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Understanding Pharmacokinetics and Pharmacodynamics Through Computer Simulation: I. The Comparative Clinical Profiles of Fentanyl and Alfentanil

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The authors have used computer simulation to examine the time course of the plasma concentration, estimated effect site concentration, and the intensity of the central nervous system (CNS) effect of fentanyl and alfentanil. The simulations were performed over a range of clinically equivalent doses. Simulations of the changes in the processed electroencephalogram (EEG) was used as a reflection of drug induced CNS effect. The simulations reveal that the rate of equilibration between effect site and plasma concentrations can explain differences in the clinical time course of drug effect between these opioids. The onset of fentanyl EEG drug effect is delayed relative to alfentanil and the duration of action is longer. Pharmacokinetic differences do not explain the disparity seen in the time courses of EEG drug effect. Alfentanil and fentanyl have similar plasma disposition curves during the first 90 min. The concentrations at the effect site are, however, quite different. The simulations illustrate how fentanyl's slow blood:brain equilibration can dampen the rate of rise and fall of effect site concentrations. As a mechanism for terminating effect, redistribution of opioid from effect site to other body regions is less relevant for fentanyl compared with that for alfentanil. The evanescent clinical effects of alfentanil can be explained by the rapid blood:brain equilibration. Computer simulation is a useful tool for revealing relevant determinants of the complex relationship between dose and the time course of effect. (Key words: Anesthetics, intravenous: alfentanil; fentanyl. Pharmacodynamics; alfentanil; fentanyl. Pharmacokinetics: alfentanil; fentanyl.)

THE TIME COURSE of pharmacologic effect following iv administration of anesthetics arises from pharmacokinetic and pharmacodynamic processes. Pharmacokinetics describes the relationship between dose and the time course of anesthetic concentration in blood and tissues. Pharmacodynamics characterizes the interaction of the anesthetic with the end organ or receptor, and the translation of this interaction into pharmacologic response.

The physicochemical, pharmacokinetic, and pharmacodynamic characteristics of the two opioids, alfentanil and fentanyl, are dissimilar.[1–4] Pharmacokinetically, fentanyl has larger initial and steady-state distribution volumes and higher distribution (rapid and slow intercompartment clearance) and metabolic clearances compared with those for alfentanil. Fentanyl's terminal elimination phase exceeds that of alfentanil. Pharmacodynamically, Scott *et al.*[1] have shown that fentanyl has a significantly slower half-time of plasma-effect site equilibration. Alfentanil is less potent than fentanyl as judged by a higher IC_{50} (opioid concentration required to produce 50% of maximal narcotic effect). The differences in pharmacokinetics and pharmacodynamics of alfentanil and fentanyl produces different clinical drug effect characteristics of the two opioids.

In performing the above fentanyl/alfentanil pharmacokinetic and pharmacodynamic research, Scott *et al.*[1] characterized the EEG pharmacodynamics of alfentanil and fentanyl. These authors used the EEG spectral edge frequency as a measure of opioid effect on the brain. The primary utility of the processed EEG as a measure of drug effect is that it is a continuous measure of drug effect that allows pharmacodynamic quantitation. This is in contrast to clinical measures of effect such as movement/no movement in response to surgical stimuli that are quantal (yes/no) measures rather than continuous. Although these quantal effect measurements are clinically relevant, they possess poor information content which confounds efforts to characterize continuous concentration/effect relationships. The processed EEG may be useful as a reflection of clinical depth of anesthesia since the opioid concentration required to produce major slowing in EEG frequency lies within the accepted clinical plasma concentration range for opioid-induced anesthesia.[1–4] The concentration range for clinical anesthesia and EEG slowing for fentanyl and alfentanil are presented graphically in figures 1 A and B.

Once the pharmacokinetics and the pharmacodynamics of an opioid have been characterized, a combined pharmacokinetic/pharmacodynamic model can be written to predict the time course of drug effect. Such a model would describe the time course of drug concentration in blood and the site of action as well as the time course of drug effect after any dosing regimen. We have developed a microcomputer-based pharmacokinetic/pharmacodynamic simulation program that permits three-dimensional

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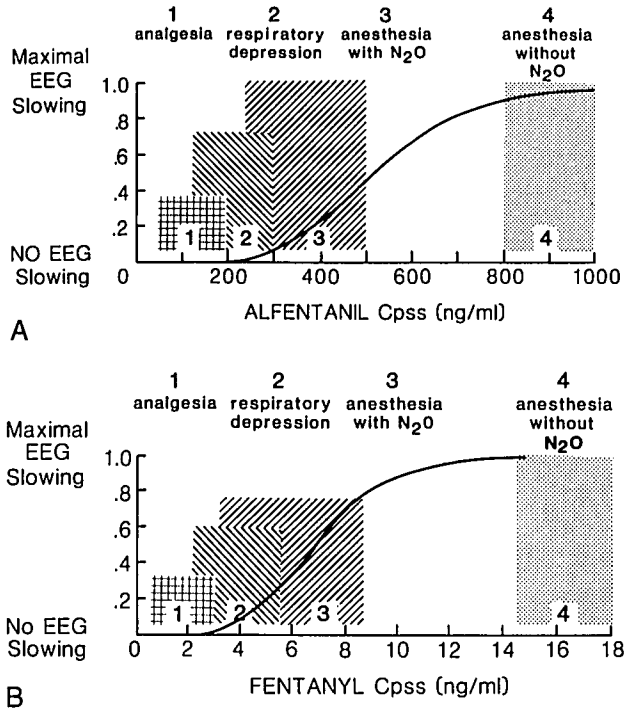

