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# *Pharmacokinetic Parameters Relevant to Recovery from Opioids*

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***Background:*** **Several recent studies have suggested that the terminal half-lives of many drugs do not predict the rate of washout of drug after the relatively short durations of infusions used in anesthesia. Many anesthetic drugs fit a three-compartment mamillary model, with three volumes of distribution (central [$V_1$] and peripheral [$V_2$ and $V_3$]) and three clearances (elimination or metabolic [$Cl_1$] and distribution [$Cl_2$ and $Cl_3$]). It has been suggested that a large $V_3$:$Cl_3$ ratio contributes to rapid recovery after infusion. We investigated the role of each of these primary pharmacokinetic parameters to determine values of each that would contribute to rapid recovery after various dosing schemes.**

***Methods:*** **Three sets of computer simulations were performed based on a three-compartment mamillary model for fentanyl, alfentanil, and sufentanil. Set I predicted the change in plasma concentration of each drug after a bolus if each pharmacokinetic parameter were independently increased by 5%. Set II predicted the time for an 80%, 50%, or 20% decrease in plasma concentration after infusions of varying duration (the 80%, 50%, and 20% decrement time, respectively) if each pharmacokinetic parameter were independently increased by 5%. Set III calculated the percent change in each pharmacokinetic parameter alone that would give a 30% shorter decrement time after infusions of varying duration.**

***Results:*** **Set I demonstrated that after a bolus dose to obtain identical initial plasma concentrations, the drug with a larger $V_1$ had a higher plasma concentration than did the parent drug at all subsequent times. The drug with a larger $Cl_1$ had a lower plasma concentration than did the parent drug at all times. A larger $V_2$, $V_3$, $Cl_2$, or $Cl_3$ led to a lower plasma concentration at times soon after the bolus and subsequently to a higher plasma concentration than did the parent drug. Set II demonstrated that after an infusion, increasing $V_1$ led to a longer decrement time and increasing $Cl_1$ led to a shorter decrement time for infusions of all durations. Increasing $V_2$, $V_3$, $Cl_2$, or $Cl_3$ led to a shorter decrement time when the infusion had been short and when a small decrease in plasma concentration was desired. Increasing each of these four parameters led to a longer decrement time when the infusion had been long and when a larger decrease in plasma concentration was desired. Set III demonstrated that a smaller $V_1$ or a larger $Cl_1$ always led to a shorter decrement time. For infusions of short duration and for a small decrease in plasma concentration, a larger $V_2$, $V_3$, $Cl_2$, or $Cl_3$ led to the desired decrease in decrement time. For infusions of longer duration and for larger decreases in plasma concentration, a smaller $V_2$, $V_3$, $Cl_2$, or $Cl_3$ was able to decrease the decrement time by 30%.**

***Conclusions:*** **This study proposes qualitative guidelines for pharmacokinetic properties desirable in anesthetic drugs. If a rapid decrease in plasma concentration is desired after an infusion, it is always beneficial to have a small $V_1$ and a large $Cl_1$. For infusions of short duration, after which only a small decrease in plasma concentration is required, it is beneficial to have a larger $V_2$, $V_3$, $Cl_2$, and $Cl_3$. For infusions of longer duration, after which a large decrease in plasma concentration is desired, it is beneficial to have a smaller $V_2$, $V_3$, $Cl_2$, and $Cl_3$. These proposals may be beneficial for planning clinical trials of new drugs. (Key words: Analgesics, opioid: alfentanil; fentanyl; sufentanil. Pharmacokinetics.)**

IN the past several years, it has been repeatedly demonstrated that the terminal half-life does not reliably predict the rate of decrease in concentration of drugs used in anesthesia—a concept that goes against traditional pharmacokinetic teaching.[1–3] Shafer and Varvel demonstrated that even though the terminal half-life of sufentanil is longer than those of fentanyl and alfentanil, its effect-site concentration decreases more quickly than that of the latter two drugs when given as an infusion of several hours' duration.[1] In their report, Shafer and Varvel translated the pharmacokinetics of these three drugs into a series of recovery curves, which clearly illustrated the effect of infusion duration on the time required for a given decrease in effect site concentration. These curves led Hughes *et al.* to introduce the concept of "context-sensitive half-time," the time for a 50% decrease in plasma concentration.[2] They showed for fentanyl, alfentanil, sufentanil, propofol, thiopental and midazolam that although context-sensitive half-time always increased with increasing infu-

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sion duration, in no case did it ever reach the terminal half-life. Between drugs there was no consistent correlation between context-sensitive half-time and terminal half-life, even after infusion to steady state.

In search of further understanding of the factors that did contribute to a shorter context-sensitive half-time, Hughes *et al.*[2] examined the pharmacokinetics of each drug in terms of rate constants. They used a three-compartment mamillary model (except for midazolam, which had not been parameterized that way yet), which can also be described by these six independent parameters: three volumes of distribution (central [$V_1$] and peripheral [$V_2$ and $V_3$]) and three clearances (elimination or metabolic [$Cl_1$] and distribution [$Cl_2$ and $Cl_3$]). In these terms, they noted that a large $V_3$:$Cl_3$ ratio correlated with a shorter context-sensitive half-time after infusions that had not yet reached steady state, and a small $Cl_3$:$Cl_1$ ratio correlated with a shorter context-sensitive half-time after an infusion to steady state.

