimination. Rather, alfentanil's more rapid plasma-effect site equilibration results in a relatively larger peak effect site concentration from the bolus dose (fig. 2B), which permits a relatively smaller dose to be used. This smaller dose results in a faster decrease in effect site concentration when com-

TABLE 2. Opioid Concentrations that Ablate Responsiveness to Intraoperative Noxious Stimuli, Permit Adequate Ventilation on Emergence

	Fentanyl	Alfentanil	Sufentanil
Induction and intubation			
Thiopental	3-5 ²⁷	250-400 ²⁷	0.4-0.6 ^{28,29†}
O ₂ /N ₂ O only	8-10*	400-750 ^{30,31}	0.8-1.2 ³²
Maintenance			
N ₂ O/Potent vapor	1.5-4 ³³	100-300*	0.25-0.5 ²⁸
O ₂ /N ₂ O only	1.5-10 ^{27,34}	100-750 ^{27,30,31,35}	0.25-1.0 ³²
O ₂ only	15-60 ^{33,36-38}	1000-4000 ^{39†,40†}	2-8 ^{39†,40†}
Adequate ventilation on emergence	1.5 ⁴¹	125 ^{30,31,35,42}	10-60 ¹⁵ 0.25 ^{28,32}

Opioid concentrations in ng/ml.

Steady-state plasma concentrations were unavailable for several of the ranges shown above, so the effect site opioid concentrations were calculated with the pharmacokinetic parameters shown in table 1.

* Effect site concentrations calculated from doses recommended by pharmaceutical company.

† Effect site concentrations calculated from doses reported by investigator.

pared with the doses of fentanyl or sufentanil required to reach the same peak effect (figs. 3A and B).

Brief Infusions

The simulation of a brief infusion (fig. 4) shows that the relatively rapid recovery from peak effect after a bolus of alfentanil is lost if the peak effect must be maintained, even if for only a brief time. The infusion required to maintain alfentanil's peak effect offsets the advantage obtained from alfentanil's rapid blood-brain equilibration. If the peak effect must be maintained for several minutes, then there will be very little difference in the offset of drug effect between fentanyl, alfentanil, and sufentanil.

Long Infusions

Figures 5 and 6 can be used to select the appropriate opioid based on the anesthetic technique, the desired time course of recovery, and the anticipated duration of surgery. As can be seen from table 2, the opioid concentrations used to supplement general anesthesia when nitrous oxide and a potent vapor are used range from being one to two times larger than the concentration required at the conclusion of the anesthetic. Depending on the inhaled concentration of the potent vapor, it may only be necessary to maintain an opioid concentration that is approximately 20% higher than the desired concentration at the conclusion of the anesthetic. In this case, recovery will be

rapid for all three opioids, although alfentanil or sufentanil should produce a faster recovery than fentanyl for operations longer than 2 h (fig. 6A).

When using nitrous oxide without a potent vapor (*i.e.*, nitrous oxide-opioid technique), the necessary effect site opioid concentration required for maintenance of anesthesia is roughly twice as large as the concentration desired at emergence, although the range is large. The anesthesiologist therefore seeks a 50% decrease from the intraoperative effect site opioid concentration after termination of the infusion (fig. 6B). Sufentanil would be a rational selection for a nitrous oxide-opioid anesthetic lasting less than 8 h. Alfentanil would be preferable for operations longer than 8 h if postoperative tracheal extubation (rather than overnight ventilation of the lungs) was desired. Figure 6B also suggests that fentanyl may be a very poor choice for a nitrous oxide-opioid technique longer than 1 h. After the first hour, the time required for a 50% decrease in effect site fentanyl concentration very rapidly increases to greater than 2 h.

Table 2 shows that the opioid concentrations must decrease by 80-90% for adequate ventilation after an opioid-oxygen (*e.g.*, "cardiac") anesthetic. If a rapid emergence is desired after an opioid-oxygen anesthetic technique, then sufentanil is the drug of choice for infusions shorter than 3 h (fig. 6C). For operations longer than 3 h, alfentanil is the drug of choice. With either drug, 2-4 h will still be required for the effect site concentrations to decrease to acceptable levels.