FIG. 1. The overlap between alfentanil (*A*) and fentanyl (*B*) steady-state plasma concentrations required to produce EEG slowing and concentrations required to produce clinical stages of anesthesia. Anesthesia without nitrous oxide refers to "cardiac" anesthesia when the opioid is supplemented with a benzodiazepine or scopolamine to produce amnesia. Data have been adapted from references 1–4.

graphic display of the time course of pharmacologic events. The third dimension permits the examination, in a continuous manner, of the influence of varying an essential characteristic of the model on the time course of drug concentration or drug effect. In this report we have used the pharmacokinetic/pharmacodynamic model of fentanyl/alfentanil-induced slowing of the EEG to compare the clinical pharmacology of fentanyl and alfentanil following the administration of a range of clinically relevant doses. We examined the time course of opioid concentrations in plasma, at the theoretical effect site, and the degree of drug effect as expressed by the 95% EEG spectral edge frequency.

Methods

We used the pharmacokinetic/pharmacodynamic models indicated in figure 2 to perform computer simulations of plasma concentrations *versus* time, effect site concentration (Ce) *versus* time, and the resulting EEG effect (spectral edge) *versus* time courses following different doses of fentanyl and alfentanil. The pharmacokinetic and pharmacodynamic parameters of fentanyl and alfentanil disposition and effect used in these simulations are presented in table 1. They were adapted from those estimated by Scott *et al.*[1] The simulations were performed on a Hewlett-Packard® model 9816 computer using graphic software developed in our laboratory. Input doses into the central compartment (which is analogous to iv administration) ranges from 3–9 mg for alfentanil and 0.5–1.5 mg for fentanyl and were administered over 6 s. The simulations are rather straightforward once three-dimensional graphic software is available. Our simulator generates plasma concentration, Ce, or spectral edge as the dependent variable along a grid of time-infusion rate pairs. The equations used in the plasma concentration *versus* time simulations are presented in Appendix 1, and the equations used in the simulations of the Ce *versus* time

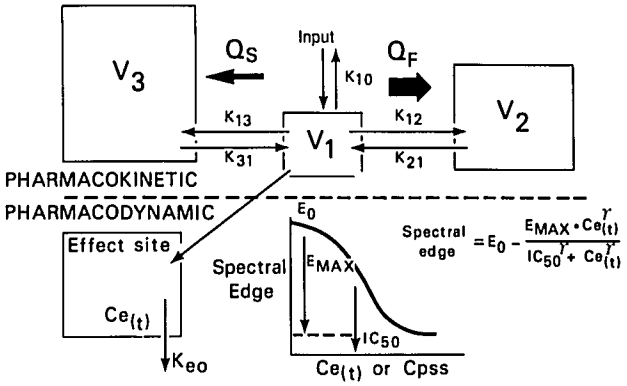

FIG. 2. The combined pharmacokinetic-pharmacodynamic model. The time course of opioid concentrations can be described with a three-compartment pharmacokinetic model (top half of figure). This model derives concentrations in the effect site. The resulting effect site concentrations are translated into the EEG effect using an inhibitory sigmoid E_{max} model (lower half of figure).

TABLE 1. Pharmacokinetic and Pharmacodynamic Parameters Used for Simulation

Parameter	Units	Alfentanil	Fentanyl
Pharmacokinetic			
Elimination clearance	ml/min	195	574
Fast distribution clearance	ml/min	1266	4005
Slow distribution clearance	ml/min	224	1952
Central volume	liters	2.2	12.7
Steady-state volume	liters	21.9	339
Rapid distribution half-life	min	0.8	1.47
Slow distribution half-life	min	16	24.4
γ half-life	min	128	533
Administered dose	mg	3–9	0.5–1.5
Pharmacodynamic			
K_{eo} rate constant	l/min	0.63	0.11
K_{eo} half-life	min	1.1	6.4
IC_{50}	ng/ml	520	6.9
E_{max}	Hz	15	15
E_0	Hz	20	20
Slope factor	—	4.8	4.9

Adapted from Scott *et al.*[1]

simulations are presented in Appendix 2. The effect *versus* time simulations were performed using the pharmacodynamic equation presented in figure 2 using the effect site concentrations from the effect site concentration *versus* time simulation. Approximately 1500 time-infusion rate response trios are output per simulation. The output of these simulations are then presented as three-dimensional graphs. The other parameters in the equations presented in table 1 are held as constants during the simulation. Although in this report we varied infusion rates, any parameter in the appendices may be assigned as an independent variable. This permits the exploration of additional relevant factors on the time course of pharmacologic effect with the same software.

Results

Figures 3, 4, and 5 show the three-dimensional output of computer simulations of drug concentration and effect over three different periods during drug administration: 0–4.75 min, 0–24 min, and 0–90 min. We presented the simulations over three time scales so the unique features of each time frame are more easily revealed.

The time courses of plasma concentration *versus* time *versus* dose for alfentanil are presented in figures 3 A, 4 A, and 5 A; for fentanyl in 3 D, 4 D, and 5 D. The output for alfentanil effect site concentration *versus* time *versus* dose is presented in figures 3 B, 4 B, and 5 B; for fentanyl in 3 E, 4 E, and 5 E. The effect *versus* time *versus* dose profiles for alfentanil are presented in figures 3 C, 4 C, and 5 C; and for fentanyl in 3 F, 4 F, and 5 F, respectively. Except for the time frame, the conditions for the fentanyl and alfentanil simulations are the same in figures 3–5.