In this study we further examined $V_1$, $V_2$, and $V_3$ and $Cl_1$, $Cl_2$, and $Cl_3$ to determine the role of each in the decrease of plasma drug concentration. We used computer simulations to determine explicitly the direction and magnitude by which each volume or clearance term influenced the rate of decrease in plasma drug concentration after drug administration. We evaluated these effects on the time for a 20%, 50%, or 80% decrease in plasma concentration after infusions of varying durations. For simplicity, we called these times "20% decrement time," "50% decrement time," and "80% decrement time," respectively. The 50% decrement time therefore is identical to the context-sensitive half-time. The term "decrement time" emphasizes that we are referring only to the decrease in plasma concentration, as opposed to "recovery," which implies a clinical effect. Plasma concentration is only one of the many determinants of clinical recovery.

The drugs we evaluated were fentanyl, alfentanil, and sufentanil, because these compounds have very different pharmacokinetic properties. We chose to examine plasma concentration rather than effect site concentration to minimize the number of variables examined in this very complex study. The effect site concentration is always driven by the plasma concentration; the difference is negligible except after boluses or very short infusions.

Our primary goal was to increase our understanding of the influence of volumes and clearances on the rate of offset of drug effect and thus to increase our insight into the behavior of drugs commonly used in anesthesia. A secondary goal was to identify potentially desirable pharmacokinetic properties of new drugs. It may not be possible to change the volumes or clearances of existing drugs, but new drugs may be synthesized with specific goals in mind. In addition, once the pharmacokinetic parameters of a new drug are identified, it should be possible to use this information to choose appropriate applications for this drug. We hoped that the results of this investigation would contribute to more rational dosing of the drugs, old and new, used in the practice of anesthesia.

## Materials and Methods

The pharmacokinetic parameters for fentanyl and alfentanil were those reported by Scott and Stanski.[4] The sufentanil pharmacokinetic parameters were those described by Hudson *et al.* for patients undergoing abdominal aortic surgery.[5] We used the pharmacokinetic parameterization of these results as reported by Shafer and Varvel[1] (table 1). We chose these parameter sets because they were the ones used by Shafer and Varvel[1] and Hughes *et al.*[2] in their analyses, on which we are expanding.

The computer simulations were performed on an IBM-compatible personal computer running DOS (Microsoft, Redmond, WA) with programs written in the C language by one of the authors (S.L.S.).‡ The simulations used Euler's numeric approximation of the differential equations describing drug flow between the compartments of a three-compartment model with a step size of 1 s.

**Table 1. Pharmacokinetic Parameters**

| | Fentanyl | Alfentanil | Sufentanil |
|---|---|---|---|
| $V_1$ (L) | 12.7 | 2.19 | 17.8 |
| $V_2$ (L) | 50.2 | 6.70 | 47.3 |
| $V_3$ (L) | 295 | 14.5 | 476 |
| $Cl_1$ (L/min) | 0.625 | 0.199 | 1.16 |
| $Cl_2$ (L/min) | 4.82 | 1.43 | 4.84 |
| $Cl_3$ (L/min) | 2.27 | 0.247 | 1.29 |

‡ The software used in this investigation and other software useful in predicting concentrations and decrement times is available by request from the authors or on the Internet at nm.icon.iserver.paloalto.med.va.gov.

*Set I: Plasma Concentration after Bolus Injection*

We first examined the influence of each pharmacokinetic parameter on the plasma concentration after a bolus injection of either fentanyl, alfentanil or sufentanil. We initially simulated the plasma concentrations (concentration$(t)_{orig}$) at specific time points from 0 to 600 min after a bolus injection of opioid to achieve an initial concentration of 100 ng/ml (an arbitrarily chosen concentration). In the next six simulations we independently increased each pharmacokinetic parameter by 5% while the other five parameters remained at their original values. We then calculated the plasma concentrations (concentration$(t)_{new}$) at each time point after a bolus injection to achieve the same initial concentration.

We defined the influence of a 5% increase in each parameter on the plasma concentration at each time point $t$ as:

$$\text{percent change in concentration}(t) = \frac{\text{concentration}(t)_{new} - \text{concentration}(t)_{orig}}{\text{concentration}(t)_{orig}} \times 100\% \quad (1)$$

This value, divided by the change in parameter, is approximately proportional to the partial derivative of concentration with respect to the parameter ($\partial$ concentration/$\partial$ parameter). We chose a 5% change rather than a 10% or 15% change because the smaller value would more closely approximate the partial derivative.

We also simulated a 5% decrease in each pharmacokinetic parameter and performed the above calculations. This was done, in part, to determine the linearity of the function relating concentration to a given pharmacokinetic parameter at the time of the observation.

*Set II: Decrement Time after Continuous Infusion*

The next set of simulations investigated the influence of a 5% increase in each volume and clearance parameter on the time required for a given decrease in concentration after a continuous infusion of each opioid (*i.e.,* the decrement time). We simulated a "bolus-elimination transfer" (BET) type of infusion,[6] consisting of a bolus followed by an exponentially declining infusion rate to immediately achieve and then maintain a steady plasma concentration. Although such an infusion can only be produced by a computer controlled infusion pump, we based our analysis on this type of infusion because it provided a standard approximation of whatever combination of boluses and infusions anesthesiologists are likely to apply clinically when trying to maintain a constant level of opioid effect.[1,2,7,8]

We simulated the plasma concentrations from BET-style infusions of 0–600-min duration. At specific time points, the infusion was terminated and the time calculated for a 20%, 50%, or 80% decrease in plasma concentration (the 20%-, 50%-, and 80% decrement times, respectively). We then performed six additional simulations, in which each volume and clearance was increased by 5% while the other parameters remained at their original values. These six simulations again used a BET-style infusion, which was terminated at the same time points as in the initial simulation.

