The pharmacokinetics of fentanyl, sufentanil and alfentanil: A comparative review

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Pharmacokinetics can be defined as the rate of change of drug concentration mathematically expressed in units of concentration per unit of time. Fentanyl, sufentanil and alfentanil are eliminated by hepatic microsomal enzyme activity. Fentanyl has the longest elimination half-time (t½B) of 219 minutes. Sufentanil has an intermediate t½B of 164 minutes, and alfentanil has the shortest t½B, 94 minutes.

The volume of distribution (Vd) of fentanyl is 4 L/kg, while the Vd of sufentanil is 1.74 L/kg and the Vd of alfentanil is 0.71 L/kg. The volume of distribution for fentanyl is greater than that of its analogues, because fentanyl has different physiochemical properties. The physiochemical properties that affect Vd are ionization, n-octanol: water partition coefficient, and degree of plasma protein binding. Given a drug with a high hepatic clearance like fentanyl, the only mechanism to shorten the t½B is to decrease the Vd.

Age-related differences have a significant effect on the t½B of fentanyl and its analogues. The t½B of fentanyl is 945 minutes in patients older than 60 years. The t½B of sufentanil is 44 minutes in patients younger than 17 months. The t½B of fentanyl is 40 minutes in children. These variations are due to changes in blood flow, hepatic microsomal activity and altered volumes of distribution.

The availability of descriptive pharmacokinetic data offers the potential to control the intensity and duration of effect of intravenous anesthetic agents. This is an advantage which no longer applies exclusively to inhalation agents. This element of control can be achieved through an understanding of the relationship between dose regimens and duration of effects. Pharmacokinetic data provides a description of this relationship. Kinetics is the rate of change of drug concentration expressed in units of concentration per unit of time.

It is accepted that there is a direct relationship between the dose and the resulting concentration of a drug at its receptor. Under normal circumstances the number of available receptors remains constant. The formation of a drug-receptor complex is dependent only on the concentration of the drug. This relationship can be divided into two parts: the dose-concentration relationship (pharmacokinetics) and the concentration-effect relationship (pharmacodynamics). Because receptor availability remains constant, the pharmacodynamic relationship can be considered a fixed variable. However, the pharmacokinetic relationship can be easily ma-
Pharmaceutical properties in pharmacokinetics are a function of molecular structure. Fentanyl and its derivatives are tertiary amines. Alfentanil is the only derivative of this series for which the un-ionized form predominates at the physiologic pH of 7.4. It is the un-ionized portion of the drug molecule that readily diffuses across the lipid portion of cell membranes which constitutes the blood-brain barrier, gastrointestinal epithelium and hepatocytes.

The partition coefficient between lipid and aqueous phases is another crucial physicochemical property. The volume of distribution (Vd), duration of effects and potency will be affected by a drug's partition coefficient. At 37°C, pH 7.4, the n-octanol: water partition coefficient is 2.11 for alfentanil, 2.98 for fentanyl and 3.4 for sufentanil. The lower partition coefficient for alfentanil means that the un-ionized form of the drug cannot diffuse across lipid cellular membranes as easily as its analogues. Because it has a low partition coefficient, limiting its diffusion through cell membranes, alfentanil is less likely to form a drug reservoir. As the diffusion of the un-ionized portion of a drug is decreased, its Vd is decreased, the duration of effects is decreased and the drug becomes more predictable. The very high partition coefficient for sufentanil, followed by those of fentanyl and alfentanil, provides the physiochemical basis for the significant differences in anesthetic potency. In addition, alfentanil's low lipid solubility coupled with its predominantly un-ionized form at a pH of 7.4, impart unique distribution and receptor binding characteristics to alfentanil.

All drugs of this group show a marked binding dependence on the concentration of plasma proteins. At 37°C, pH 7.4 the percent concentration of plasma protein binding for fentanyl is 43.4%, for sufentanil it is 69.9%, and alfentanil is 85.3% bound. This is an additional characteristic of alfentanil that limits the entry of alfentanil into the central nervous system, decreasing its potency and decreasing the Vd.

Pharmacokinetic terminology

These physiochemical properties will affect pharmacokinetic data. The compartment model, with its descriptive symbols, has become a popular tool in analytical pharmacological research. The simplest form, the one compartment model, assumes that a drug is injected into, distributed throughout and eliminated from a single compartment. This conceptual tool, or approach, provides a mathematical modeling to describe the distribution and elimination phases of a drug.