Time Course during the First 5 Minutes

Figure 3 illustrates the simulated time courses for the onset of drug effect. Note that the dose axes on the effect *versus* time *versus* dose profiles (3 C and F) have been inverted relative to the remaining panels for clarity. Following rapid iv administration, alfentanil or fentanyl plasma concentrations rise rapidly and then decline in an exponential manner (figs. 3 A and D). Following the highest alfentanil dose, a peak plasma concentration of 4500 ng/ml is attained while fentanyl plasma concentrations peak at 150 ng/ml. In the first 4.5 min, alfentanil plasma concentrations decline to one-tenth of their peak concentration. Over the same period, fentanyl concentrations decay about the same amount, decreasing to approximately 15 ng/ml at the highest dose. Although the

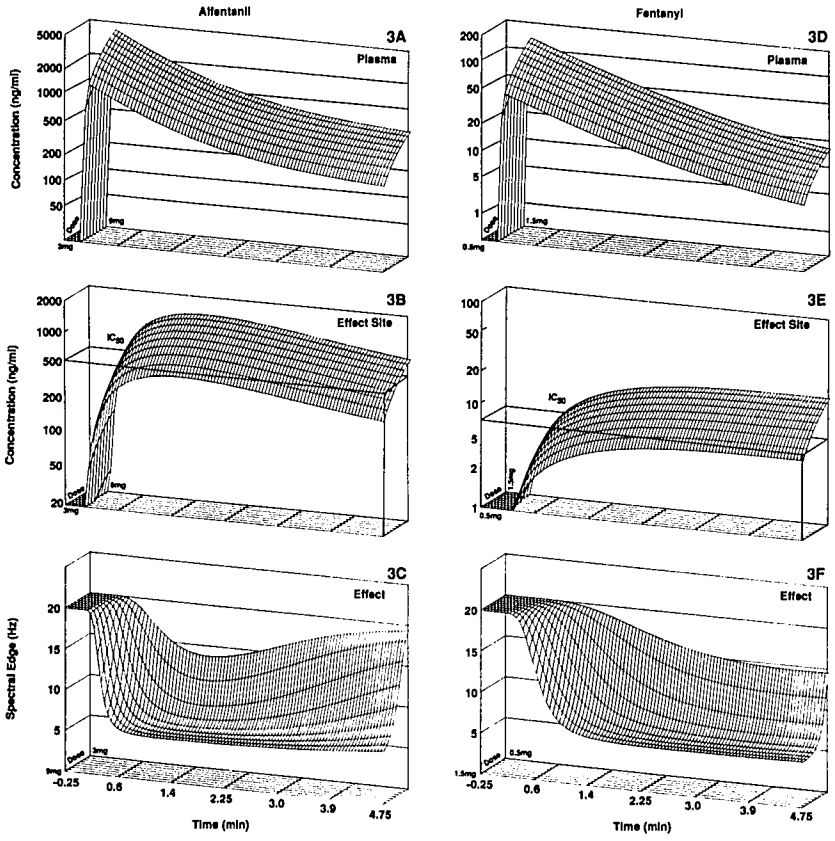

FIG. 3. Simulated concentration and effect time courses of alfentanil and fentanyl over the first 4.75 min following 3–9 mg injections of alfentanil or 0.5–1.5 mg of fentanyl. Plasma concentrations are illustrated in figures 3A and D. The resulting concentrations in the hypothetical effect site are illustrated in figures 3B and E. The IC_{50} frame reveals the time when receptors are more than 50% occupied by opioid. Fentanyl demonstrates a slow rise in effect site concentrations following rapid administration. Figures 3C and F illustrate the simulated effect time course. The dose axis has been inverted for clarity.