We calculated the 20%-, 50%-, and 80% decrement times for each set of parameters at each time point. We defined the influence of a 5% increase in each pharmacokinetic parameter on the time required for a given decrease in plasma concentration after termination of an infusion as:

$$\text{percent change in decrement time}(X,t) = \frac{\text{decrement time}(X,t)_{new} - \text{decrement time}(X,t)_{orig}}{\text{decrement time}(X,t)_{orig}} \times 100\% \quad (2)$$

where $X$ = the desired percentage of decrease in plasma concentration and $t$ = the infusion duration. This value, divided by the change in parameter, approximates the partial derivative of decrement time with respect to the parameter ($\partial$ decrement time/$\partial$ parameter).

*Set III: Desired Change in Parameter*

The next set of simulations examined what changes would be necessary in the volumes or clearances of fentanyl, alfentanil, and sufentanil to produce a 30% faster decrease in plasma drug concentration after termination of a continuous infusion (*i.e.,* a 30% smaller decrement time). As described above, the simulations again used a BET-style infusion of 0–600-min duration. At specific time points, the infusion was terminated and the 20%, 50%, and 80% decrement times were calculated.

The simulation program then examined each pharmacokinetic parameter to determine the change in that parameter *alone* that would produce a 30% shorter decrement time for an BET infusion of the same duration. This was expressed as:

percent change in parameter required to decrease decrement time by 30%$(X,t)$

$$= \frac{\text{parameter}(X,t) - \text{parameter}(X,t)_{\text{orig}}}{\text{parameter}(X,t)_{\text{orig}}} \times 100\% \quad (3)$$

A 30% faster decrease was selected on the assumption that it was close to the minimum change that would be clinically discernible, given the underlying variation in both pharmacokinetics and pharmacodynamics in a given patient. The parameter value that would produce a 30% shorter decrement time was determined using a numeric Gauss-Newton minimization technique with software written by one of the authors (S.L.S.).

## Results

*Set I: Plasma Concentration after Bolus Injection*

The top graph in figure 1 shows the difference between the concentration of fentanyl and the concentration of fentanyl modified to have a 5% increase in each volume term, calculated as in equation 1. It is important to note that at time 0 (immediately upon bolus injection), each curve has a value of 0, because the concentration of each "drug," as well as of fentanyl is 100 ng/ml at time 0. All differences between the curves, as described below, refer to times greater than 0.

The top graph of figure 1 demonstrates that the drug with a larger $V_1$ had a higher plasma concentration than did fentanyl at all times after the bolus. Increasing $V_2$ initially led to lower plasma concentrations, but after 50 min led to higher concentrations than fentanyl. Increasing $V_3$ led to lower plasma concentrations at all times after the bolus. The middle and bottom graphs of figure 1 show analogous curves for alfentanil and sufentanil. The shapes of all the curves were essentially the same, with the following exceptions: increasing the $V_3$ of alfentanil eventually led to a higher concentration, after 210 min.

The top graph in figure 2 shows the concentration difference for 5% increases in fentanyl's clearances. Increasing $Cl_1$ decreased the plasma concentrations at all times. Increasing $Cl_2$ initially decreased the plasma concentration. However, after 6 min the increase in $Cl_2$ led to higher concentrations. Increasing $Cl_3$ also initially led to lower concentrations, then to higher concentrations after 100 min. The middle and bottom

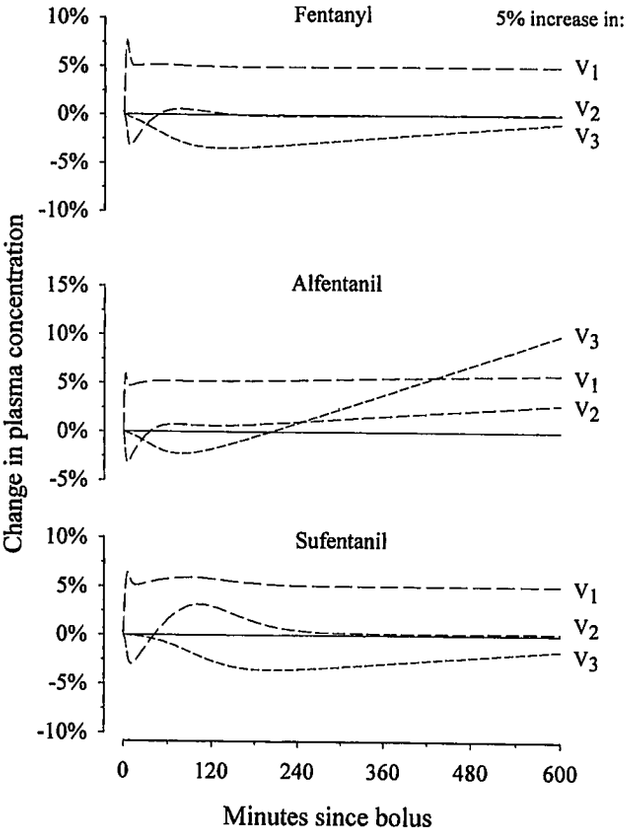


**Fig. 1. Difference (dashed lines) in plasma concentration after a bolus between the parent drug (fentanyl, alfentanil, or sufentanil) and that drug with a 5% increase in a volume of distribution (central [$V_1$] or peripheral [$V_2$ or $V_3$]).**

graphs of figure 2 show similar relations for alfentanil and sufentanil. The shapes of the curves are essentially the same, except that for alfentanil, increasing $Cl_3$ again led to higher concentrations after 360 min.