The choice of a one, two or three compartment model is determined by a drug's distribution phases. For drugs administered intravenously, several factors determine whether there will be one, two or three phases. These factors include the physiochemical properties of the drug, distribution organ size and perfusion. Distribution organ size will increase as the following occurs: (1) partition coefficient values increase, (2) binding to plasma protein decreases and (3) perfusion increases. The distribution phases are mathematically described by kinetic equations from the time of injection. After injection, fentanyl and its analogues undergo an initial rapid distribution phase, designated the pi (π) phase. The pi phase is followed by a second slower alpha (α) distribution phase. The third phase is designated the beta (β) terminal elimination phase. These phases of distribution are best described by a three compartment model.

These compartments are referred to as central and peripheral. The compartments do not necessarily correspond to specific anatomic entities. However, for most intravenous agents the central compartment consists of the highly perfused tissues, while the peripheral compartments are composed of the less perfused tissues. Drugs enter the system through the central compartment and are eliminated exclusively from this compartment. Reversible transfer occurs between central and peripheral spaces, so that the peripheral compartments act as a reservoir connected to the central compartment.

First-order pharmacokinetic data describes the movement of a drug between these compartments.

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In the compartmental model, $K_{12}$, $K_{21}$, $K_{13}$ and $K_{31}$ are first-order rate constants associated with drug transfer between the compartments. The elimination rate constant ($K_{10}$), describes drug elimination or biotransformation from the body\(^{10,11}\) (Figure 1). The diffusion gradient, or distribution is from the central compartment ($C_1$) to the peripheral compartments ($C_2$, $C_3$). This diffusion occurs at a rate ($K_{12}$, $K_{13}$ values) that is determined by the drug's partition coefficient and blood flow to the tissues.\(^1\) Over a period of time an equilibrium will be reached between the central and peripheral compartments. As this occurs the return of drug from the peripheral compartments ($K_{21}$, $K_{31}$ values) tends to maintain the plasma levels within the central compartment.\(^1\)

A rate limiting step to the overall elimination process ($K_{10}$, $t_{1/2B}$ values) is the formation of a drug reservoir. If a drug undergoes extensive tissue uptake a reservoir is formed. The extent of tissue uptake can be estimated by noting the following values: (1) a low percent protein bound value, (2) a high partition coefficient, (3) a high $K_{13}$ value and (4) a low $K_{31}$ value.\(^{3,8}\) Any drug reservoir will limit the rate at which elimination ($K_{10}$, $t_{1/2B}$) will take place from the central compartment. This occurs because a drug is slow to return from the peripheral compartments ($C_2$, $C_3$).\(^8\)

The practical significance of the peripheral compartments and their values ($K_{12}$, $K_{21}$, $K_{13}$, $K_{31}$) is the following: (1) large $K_{12}$, $K_{13}$ values with large $V_{d_{2-3}}$ values represent extensive uptake of a drug into the peripheral compartments; (2) as equilibrium is reached, re-entry of a drug ($K_{21}$, $K_{31}$ values) into the central compartment can maintain plasma drug levels; (3) if the rate of drug return from the peripheral compartments is slow (small $K_{21}$, $K_{31}$ values), the rate of elimination will be prolonged.\(^3\) In addition, any residual drug present in the peripheral compartments at the time of repeat dosing

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**Figure 1**

Three compartment model

![Diagram](image-url)

Vdc: Volume of distribution central compartment.

$V_{d_2}$: Volume of distribution peripheral compartments two and three.

$K_{10}$: Elimination rate constant from central compartment.

$t_{1/2B}$: Terminal elimination half time is the time in which 50% of the available drug is eliminated from the central compartment.

$K_{12}$: Rate constants representing drug transfer from central to peripheral compartments.

$K_{21}$: Rate constants representing drug transfer from peripheral to central compartment.

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will decrease the time it takes for distribution to occur. This can cause an extended elimination time and increase the incidence of cumulative drug effects.

There are three additional, interrelated conceptual terms of importance to this review of pharmacokinetic data. First, there is the Vd, expressed in units of L/kg. This is the volume of plasma and tissues which will contain all the drug present in the body. At equilibrium this value is expressed as volume of distribution at steady state (Vdss). The second parameter is the clearance of the drug (cl). Clearance is that portion of distribution volume from which drug is completely eliminated in units of time by metabolism and excretion. The third term is the half-time (t½). A first order kinetic process is usually described in terms of its half-time, rather than in terms of its elimination rate constant (K10). Half-time is the time in which 50% of the available drug is eliminated.

Review of data

The descriptive pharmacokinetic data of fentanyl, sufentanil and alfentanil is found in Table I. This data was obtained from studies performed on adult surgical patients, ASA classification I or II. It is helpful to review this data and the implied anesthetic implications.