The time required for the effect site fentanyl and sufentanil concentrations to decrease by a given percentage increases over at least the first 10 h of the infusion (figs. 5A and C). After 4 h, the time required for a percentage decrease in alfentanil concentration does not increase (fig. 5B). Thus, alfentanil is probably the drug of choice for infusions longer than 10 h for which rapid termination of drug effect is still desired. For example, a continuous

TABLE 3. Pharmacodynamic Parameters Describing the Effect Site Concentration-EEG Response Relationship

	Fentanyl	Alfentanil	Sufentanil
IC ₅₀ for EEG depression (ng/ml)	7.8 ² 6.9 ⁴ 8.1 ⁵	480 ² 520 ⁴	0.69 ⁵
γ (steepness)	4.3 ²	4.8 ²	6.2 ⁵

alfentanil infusion might be a rational choice to provide analgesia the night after cardiac surgery when the therapeutic goal is a rapid decline in effect site alfentanil concentration the next morning before scheduled extubation.

For outpatient anesthesia, a critical end point is satisfactory mental status at the time of discharge from the recovery room, along with ventilation at the conclusion of the anesthetic. If an opioid-nitrous oxide technique requires a decrease of 50% in effect site concentration from the intraoperative concentration to the concentration desirable at emergence from anesthesia, then the percentage decline necessary for fully awake mental status at the time of recovery room discharge is obviously much greater than 50%. Although no studies have documented the desirable opioid concentration at the time of discharge for outpatients, it is likely to represent a decline of between 70 and 90% of the concentration that would be required during maintenance of anesthesia when using an nitrous oxide-opioid technique. Two conclusions can be drawn from figure 6C. If we assume that the threshold opioid concentration for discharge from the recovery room represents an 80% decrease from the intraoperative concentration: 1) sufentanil will produce the desired 80% decrease faster than alfentanil for operations lasting less than 3 h, and 2) a nitrous oxide-opioid technique will require 1 h of recovery time before discharge, even for very short operations.

VALIDATION OF SIMULATIONS

These simulations can never be fully validated by clinical studies. The curves shown in figures 5A-C contain many data points. Validating each data point would require studies on 5-10 patients. Thus, 50-100 patients would have to be studied to validate only ten data points on each curve. Because there are nine curves per opioid, the family of curves for each opioid would require studying 450-900 patients, or studying 1,350-2,700 patients for all three opioids.

Data consistent with the observations in these simulations have been obtained elsewhere. A recent double-blind study by From *et al.* compared emergence after fentanyl, alfentanil, and sufentanil infusions, with 70% nitrous oxide, in patients having craniotomy.²³ The authors of this study used a standardized opioid infusion technique for each of the three drugs. Because the authors did not measure drug concentrations, we simulated the concentrations using the fentanyl, alfentanil, and sufentanil pharmacokinetic parameters shown in table 1. Based on the published duration of surgery, the initial opioid infusion rate, and the interval between termination of the infusion and the end of surgery, the simulations predict that the fentanyl, alfentanil, and sufentanil concentrations when the infusions were terminated were 2.5, 190, and 0.21 ng/ml, respectively. As can be seen from table 1, these con-

centrations are at the low end of the opioid-nitrous oxide concentration range. Consistent with the prediction that the patients were rather lightly anesthetized, most of the patients required either a beta blocker, hydralazine, or both, as well as supplementary intraoperative opioids (not included in the simulations) to provide hemodynamic stability.

The simulations predict fentanyl, alfentanil, and sufentanil concentrations of 1.8, 88, and 0.09 ng/ml, respectively, at the time of extubation in the study by From *et al.* Thirty minutes after arrival of the patient in the recovery room, the predicted fentanyl, alfentanil, and sufentanil concentrations were 1.7, 72, and 0.08 ng/ml. The simulations thus predict that the patients receiving fentanyl should have been more drowsy than those receiving alfentanil or sufentanil, concentrations of which are both well below the threshold emergence concentration. The authors did report a trend toward increased drowsiness in the patients receiving fentanyl, although this did not reach statistical significance.