The results of decreasing each of the volumes and clearances by 5% were essentially mirror images of the results of increasing the parameters by 5%.

*Set II: Decrement Time after Continuous Infusion*

The top graph in figure 3 shows the difference between the 80% decrement times for fentanyl and the 80% decrement times for 5% increases in $V_1$, $V_2$, and $V_3$. An increase in $V_1$ always increased the 80% decrement time. An increase in $V_2$ decreased the 80% decrement time after brief infusions, but increased the 80% decrement time after infusions of greater than 8 min. An increase in $V_3$ also led to a shorter 80% decrement time after short infusions and to a longer 80% decrement time after infusions greater than 90 min.

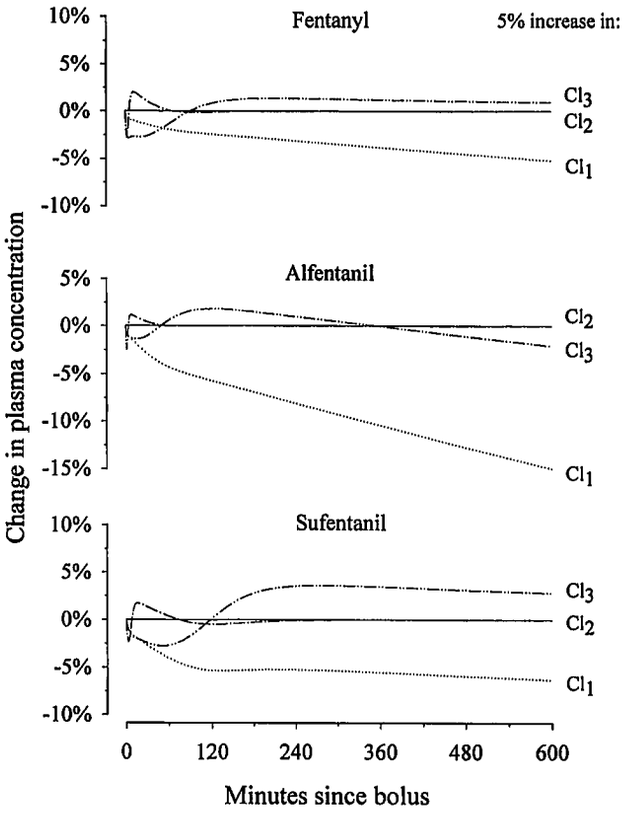


**Fig. 2. Difference (dashed lines) in plasma concentration after a bolus between the parent drug and that drug with a 5% increase in a clearance parameter (elimination or metabolic [$Cl_1$] or distribution [$Cl_2$ and $Cl_3$]).**

The middle and bottom graphs of figure 3 show the analogous curves for 50% and 20% decrement times for fentanyl. Increasing $V_1$ uniformly increased the 50% and 20% decrement times. Increasing $V_2$ or $V_3$ decreased the 50% and 20% decrement times after short infusions, but increased the 50% decrement time after longer infusions.

The top graph of figure 4 shows the change in 80% decrement times after modifying fentanyl's clearances. Increasing $Cl_1$ always decreased the 80% decrement time. Increasing $Cl_2$ decreased the 80% decrement time after a very short infusion, then increased the 80% decrement time for infusions longer than 2 min. A 5% increase in $Cl_3$ also decreased the 80% decrement time after short infusions, then increased the 80% decrement time after infusions greater than 12 min.

The middle and bottom graphs of figure 4 show the effects on the 50% and 20% decrement times for fentanyl. Increasing $Cl_1$ uniformly decreased all the decrement times. Increasing $Cl_2$ or $Cl_3$ decreased the 50% and 20% decrement times after short infusions, but increased the 50% and 20% decrement times after longer infusions.

The corresponding graphs for alfentanil and sufentanil were similar in shape to the graphs in figures 3 and 4, with the following exceptions. For alfentanil, increasing $V_3$ eventually led to longer 20%, 50%, and 80% decrement times, whereas for sufentanil, this effect was only seen in the 80% decrement times.

*Set III: Desired Change in Parameter*

The top graph of figure 5 shows the changes in volumes required to cause a 30% decrease in the 50% decrement time for fentanyl (*i.e.*, the change required to make the concentration decrease more quickly). The bottom graph shows the changes in clearances required