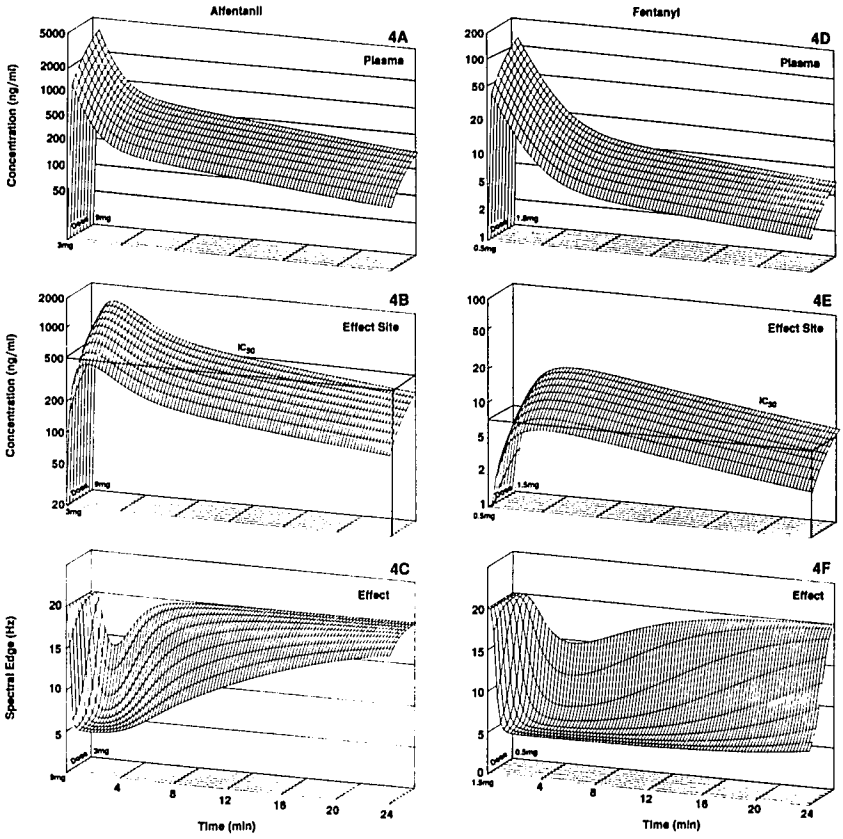

FIG. 4. Simulated concentration and effect time courses of alfentanil and fentanyl over the first 24 min following 3–9 mg injections of alfentanil or 0.5–1.5 mg of fentanyl. Plasma concentrations are illustrated in figures 4A and D. The resulting concentrations in the hypothetical effect site are illustrated in figures 4B and E. Alfentanil effect is terminated by redistribution of opiate from the effect site. Figure 4C and F illustrate the simulated effect time course. Alfentanil effect is "pulse-like" while the fentanyl effect time course is extended.

concentration scales for these two opioids is different, the relative rate and extent of plasma concentration decay are essentially identical.

The effect site concentration *versus* time *versus* dose profiles for the two opioids are very different, as shown in figures 3 B and E. The IC_{50} (effect site concentration at 50% of maximal EEG brain depression) is marked on each graph. At the highest alfentanil dose, concentrations at the effect site exceed IC_{50} within 30 s of administration. Concentrations at the effect site peak within 1.5 min regardless of dose. The rapid rise in effect site concentration results from the large K_{eo} of alfentanil.

For fentanyl, the slower rate of equilibration with the effect site, resulting from a smaller K_{eo}, attenuates the rise in concentrations at the effect site (fig. 3 E). At the highest fentanyl dose, concentrations at the effect site cross the IC_{50} concentrations within 30 s. Note that these concentrations do not reach a peak during the first 5 min regardless of fentanyl dose.

The rising concentration of opioid at the effect site produces progressive brain depression and is illustrated as a decrease in EEG spectral edge frequency (figs. 3 C and F). With the highest dose of alfentanil, the spectral edge asymptotically approaches maximum depression within 0.5 min (fig. 3 C). The rate and extent of spectral edge depression decreases with decreasing doses of alfentanil. The minimal spectral edge at the lowest alfentanil dose occurs at 1.5 min, at the same time that concentrations at the effect site peak. With the highest doses, the apparent peak effect occurs earlier. However, the true maximal effect occurs at the same time regardless of dose. Although it is not readily apparent in figure 3, maximal effect occurs at 1.5 min with the highest alfentanil dose. Spectral edge is infinitesimally lower at 1.5 min than it is at 1 or 2 min. After the peak effect is reached, the spectral edge recovers toward baseline. The rate of recovery is faster with lower doses; the EEG recovers to baseline in 5 min with this lowest alfentanil dose.

The effect *versus* time *versus* dose profile for fentanyl (fig. 3 F) over the first 5 min is quite different from that of alfentanil; in particular, the rate of onset is much slower. For the highest dose of fentanyl the spectral edge asymptotically reaches an *apparent* maximal slowing (5 Hz) by 1 min. With the lowest fentanyl dose, maximal effect is first achieved at 5 min. Notice the relationship between the intensity of effect (figs. 3 C and F) and the concentration of drug at the effect site (fig. 3 B and E). For both drugs, when the spectral edge is below 12.5 Hz, or one-half the maximal effect, effect site concentrations are above the IC_{50}. Thus, the rate of onset of drug effect is