Our own studies on computer-controlled infusions of fentanyl and alfentanil also support the results of these simulations.^{6,7} The patients in our prior studies received fentanyl or alfentanil for operations of varying durations. Blood samples were also taken postoperatively in many patients to document the decrease in plasma concentrations after termination of the infusions. Our results, both during the infusion and after termination of the infusion, demonstrated fairly good agreement with the fentanyl and alfentanil pharmacokinetics described by Scott and Stanski.²

Because sufentanil is extremely potent, it is difficult to measure the plasma concentrations achieved during most anesthetics. We used the pharmacokinetics described by Hudson *et al.*³ because of the length of sampling in that study. However, Hudson *et al.* studied only patients having repair of abdominal aortic aneurysms, a population that is not representative of the general surgical patient population. Bovill *et al.*, studying sufentanil pharmacokinetics in healthy surgical patients, found rapid-distribution, slow-distribution, and elimination half-lives for sufentanil of 1.4, 18, and 164 min, respectively.²⁴ Although these are faster than the half-lives reported by Hudson *et al.*,³ there is little difference between the times required for 20 and 50% decreases in effect site sufentanil concentration predicted by either sufentanil pharmacokinetic parameter set (fig. 7). For infusions of less than 3 h duration, the sufentanil pharmacokinetics reported by Hudson *et al.* predict that the effect site concentration will decrease 80% more rapidly after termination of the infusion than predicted by the pharmacokinetics reported by Bovill *et al.* For longer infusions, the sufentanil pharmacokinetics of Bovill *et al.* predict the effect site concentration will decrease by 80% more rapidly.

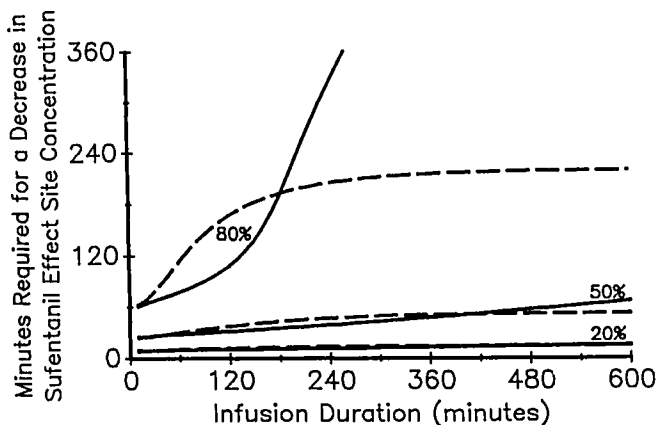


FIG. 7. Comparison of the sufentanil recovery curves predicted by the pharmacokinetics reported by Hudson *et al.*³ (solid lines) with the recovery curves predicted by the pharmacokinetics reported by Bovill *et al.*²⁴ (dashed lines).

We do not know whether the correct sufentanil pharmacokinetics are those reported by Bovill *et al.* or those reported by Hudson *et al.* However, the speed of recovery from sufentanil predicted by either pharmacokinetic parameter set remains faster than the predicted speed of recovery from alfentanil for procedures lasting less than several hours. Thus, our conclusions do not change despite uncertainty regarding the correct sufentanil pharmacokinetics.

Although EEG slowing is a different opioid effect than either analgesia or respiratory depression, clinical studies have documented rates of onset of opioid effect that agree with those shown in figure 2, which is based on the EEG.^{2,4,5} For example, the time to the peak effect site concentration for these three drugs agrees with the measured time of peak ventilatory depression.²⁵ In addition, the similar rate of onset for fentanyl and sufentanil predicted with the use of the EEG as a measure of drug effect has been documented in clinical studies.²⁶

The decline in effect site concentration, rather than the plasma concentration, was modeled to provide as accurate a simulation as possible. The transfer of drug from the plasma to the effect site in these simulations was modeled with the use of parameters derived from EEG analysis. Because the EEG is not, *per se*, a measure of opioid anesthetic depth, we repeated these simulations to examine the relationship between infusion duration and the decline in plasma concentration after termination of an infusion. These simulations predicted slightly faster recovery at all time points, but the shapes and positions of the curves relative to each other are the same as shown in figure 5. Thus, the conclusions regarding opioid selection for continuous infusions were not influenced by the use of an effect compartment model. By contrast, the recommendation of a single bolus dose of alfentanil for an

evanescent effect was entirely based on the effect compartment model.