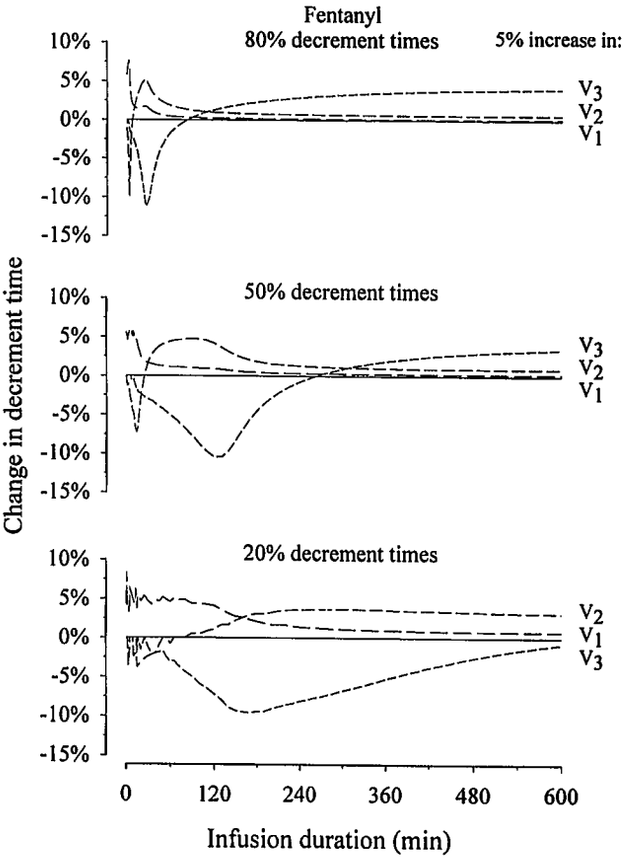


**Figure 3. Difference (dashed lines) in time for an 80%, 50%, or 20% decrease in plasma concentration after an infusion between fentanyl and fentanyl with a 5% increase in a volume of distribution (central [$V_1$] or peripheral [$V_2$ or $V_3$]).**

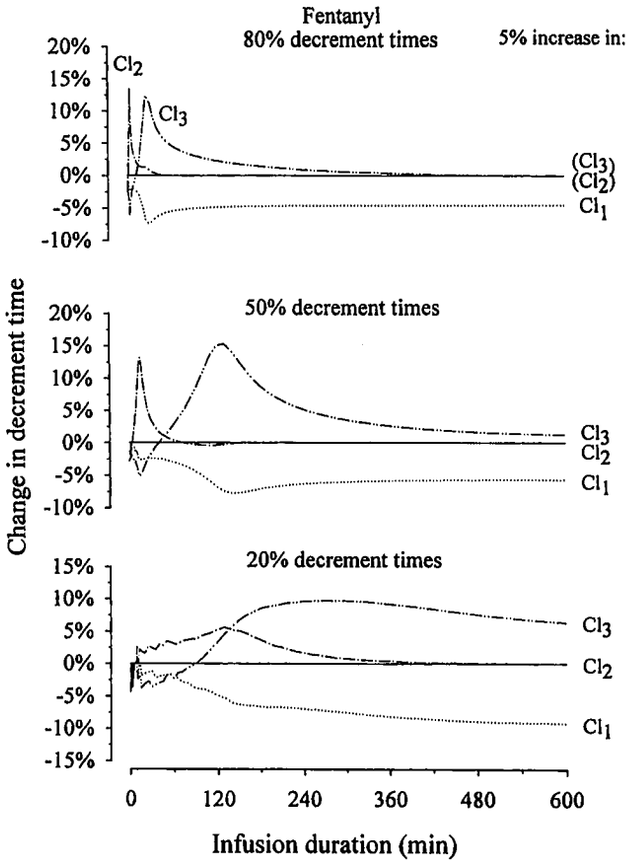


**Fig. 4. Difference (dashed lines) in time for an 80%, 50%, or 20% decrease in plasma concentration after an infusion between fentanyl and fentanyl with a 5% increase in a clearance parameter (elimination or metabolic [$Cl_1$] or distribution [$Cl_2$ or $Cl_3$]).**

to achieve the same results. The curves were extremely complex.

For almost every curve, there were certain infusion durations for which there was no solution; *i.e.,* there was no value of that parameter that could make a 30% reduction in 50% decrement time. In the top graph of figure 5, for those infusion durations for which there was a solution, we can see that a smaller $V_1$ was always beneficial. A larger $V_2$ was beneficial for short infusions (less than 25 min), and a smaller $V_2$ was beneficial for longer infusions. Likewise, a larger $V_3$ was beneficial for infusions less than 270 min, and a smaller $V_3$ was beneficial for longer infusions.

In the bottom graph of figure 5, for those infusion durations for which there was a solution, we can see that a larger $Cl_1$ was always beneficial. A larger $Cl_2$ was beneficial for very short infusions (less than 2 min), and a smaller $Cl_2$ was beneficial for somewhat longer infusions (11–70 min). Similarly, a larger $Cl_3$ was beneficial for short infusions, and a smaller $Cl_3$ was beneficial for longer infusions.

The curves pertaining to the 20% and 80% decrement times for fentanyl and all of the curves for alfentanil and sufentanil are not depicted, but they were equally complex. The patterns were essentially the same.

## Discussion

To understand the results of the simulations, it is necessary to review the three phases of washout. Drugs travel between compartments based on gradients of apparent concentration (amount in compartment divided by the volume of distribution of that compartment). During the rapid distribution phase, the apparent concentration of drug is greatest in $V_1$, so it flows out of $V_1$ into both $V_2$ and $V_3$, and is also cleared from $V_1$ *via* elimination. Entering the slow distribution phase, the apparent concentration in $V_1$ decreases to less than that in $V_2$, so drug starts flowing from $V_2$ back into $V_1$. During this time drug continues to flow from $V_1$ into $V_3$ and from $V_1$ out of the body. During the terminal phase, the apparent concentration in $V_1$ has decreased to less