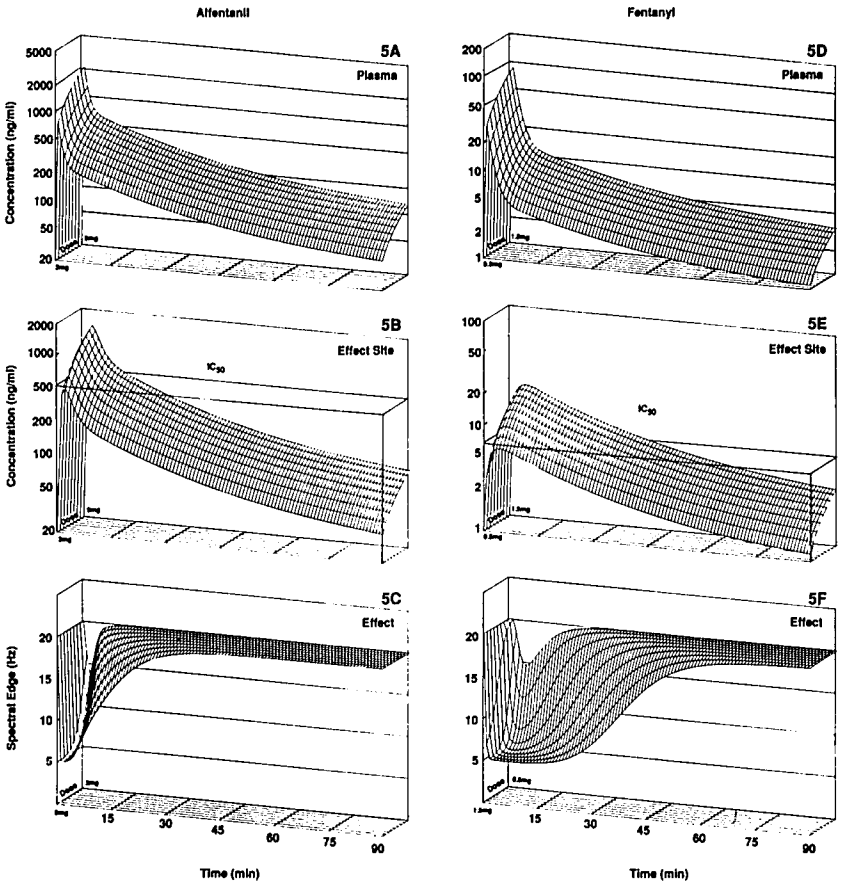

FIG. 5. Simulated concentration and effect time courses of alfentanil and fentanyl over the first 90 min following 3–9 mg injections of alfentanil or 0.5–1.5 mg of fentanyl. Plasma concentrations are illustrated in figures 5A and D. Except for the scale, the shape of the plasma decay curves are remarkably similar. The resulting concentrations in the hypothetical effect site are illustrated in figures 5B and E. Figures 5C and F illustrate the simulated effect time course. Following clinically equivalent doses, alfentanil demonstrates rapid onset and termination of effect relative to fentanyl.

related in part to the rate of rise in effect site concentrations.

TIME COURSE DURING THE FIRST 24 MINUTES

The time frame of concentration and effect was expanded to 24 min in figure 4. A biphasic decline in concentrations is now revealed for both opioids (figs. 4 A and D). The plasma concentration *versus* time profiles are not remarkably different, except for the concentration scales. By 24 min, plasma concentrations have declined to approximately 5% of peak concentrations. The first distribution phase of alfentanil is more rapid than that for fentanyl (table 1); however, distribution is slightly less extensive than for fentanyl (concentrations for fentanyl decline more during this distribution phase than for alfentanil).

Examining the effect site concentration *versus* time *versus* dose profiles over 24 min reveals major differences between alfentanil and fentanyl. The alfentanil concentration *versus* time *versus* dose profile demonstrates the biphasic nature observed in the plasma concentration *versus* time profile. The initial alfentanil plasma distribution phase redistributes the opioid from the effect sites, rapidly reducing concentrations below the IC_{50}. The close relationship between alfentanil effect site concentrations with plasma concentrations results from the rapid equilibration between plasma and effect sites, (*i.e.*, alfentanil has a large K_{eo} relative to fentanyl). This large K_{eo} somewhat dampens the rise and fall of effect site concentrations relative to plasma concentrations. Concentrations of alfentanil at the effect site reach a peak that is only about 30% of peak plasma concentrations. While alfentanil plasma concentrations decline by approximately 95% during the first 24 min, concentrations at the effect site decline by only 75%.

The smaller fentanyl K_{eo} eliminates the biphasic nature of the profile that was seen for alfentanil, such that concentrations at the effect site decline in a monoexponential fashion during the first 24 min. The redistribution of fentanyl from plasma to other tissues is less important in reducing concentrations at the effect site, relative to alfentanil. The smaller K_{eo} has a large dampening effect that attenuates the extent of the rise and fall in concentrations of fentanyl at the effect site. Concentrations at the effect site peak at approximately 5 min (compared with 1.5 min for alfentanil) and are only 12% of the peak plasma concentrations (as compared with a 30% difference for alfentanil). During the first 24 min, concentrations of fentanyl at the effect site are reduced by 60% from the peak amount; in alfentanil concentrations at the effect site drop

by 75% during the same period. At the largest fentanyl dose, concentrations are still above IC_{50} during the first 24 min, while alfentanil concentrations are almost half of the IC_{50} at 24 min.

The rapid distribution then redistribution of alfentanil out of the effect site produces a rapid onset and offset of effect (fig. 4 C). Within 4–10 min, alfentanil drug effect decreased to at least 50% of the peak effect. Even at the highest dose effect has almost returned to baseline within 24 min. In contrast, the fentanyl effect *versus* time *versus* dose profile demonstrates slow recovery (fig. 4 F), except in low doses. Low doses produce a delayed onset of effect and a reduced peak intensity. To achieve rapid onset of fentanyl effect, large doses must be administered. This "overdose" produces supramaximal effect site concentrations for extended periods. At 24 min the effect *versus* time profile for the highest fentanyl dose is just beginning to move away from peak effect. Thus, rapid onset of action can still be achieved with fentanyl. High doses produce high plasma concentrations that effectively drive drug into the effect site; however, the price that must be paid for the rapid onset of action is a prolonged and intense effect.

Time Course during the First 90 Minutes

Figure 5 illustrates the time courses over 90 min. Plasma concentrations have declined to 3 and 2.5% for alfentanil and fentanyl, respectively, at 90 min (fig. 5 A and B). The rate of decline in plasma concentrations during this 90-min period is similar for the two opioids; however, the initial distribution for fentanyl is more extensive.

A primary difference between the alfentanil and fentanyl effect site concentration profiles is the overall shape of the surfaces (figs. 5 B and E). The alfentanil effect site concentration *versus* time *versus* dose profile shows a rapid rise in concentration after administration followed by a biphasic decline. As stated above, the two phases seen in this simulation are distribution phases; the elimination of alfentanil is not reflected in the decay until more than 90 min has passed. The initial distribution phase evident in the effect site concentration *versus* time profile is a major determinant for the termination of alfentanil effect. Effect site concentrations are reduced to below the IC_{50} concentration by this rapid distribution phase. Effect site concentrations remain above the IC_{50} concentration for only a small portion of the total simulation time. This leads to the rapid onset and dissipation of effect (fig. 5 C). The effect *versus* time *versus* dose profile of alfentanil exhibits an impulse-like character. Even with the large dose, alfentanil effect is completely dissipated in less than 30 min. Maximal effect can only be sustained for approximately 4 min.