PHARMACOKINETIC INTERPRETATION

Despite the very different half-lives for these three drugs (table 1), the curves showing plasma concentrations after bolus injection are remarkably similar (fig. 1) for the first 90 min. Comparing the half-lives of alfentanil and sufentanil would not have predicted the more rapid recovery from sufentanil predicted from these simulations, for the following reason.

Half-lives are often discussed and compared as if they were the only pharmacokinetic parameters that describe drug behavior. That is incorrect. The plasma concentration of most intravenous anesthetic drugs after a bolus dose is described by a triexponential equation of the form

$$C_p(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where $C_p(t)$ is the plasma concentration at time t ; A, B, and C are coefficients describing the relative contributions of each exponential term; and α , β , and γ are the hybrid rate constants corresponding to the rapid-distribution half-life, the slow-distribution half-life, and the elimination half-life, respectively.

The curves shown in figures 1A–C are the solutions for fentanyl, alfentanil, and sufentanil, respectively, for this triexponential equation where $A + B + C = 100\%$. The rapid- and slow-distribution half-lives are $\ln(2)/\alpha$ and $\ln(2)/\beta$, respectively, whereas the elimination half-life is $\ln(2)/\gamma$. Because the meaning of the coefficients is somewhat more obscure than the meaning of the half-lives, the coefficients often are ignored when drugs are compared. There is no justification for this. The disposition function is described by six parameters (three coefficients and three hybrid rate constants), each of which contributes to the overall model.

The relationship between the rate constants and coefficients can be illustrated in familiar terms: home mortgages. Imagine a total of \$100,000 is borrowed by taking out three unusual mortgages: one relative will loan you money on the condition that you pay back 25% of the outstanding principle each month and two other relatives insist that you pay back 10 and 1% of the outstanding principle each month, respectively. These represent rate constants of 0.25, 0.1, and 0.01 months⁻¹ and half-lives of 2.8, 7, and 69 months, respectively. How fast you pay off your mortgage depends on how you divide the \$100,000 loan among the three relatives. If the bulk of the mortgage is borrowed from the last relative (1% payback per month), you will pay the mortgage back far more slowly than if the bulk of the mortgage is borrowed from the first relative (25% payback per month).

In just the same way, the coefficients in the triexpo-

nential equation partition the half-lives and exert a large, although often unappreciated, influence on the rate of the decrease of the plasma drug concentration. Table 1 shows fractional coefficients, such that $A + B + C = 100\%$. To continue with our analogy, 99% of a bolus of sufentanil is "paid back" at the more rapid rates, *versus* only 95% for alfentanil. One effect of this is the relatively lower sufentanil concentration between 90 and 180 min after bolus injection (fig. 1B).

We can understand sufentanil's relatively rapid recovery after infusions in pharmacokinetic terms as well. Sufentanil's long half-lives result primarily from a large "slow" compartment with low clearance. The large volume and low clearance for the slow-distribution compartment are partly responsible for the relatively rapid decrease in effect site concentration after continuous infusions. During an infusion, the slow-distribution compartment acts as a reservoir that continues to fill over many hours. Thus, when the infusion is terminated, the compartment initially *continues* to fill and thereby helps to reduce the plasma (and effect site) concentration. This slow-distribution compartment empties slowly as well. This slow emptying allows the plasma concentrations to decrease to less than the concentrations in the slow compartment before the relative concentrations in the two compartments equilibrate during the elimination phase.

Pharmacokinetic studies often compare the pharmacokinetics of two related drugs or the pharmacokinetics of a single drug in two different populations. Such comparisons usually take the form of a table, such as table 1, which lists pharmacokinetic parameters. Given the pharmacokinetic and pharmacodynamic assumptions previously mentioned, these computer simulations demonstrate that the relative duration of drug effect cannot be gleaned from simply comparing half-lives. We hope that these simulations will provide an impetus for future investigators to more critically examine the relationship between pharmacokinetic parameters and the recovery from drug effect.

The effect site opioid concentration for fentanyl, alfentanil, and sufentanil can be modeled by combining our knowledge of the pharmacokinetics of these drugs with our understanding of the rate of equilibration between the plasma and the effect site. Simulations, such as performed here, offer insights into this complex system that can be used to make rational decisions in designing opioid dosing regimens and selecting opioids.

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