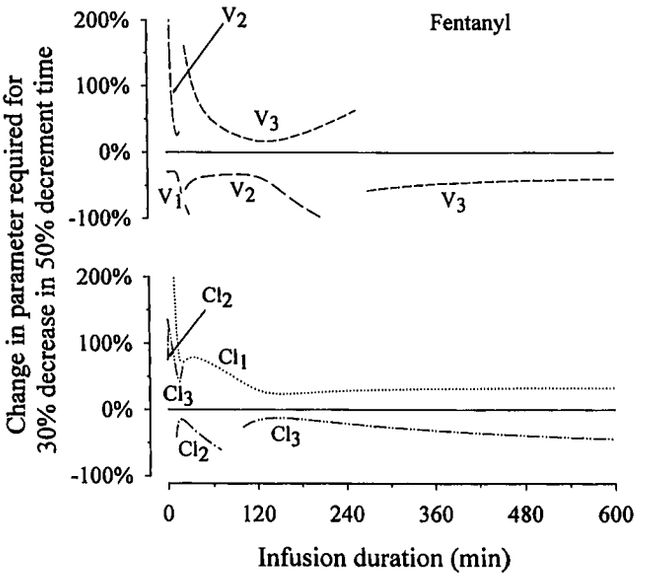


**Fig. 5. Amount (dashed lines) each parameter would have to change to decrease by 30% the time for a 50% decrease in plasma concentration after an infusion of fentanyl.**

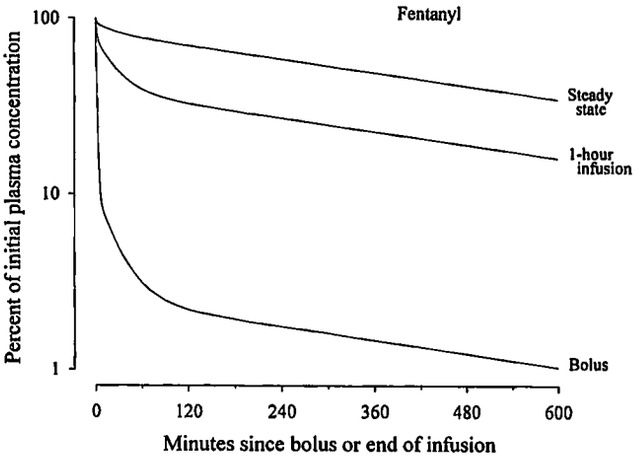


**Fig. 6. After a bolus of fentanyl, the concentration–time curve can be easily divided into three phases. After an infusion, the first two phases become less prominent, especially after an infusion to steady state.**

than that in both $V_2$ and $V_3$, so drug is returning from both $V_2$ and $V_3$ back into $V_1$. During this phase drug continues to be removed from the body.

After a bolus, the three phases are the most distinct, as illustrated for fentanyl in figure 6. After infusions, especially long ones, the first and second phases are very short, as the apparent concentrations in $V_2$ and $V_3$ are higher by the end of the infusion, so less drug may distribute there.

*Set I: Plasma Concentration after Bolus Injection*

Immediately after a bolus, $V_1$ contains the entire dose of drug. The larger $V_1$ is, the more drug will be required to achieve the desired concentration, and the longer it will take to clear during all three phases. As for $V_2$, a larger $V_2$ should increase the amount of drug distributed there during the first phase, as it would take longer for the apparent concentration in $V_2$ to exceed that in $V_1$; on the other hand, a larger $V_2$ may slow the second and third phases by providing more drug to give back to $V_1$. Similarly, a larger $V_3$ should increase the amount of drug distributed there during the first two phases, but may slow the third phase.

A larger $Cl_1$ should always accelerate the decrease in plasma concentration. A larger $Cl_2$ should initially help remove drug from $V_1$ during the first phase, but then may lead to relatively higher concentrations in the second and third phases by facilitating drug reentry into $V_1$. Likewise, a larger $Cl_3$ should accelerate the decrease in concentration during the first and second phases, but may lead to a higher concentration during the third phase. These hypotheses are summarized in table 2.

Applying these concepts to the results of our simulations, we can see from figure 1 that a larger $V_1$ was always associated with higher relative concentrations after a bolus. This correlates with the larger amount of drug administered, which then needed to be distributed and eliminated. A larger $V_2$, as expected, initially led to lower concentrations, as more drug was able to distribute there, but eventually led to higher concentrations as there was more of it to return back into $V_1$. A larger $V_3$ also initially led to lower concentrations, as more drug was able to distribute there. For alfentanil, a larger $V_3$ eventually led to higher concentrations, as there was more drug to return back into $V_1$. For fentanyl and sufentanil, the concentration difference between the parent drug and the modified drug progressively decreased with time, presumably by the same mechanism as for alfentanil.

A larger $Cl_1$ was always beneficial, as expected. A larger $Cl_2$ did initially lead to lower concentrations as more drug was able to distribute to $V_2$, but later led to higher concentrations as it flowed back more freely into $V_1$. Likewise, a larger $Cl_3$ led to lower concentrations during the first two phases, then to higher concentrations as drug flowed back into $V_1$. For alfentanil a larger $Cl_3$ again led to lower concentrations after 360 min after a bolus. The reasons for this behavior are not clear; perhaps the larger $Cl_3$ allows earlier depletion of drug in $V_3$, which allows the plasma concentration to decrease further than it normally would.

The results of the simulations done by decreasing each parameter again confirm the hypotheses set forth in this section.