Fentanyl exhibits an effect site *versus* time *versus* dose profile that is quite different from alfentanil. Effect site concentrations rise more slowly and then decay in an apparent monoexponential fashion. The two distribution phases evident in the plasma concentration *versus* time *versus* dose profile for fentanyl are not seen in the effect site concentration profiles. Because rapid redistribution is not apparent at the effect site, fentanyl effect site concentrations remain above the IC_{50} concentration for an extended period during this simulation. This leads to an extended effect profile (fig. 5 F). With the largest dose, almost 1 h must lapse before the effect is completely dissipated. With the highest dose, maximal effect is sustained for more than 25 min. Over the same period with equivalent doses the alfentanil effect has completely dissipated.

If the simulation was extended beyond 12 h, the third and final elimination phase would be evident for both opioids. To illustrate the triphasic disposition kinetics, simulations were performed using the parameters in table 1 with doses of 9 mg of alfentanil and 1.5 mg of fentanyl. Figures 6 A through C illustrate the plasma concentration time course for alfentanil and fentanyl obtained from this simulation over 9, 90, and 900 min, respectively. The solid line represents alfentanil plasma concentrations, while the dashed line depicts fentanyl plasma concentrations. Following the 0.5-min infusion, the initial rapid distribution phase of the two opioids are seen in figure 6 A. This first phase is completed within the first 10 min for both opioids and remains in the second slower distribution phase for the first 90 min following administration (fig. 6 B). This is the same time scale that was used for the simulations in figure 5. Notice that the shape of the plasma concentration *versus* time profiles are essentially identical for both opioids except for the differences in scale. Alfentanil and fentanyl are declining in parallel during the initial 1.5 h following administration. Only when the time

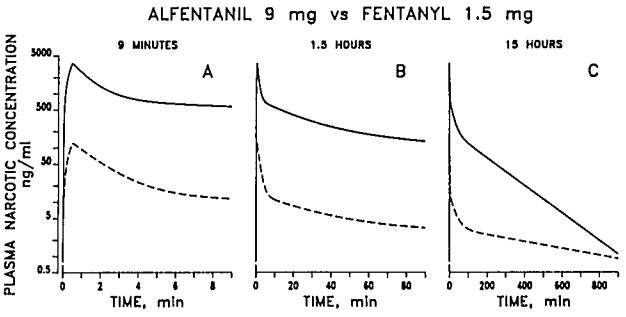

FIG. 6. Simulated plasma concentration time courses of alfentanil and fentanyl following 9 and 1.5 mg doses, respectively. The time scale has been progressively expanded to reveal the essential disposition features over 9 min (*A*), 90 min (*B*), and 900 min (*C*). Fentanyl concentrations are displayed as dashed lines while alfentanil concentrations are denoted as a solid line. The initial distribution phase of fentanyl is more extensive and continues for a longer time than alfentanil (*A*). Over 90 min (*B*) the disposition of both drugs are similar (this is the same time scale as in fig. 5). Only until the simulation is extended beyond 1.5 h does the slower fentanyl elimination phase become evident (*C*).

scale is extended beyond 1.5 h, and the terminal elimination phase is reached, is the more rapid elimination of alfentanil relative to fentanyl apparent. Then the pharmacokinetic differences in plasma between these two opioids become evident.

Discussion

Table 1 describes the pharmacokinetics and dynamics of fentanyl and alfentanil that were derived by Scott *et al.*[1] These authors used the EEG spectral edge frequency as a measure of opioid effect on the brain. Pharmacokinetically, fentanyl has larger initial and steady-state distribution volumes and higher distributional and metabolic clearances compared with those for alfentanil. The duration of the fast and slow distribution phases and the terminal elimination phase of fentanyl exceed those for alfentanil. Pharmacodynamically, fentanyl has a significantly slower half-time of plasma effect site equilibration. Alfentanil is less potent than fentanyl as judged by a higher IC_{50}.

Once the pharmacokinetics and pharmacodynamics of an anesthetic are well characterized, this information can be used in a mathematical simulation to examine the influence of changing any parameter on the time course and intensity of drug effect. Such simulations can be useful as teaching tools in examining the consequences of altered pharmacokinetics or pharmacodynamics. To perform such simulations, information on the pharmacologic character of the anesthetic is needed.

The techniques used to characterize the pharmacokinetics of a drug are well described.[5] The characterization of the pharmacodynamic parameter of an anesthetic agent presents greater difficulty.[6] A major problem arises in choosing a measure of anesthetic effect, especially anesthetic depth. In the operating room, anesthesia may often be viewed as a quantal phenomena. The patient is either adequately or inadequately anesthetized for the particular procedure being performed. Although measures of effect such as movement/no movement in response to surgical stimulus are clinically relevant, they are not rich enough in information to convey the complete concentration effect relationship of the anesthetic. One presumes that underlying these quantal states of anesthesia a continuum of graded anesthetic depth is present. Thus, continuous measures of anesthetic effect should be sought.