Fentanyl, sufentanil and alfentanil are eliminated from the body almost exclusively by hepatic microsomal enzyme activity. The t½ of a drug is directly proportional to the Vd, and inversely proportional to the cl. Fentanyl has the longest t½ of 219 minutes, while sufentanil has an intermediate t½ of 164 minutes and alfentanil has a very short t½ of 94 minutes. Fentanyl's long t½ is attributed to its relatively large Vdss. The Vdss of fentanyl is 4 L/kg, while the Vdss of sufentanil is 1.74 L/kg, and the Vdss of alfentanil is .071 L/kg.

Alfentanil's relatively small Vd can be attributed to its high affinity for plasma proteins and low partition coefficient, or affinity for tissues. Sufentanil and fentanyl are more extensively bound to tissues because of their higher partition coefficients. In fact, the rate limiting factor in their elimination phase is the slow return to the central compartments, which is represented by their K21 and K31 values. Thus, the significant decrease in alfentanil's Vd relative to the decrease in its cl results in its shorter t½.

<table>
<thead>
<tr>
<th>Table I</th>
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<td>Pharmacokinetic data</td>
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<table>
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<tr>
<th>Parameter in Mean units</th>
<th>Fentanyl 6.4 μg/kg</th>
<th>Sufentanil 5 μg/kg</th>
<th>Alfentanil 125 μg/kg</th>
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<tbody>
<tr>
<td>Vdc (L/kg)</td>
<td>0.356</td>
<td>0.10</td>
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<tr>
<td>Vdss (L/kg)</td>
<td>3.99</td>
<td>1.74</td>
<td>0.708</td>
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<td>cl (ml/min/kg)</td>
<td>12.6</td>
<td>11.8</td>
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<tr>
<td>K12 (min⁻¹)</td>
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<td>K21 (min⁻¹)</td>
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<td>K13 (min⁻¹)</td>
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<td>K31 (min⁻¹)</td>
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<tr>
<td>K10 (min⁻¹)</td>
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<tr>
<td>t½ (min)</td>
<td>219</td>
<td>164</td>
<td>94</td>
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Because of alfentanil’s pharmacokinetic profile, its continuous infusion has been suggested as an alternative to the standard bolus technique. Studies have been conducted utilizing a variety of continuous infusion dose regimens.\(^{16-17}\) Bovill et al.\(^7\) followed a single dose of alfentanil and noted that the concentration of alfentanil drops quickly. The decline is due to the rapid alpha distribution phase.\(^{18}\) When a continuous infusion technique is used, the protocol implies a gradual filling of a drug reservoir. The longer the infusion, the more the drug will follow the kinetics, not of the rapid alpha phase with its short half-life, but of the terminal elimination phase with its longer half-life of approximately 94 minutes.\(^{18}\) This difference is due to the fact that, as a larger amount of drug is given over a period of time, it begins to fill the peripheral compartments. As this occurs, the rate of elimination from the central compartment can become prolonged. The caveat is that careful administration will be necessary if speed of recovery is to be optimized.\(^{18}\)

Age-related differences in the metabolism and volume of distribution provide additional pharmacokinetic variations. Bentley et al.\(^{19}\) demonstrated a longer t\(_{1/2}B\) for a 10 \(\mu\)g/kg intravenous bolus dose of fentanyl. The t\(_{1/2}B\) was significantly longer, 945 minutes versus 265 minutes, in patients greater than 60 years of age. The prolonged duration of effect was attributed to a decrease in hepatic microsomal enzyme activity and in hepatic blood flow.\(^{19}\) Davis et al.\(^{20}\) demonstrated a shorter t\(_{1/2}B\) for sufentanil 15 \(\mu\)g/kg, 44 minutes versus 164 minutes, in patients less than 17 months of age. Meistelman et al.\(^{21}\) measured the t\(_{1/2}B\) in children after a 20 \(\mu\)g/kg bolus dose of alfentanil. The t\(_{1/2}B\) for alfentanil was significantly shorter in children, 40 minutes versus 97 minutes, according to their data. This variation can be explained by alfentanil’s unique distribution profile. At steady state the Vd was 2.8 times larger in adults than in children with alfentanil.\(^{21}\) These age-related variations can be attributed to changes in blood flow, hepatic microsomal activity and Vd.\(^{18,21}\)

**Summary**

In conclusion, the difference between the duration of effects and potency of the opioid intravenous agents has been noted to be a function of their physiochemical properties. It is important for the reader to be aware that these studies were performed on relatively healthy subjects with a low body fat ratio.\(^5,7\) Descriptive pharmacokinetic data is subject to change, based on a variety of clinical circumstances. Predictive population pharmacokinetic studies are being generated in current literature. Predictive data will provide a more realistic estimate of the intersubject variability and the variations due to defects in internal and external validity. An appreciation for the original descriptive pharmacokinetic data provides a basis, not only for the rational utilization of intravenous anesthetic agents, but for the evaluation of predictive data that is yet to come.

**REFERENCES**


**AUTHOR**

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