**Table 2. Change in Plasma Concentration after Bolus**

| Change in Parameter | Rapid Distribution Phase | Slow Distribution Phase | Terminal Phase |
|---|---|---|---|
| $\uparrow V_1$ | ↑ | ↑ | ↑ |
| $\uparrow V_2$ | ↓ | ↑ | ↑ |
| $\uparrow V_3$ | ↓ | ↓ | ↑ |
| $\uparrow Cl_1$ | ↓ | ↓ | ↓ |
| $\uparrow Cl_2$ | ↓ | ↑ | ↑ |
| $\uparrow Cl_3$ | ↓ | ↓ | ↑ |

↑ = the modified drug (*e.g.*, fentanyl but with a 5% larger $V_1$) is expected to have a higher plasma concentration during this phase than the parent drug (*e.g.*, fentanyl); ↓ = the modified drug is expected to have a lower plasma concentration during this phase than the parent drug.

**Table 3. Change in Decrement Time after Infusion**

| Change in Parameter | Short Infusion | Long Infusion | Small Decrease Required | Large Decrease Required |
|---|---|---|---|---|
| ↑$V_1$ | ↑ | ↑ | ↑ | ↑ |
| ↑$V_2$ | ↓ | ↑ | ↓ | ↑ |
| ↑$V_3$ | ↓ | ↑ | ↓ | ↑ |
| ↑$Cl_1$ | ↓ | ↓ | ↓ | ↓ |
| ↑$Cl_2$ | ↓ | ↑ | ↓ | ↑ |
| ↑$Cl_3$ | ↓ | ↑ | ↓ | ↑ |

↑ = the modified drug is expected to have a longer decrement time under these conditions than the parent drug; ↓ = the modified drug is expected to have a longer decrement time under these conditions than the parent drug.

*Set II: Decrement Time after Continuous Infusion*

Whereas after a bolus, most of the decrease in concentration occurs during the first phase, as we can see in the bottom curve in figure 6, after an infusion, less of the decrease in concentration occurs during the first and second phases, as $V_2$ and $V_3$ are more full and are able to equilibrate with $V_1$ more quickly. Accordingly, after a very brief infusion, the effects of the parameters on the rapid distribution phase would be most important in determining the decrement time, whereas after a long infusion the effects on the terminal phase would be more important. In addition, for any given infusion duration, the larger the decrease required, the more important the effects on the third phase would be. So for short infusions and a small required decrease in concentration, increasing each parameter should lead to a shorter decrement time for all but $V_1$; for long infusions and a large required decrease in concentration, increasing each parameter should lead to a longer decrement time for all but $Cl_1$. These hypotheses are summarized in table 3.

As expected, a larger $V_1$ always led to a longer decrement time, and a larger $Cl_1$ always led to a shorter decrement time. For short infusions, a larger $V_2$, $V_3$, $Cl_2$ or $Cl_3$ led to shorter decrement times. For longer infusions, each led to longer decrement times.

As the infusions increased in length, the increases in $V_2$, $V_3$, $Cl_2$ and $Cl_3$ each made a transition from causing shorter decrement times to causing longer decrement times. In addition, as infusion duration increased, $Cl_2$ was the first parameter to make this transition, then $V_2$, $Cl_3$, and $V_3$, in that order. When a larger decrease in concentration was required, each transition occurred after shorter infusions; this finding correlates with the increased importance of the third phase when a larger decrease is required.

The results for alfentanil and sufentanil are similar to those for fentanyl. The earlier transitions for $Cl_2$, $V_2$, $Cl_3$, and $V_3$ for alfentanil relate to alfentanil's small volumes and important third phase; the later transitions for sufentanil reflect the greater importance of its redistribution phases.

*Set III: Desired Change in Parameter*

Although this set of simulations may seem very convoluted, it actually comes the closest to determining the characteristics that lead to the fastest decrement times. As above, for short infusions and a small required decrease in concentration—where the first phase is likely to be important—a decrease in $V_1$ or an increase in any other parameter should decrease decrement time. Likewise, for long infusions and a large required decrease in concentration—where the third phase is likely to be important—an increase in $Cl_1$ or a decrease in any other parameter should decrease the decrement time. These projections are summarized in table 4.

The results confirm that for a more rapid washout from an infusion, it is always better to have a small $V_1$ and a large $Cl_1$. For short infusions and for a small decrease in concentration, larger $V_2$, $V_3$, $Cl_2$ and $Cl_3$ are beneficial. For long infusions and for a large decrease in concentration, smaller $V_2$, $V_3$, $Cl_2$ and $Cl_3$ are beneficial. As for clinical indications between these extremes, it is difficult to predict the parameters required without doing specific simulations.

It is interesting to note that for each drug, there was a range of conditions where both a larger $V_3$ and a smaller $Cl_3$ were beneficial. This correlates with the findings of Hughes *et al.*[2] that a higher $V_3$:$Cl_3$ ratio is beneficial if steady state has not yet been reached, but points out that this is valid for only some infusion du-

**Table 4. Change in Parameter Leading to a Faster Decrement Time**

| Parameter | Short Infusion | Long Infusion | Small Decrease Required | Large Decrease Requried |
|---|---|---|---|---|
| $V_1$ | ↓ | ↓ | ↓ | ↓ |
| $V_2$ | ↑ | ↓ | ↑ | ↓ |
| $V_3$ | ↑ | ↓ | ↑ | ↓ |
| $Cl_1$ | ↑ | ↑ | ↑ | ↑ |
| $Cl_2$ | ↑ | ↓ | ↑ | ↓ |
| $Cl_3$ | ↑ | ↓ | ↑ | ↓ |

↑ = an increase in this parameter would lead to a more rapid decrement time under these conditions; ↓ = a decrease in this parameter would lead to a more rapid decrement time under these conditions.

rations and some desired decreases in concentration. Likewise, for longer infusions, both a larger $Cl_1$ and a smaller $Cl_3$ were beneficial; this supports their suggestion that a smaller $Cl_3$:$Cl_1$ ratio leads to more rapid washout after infusions to steady state.