Depression in the EEG spectral edge can be used by the anesthesiologist or clinical pharmacologist as an indication of opioid brain depression. The 95% spectral edge describes the frequency in the EEG below which 95% of the total EEG power resides. With increasing opioid concentrations and increasing brain depression, the spectral edge shifts to lower frequencies until a maximal effect occurs, characterized by pronounced δ waves (less than 4 Hz). EEG spectral edge frequency provides a continuous measure of opioid-induced EEG slowing and brain depression that can be characterized in a graded fashion. Spectral edge frequency can be related to opioid plasma concentrations and major frequency shifts can be associated with the plasma concentrations that cause clinical anesthetic effects of these agents.

Figure 1 illustrates fentanyl and alfentanil plasma concentrations required to produce depression in the spectral edge frequency.[1] The steady-state plasma concentrations required to produce clinically relevant analgesic/anesthetic states are also illustrated. The estimated plasma concentrations for producing analgesia, respiratory depression, and anesthesia have been adapted from Mouldenhauer and Hug[2] and Hug.[3,4] The decrease in EEG frequency resulting from alfentanil administration is half maximal at a plasma concentration of 520 ng/ml, a concentration in the middle to upper edge of the clinically relevant concentration range for alfentanil/N_2O anesthesia. The concentration range for EEG slowing by fentanyl is also centered in this same relevant clinical concentration range. EEG spectral edge changes induced by fentanyl and alfentanil occur at clinically relevant plasma concentrations for both drugs. With this in mind, we have used the EEG spectral edge frequency to illustrate pharmacokinetic and pharmacodynamic concepts relevant to clinical iv narcotic anesthesia.

In the absence of other more direct and easily observable measures of anesthetic effect, we believe that the EEG is a useful index for assessing the degree of brain depression induced by anesthetics. Further research is necessary to calibrate the EEG with traditional, clinical signs of depth of anesthesia. At this time we feel that at least the EEG spectral edge frequency can be used in simulations to gain insight into the interactions between the pharmacokinetic and pharmacodynamic aspects of individual iv anesthetic agents.

The pharmacokinetic data used in the simulations is representative of the numerous studies that have examined fentanyl and alfentanil disposition.[7] Frequent arterial blood samples were used to characterize the distribution phases. Blood sampling was long enough and the drug detectable for a period that adequately characterized the elimination kinetics. The study reported by Scott *et al.* contains the only available data set where intense pharmacokinetic and pharmacodynamic data were simultaneously gathered.

Fentanyl exhibits an effect-site concentration *versus* time *versus* dose profile that is different from alfentanil. Concentrations at the fentanyl effect site rise slowly and then decay in an apparent monoexponential fashion. The two distribution phases for fentanyl in plasma are not visible in the effect site concentration *versus* time profiles. Because redistribution from the fentanyl effect site is slow (small K_{eo}), concentrations at the effect site remain above the IC_{50} concentration for an extended period, prolonging drug effect (fig. 5). Almost 1 h must lapse before the effect of the largest fentanyl dose is completely dissipated. With

the highest dose of fentanyl, maximal effect is sustained for more than 25 min. With an equivalent dose of alfentanil, its effect has completely dissipated over this period.

The rapid onset and short duration of anesthetic effect following alfentanil administration has previously been attributed to the rapid distribution and elimination of this opioid.[7] In fact, during short surgical cases (under 1½ h) the pharmacokinetic profiles of fentanyl and alfentanil are remarkably similar. The effects illustrated in figures 5 C and F are terminated by the distribution phases of both opiates. The slower equilibration of fentanyl between plasma and the effect site, relative to alfentanil, dampens the rise and fall of concentrations of fentanyl at the effect site, as compared with alfentanil, and extends the duration of action of this more lipid-soluble opioid. In order to obtain rapid onset with fentanyl, high concentrations must be achieved in the arterial plasma to drive fentanyl into the brain. By administering large doses rapid onset can be achieved, at the expense of achieving supramaximal effect and an extended duration of effect. Although alfentanil demonstrates a more rapid elimination phase than fentanyl, this is only relevant for longer surgical cases. The evanescent alfentanil effect results from a rapid equilibration of alfentanil concentrations between the blood and the effect site. Effect site concentration *versus* time profiles are more relevant to understanding the clinical effects of an anesthetic than are plasma concentration *versus* time profiles in the example we present.

The delayed equilibration of fentanyl plasma concentrations with the effect site explains the discrepancy between the intrinsic potency (the pharmacologic potency or IC_{50}; table 1) and the clinical dose potency. The ratio of alfentanil to fentanyl intrinsic potency is approximately 75:1, while the clinical dose potency is approximately 6:1 (table 1).[1] The slower equilibration of fentanyl into the effect site, relative to alfentanil, dampens the rise in opioid concentration at the effect site and effectively limits the "bioavailability" at the effect site. Peak concentrations of fentanyl at the effect site only achieve 12% of the peak concentrations in plasma, while peak concentrations of alfentanil at the effect site reach 30% of the peak concentrations in plasma (figs. 4 D and E, and figs. 4 A and B). Based on the peak concentrations at the effect site, alfentanil appears to be 2.5 times more available at the effect site than fentanyl (alfentanil peak effect of 30%/fentanyl peak effect of 12%). The ratio of the initial volume of distribution of fentanyl to alfentanil is approximately 5.7:1 (12.7 l *vs.* 2.2 l; table 1). To obtain equivalent initial plasma concentrations this volume must first be filled. Multiplying the initial volume of distribution ratio with the ratio of effect site availability and the clinical dose potency, one obtains a ratio that is not far from the observed intrinsic potency obtained by Scott *et al.* (86:1 *vs.* 75:1 in this simulation).[1] The decreased availability of fentanyl at the effect site (due to its small K_{eo} and expanded initial volume of distribution) makes fentanyl appear to be clinically less potent than it really is. The clinical dose potency of an anesthetic is determined not only by the intrinsic pharmacodynamic properties but also by pharmacokinetic characteristics.