*Clinical Applications*

The effects of volumes and clearances on decrement times, as explored in this investigation, can lead to a more complete understanding of intravenous agents frequently used in anesthetic practice. Shafer and Varvel demonstrated that alfentanil washes out more quickly than fentanyl after very long infusions.[1] Compared with fentanyl, five of its six parameters are more favorable for a long infusion: $V_1$, $V_2$, $V_3$, $Cl_2$ and $Cl_3$ are all smaller. Alfentanil's small volumes must contain less total drug to be cleared, and its small $Cl_2$ and $Cl_3$ may delay some drug from spilling back into $V_1$. Only $Cl_1$ is less favorable (smaller), but this is apparently outweighed by the other factors. As suggested by Shafer and Varvel,[1] alfentanil would be a rational choice for a long infusion where rapid recovery was desirable after the infusion was terminated.

To take another example suggested by Shafer and Varvel, sufentanil has a quicker decrease in effect-site concentration than fentanyl after a medium-length infusion.[1] This appears to be due to its larger $V_3$, larger $Cl_1$ and smaller $Cl_3$, all of which have been demonstrated to be improvements upon the respective values for fentanyl for infusions of this length. Sufentanil's smaller $Cl_3$ apparently inhibits the accumulation of drug in $V_3$ during the infusion, and its larger $V_3$ may lead to a lower apparent concentration there as well, so there is less drug to return to $V_1$ during the third phase. The $V_2$ and $Cl_2$ of the two drugs are almost identical, so their roles would be negligible, and the more beneficial smaller $V_1$ of fentanyl is apparently not as important here as the other factors. It would follow that sufentanil would be a rational choice for infusion in the operating room for cases of approximately 3 h.

Another potential application of these simulations is in guiding new drug development. Efforts could be made to produce a drug that is more rapidly cleared from the body, because a larger $Cl_1$ is always beneficial. The early data on remifentanil, an opioid metabolized by plasma cholinesterase, is promising for this reason.[9] It may also be possible to increase or decrease $V_2$ and $V_3$ by changing lipophilicity. In addition, once clinical trials are performed and a drug's volumes and clearances are determined, this information could be used to predict this drug's decrement times after infusions of varying duration. The pharmaceutical scientists could then choose the most appropriate application for the drug and tailor future studies accordingly. Realistically, because the effects of volumes and clearances are so complicated, computer simulations would be essential in clarifying these applications.

*Limitations of Study Design*

This study was designed to evaluate only one variable at a time for clarity. However, the pharmacokinetic profile of every drug described by a three-compartment model is a unique combination of three volumes and three clearances, and the interaction between the variables is yet more complex than is presented here. To increase the applicability of our simulations, we examined three different parent drugs instead of one. Although we did indeed find subtle differences, we observed no trends that invalidated our conclusions. Thus, we believe the conclusions are valid despite only examining one variable at a time, and could reasonably apply to all drugs described by three-compartment kinetics.

Our pharmacokinetic model is based on computer simulations, not discrete anatomic structures. In this model, $V_1$ includes the plasma, into which drug is injected, and from which drug is sampled. Drug uptake by the lungs and other rapidly mixing vessel-rich organs may also contribute to $V_1$. $V_3$ is usually considered to be the large, slowly cleared compartment, which most likely includes body fat. $V_2$ is probably made up of fairly rapidly equilibrating tissues, and may also include body fat. However, we emphasize that all three compartments are merely values determined by mathematical analysis of concentration over time after drug administration. Thus, the volumes and clearances should not be literally interpreted as representing specific anatomic structures or flows, respectively. There are other schemes for parameterizing these drugs that are mathematically equivalent, but volumes and clearances provide a way to conceptualize the phases of washout that the other models cannot.

Pharmacodynamics is another important aspect of rational drug design and selection not investigated in this paper. Alfentanil, for instance, has been shown to be useful as a bolus because its rapid equilibration with the effect site leads both to a quick onset and offset of effect.[1] Other factors, such as toxicity or drug interactions, also play a role in determining the appropriate drug for each clinical situation.

We have considered a rapid decrease in plasma drug concentration as uniformly beneficial in these analyses. We realize that for some clinical situations, it is desirable to have a long-lasting effect without having to use a continuous infusion. These simulations could be reanalyzed to determine which factors would lead to the slowest decrease in drug concentration. Similarly, such simulations could define optimum volumes and clearances for a rapid decrease of 50% (*i.e.,* at the end of a case), and then a slow decrease beyond, which would provide stable postoperative analgesia.

In summary, we have evaluated how individual volumes and clearances influence the decrement time after infusions of different durations. Some of our results are intuitively obvious, such as a larger $Cl_1$ always being beneficial or a smaller $V_1$ translating to a lower dose and more rapid washout. However, the findings on intercompartmental volumes and clearances are not at all obvious and add a new dimension to our understanding of recovery from anesthetic drugs. They help us explain the very different decrement times we see after a long infusion versus a short one, and help us to understand why these profiles vary between drugs. In addition, our findings will hopefully contribute to a more efficient approach to drug development, where the initial testing can be used to predict the circumstances under which the drug will ultimately be most effective.

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