In summary, we have used data from a pharmacokinetic and pharmacodynamic model to generate computer simulations that demonstrate how changing alfentanil or fentanyl bolus doses alter the plasma concentration, concentration at the effect site, and EEG effect. The use of computer simulations has significant potential to allow the clinician and scientist to understand the complex relationships of drug dose *versus* plasma concentration and degree of drug effect. Future applications could include comparison of different dosing schemes (*i.e.*, prolonged infusion), how changes in pharmacokinetic or pharmacodynamic parameters can alter response to a fixed dose, and how altered physiology (*i.e.*, age) or pathology affect anesthetic response.

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Appendix 1

Equation describing the time course of plasma concentration in a three-compartment pharmacokinetic-pharmacodynamic link model:

$$Cp(t) = \frac{K^0}{Vc}\left[\frac{(Cl_2/V_2 - \alpha)(Cl_3/V_3 - \alpha)(e^{\alpha T} - 1)e^{-\alpha t}}{\alpha(\beta - \alpha)(\tau - \alpha)} + \frac{(Cl_2/V_2 - \beta)(Cl_3/V_3 - \beta)(e^{\beta T} - 1)e^{-\beta t}}{\beta(\alpha - \beta)(\tau - \beta)} + \frac{(Cl_2/V_2 - \tau)(Cl_3/V_3 - \tau)(e^{\tau T} - 1)e^{-\tau t}}{\tau(\alpha - \tau)(\beta - \tau)}\right]$$

Cp = plasma drug concentration;
K^0 = drug infusion rate;
Vc = central volume of distribution;
V_2 = Volume of second compartment;
V_3 = Volume of third compartment;
Cl_e = elimination clearance;
Cl_2 = Distribution clearance between second and central compartments;
Cl_3 = Distribution clearance between third and central compartments;
t = time;
T = [time during infusion; infusion duration after infusion has stopped;
α = hybrid rate constant for rapid distribution phase;
β = hybrid rate constant for slow distribution phase;
τ = hybrid rate constant for terminal elimination phase.

The rate constants α, β, and τ are hybrids of all fundamental volume and clearance terms of the system. They represent the eigenvalues of the system of differential equations that describe the pharmacokinetic system. These hybrid rate parameters can be calculated from the fundamental parameters of the system as the roots of the following polynomial:

$$X^3 + A_2 \cdot X^2 + A_1 \cdot X + A_0 = 0$$

$$A_0 = (Cl_e \cdot Cl_2 \cdot Cl_3)/(Vc \cdot V_2 \cdot V_3)$$

$$A_1 = Cl_e/Vc \cdot (Cl_2/V_2 + Cl_3/V_3) + Cl_3/Vc \cdot Cl_2/V_2 + Cl_2/Vc \cdot Cl_3/V_3 + Cl_2/V_2 \cdot Cl_3/V_3$$

$$A_2 = (Cl_e + Cl_2 + Cl_3)/Vc + Cl_3/V_3 + Cl_2/V_2.$$

If we let $Q = A_1 - A_2^2/3$,
$R = (-Q^3/27)^{1/2}$,
$S = \text{Arc Cosine } (-(2 \cdot A_2^3/27 - A_1 \cdot A_2/3 + A_0)/2 \cdot R)/3$,

then the cubic roots can be obtained as follows:

$$\text{Root 1} = 2e^{\text{Log}(R)/3} \cdot \text{COS}(S) - A_2/3;$$

$$\text{Root 2} = 2e^{\text{Log}(R)/3} \cdot \text{COS}(S + 120) - A_2/3;$$

$$\text{Root 3} = 2e^{\text{Log}(R)/3} \cdot \text{COS}(S + 240) - A_2/3.$$

Since by definition $\alpha > \beta > \tau$, the hybrid rate constants are assigned the correct root by numerical magnitude. Notice that α, β, and τ are dependent on all fundamental volume and clearance terms in a complex nonlinear fashion.

Appendix 2

Equation describing the time course of the apparent effect site concentration in a three-compartment pharmacokinetic-pharmacodynamic link model with effect site connected to the central compartment:

$$Ce(t) = \frac{K^0 \cdot K_{eo}}{Vc}\left[\frac{(Cl_2/V_2 - \alpha)(Cl_3/V_3 - \alpha)(e^{\alpha T} - 1)e^{-\alpha t}}{\alpha(\beta - \alpha)(\tau - \alpha)(K_{eo} - \alpha)} + \frac{(Cl_2/V_2 - \beta)(Cl_3/V_3 - \beta)(e^{\beta T} - 1)e^{-\beta t}}{\beta(\alpha - \beta)(\tau - \beta)(K_{eo} - \beta)}\right.$$
$$\left. + \frac{(Cl_2/V_2 - \tau)(Cl_3/V_3 - \tau)(e^{\tau T} - 1)e^{-\tau t}}{\tau(\alpha - \tau)(\beta - \tau)(K_{eo} - \tau)} + \frac{(Cl_2/V_2 - K_{eo})(Cl_3/V_3 - K_{eo})(e^{K}eo^{T} - 1)e^{-K}eo^{t}}{K_{eo}(\alpha - K_{eo})(\beta - K_{eo})(\tau - K_{eo})}\right]$$

Ce = Apparent effect site concentration;
K_{eo} = Rate constant for elimination from effect compartment.
All other terms as defined in Appendix 1.