# Miller- Opioids

## Opioids

*Pharmacokinetic Features of Individual Drugs*

*Morphine*

Morphine pharmacokinetics is notably different from that of the fentanyl congeners. This difference is in large part due to morphine's comparatively low lipid solubility. Both biexponential and triexponential equations have been used to describe the pharmacokinetics of morphine. After IV injection, morphine is rapidly distributed. 361, 645, 646, 647, 648, 649, 650 In contrast to the fentanyl series, there is relatively little transient first-pass uptake of morphine by the lung. 644, 651

Morphine's physicochemical properties have important clinical implications. The pKa of morphine (8.0) is greater than physiologic pH, and thus after IV injection only a small percentage (10–20%) is un-ionized. This property, combined with its low lipid solubility, limits the ability of morphine to penetrate tissues. Thus, penetration of morphine into and out of the brain is presumably slower compared with that of other opioids. Morphine's slow brain penetration means that analgesia and respiratory effects are not reflected by plasma levels. Approximately 20 to 40 percent of morphine is bound to plasma proteins, mostly albumin. 649

Morphine is principally metabolized by conjugation and has a hepatic extraction ratio that is equal to or greater than hepatic blood flow indicating a high clearance (15–30 mL•kg– 1 •min– 1 ). 652 The kidney appears to play a key role in the extrahepatic metabolism of morphine and may account for nearly 40 percent of its clearance, 653 although there is some controversy about the importance of renal morphine metabolism. 654, 655

M3G is the major metabolite of morphine, but it does not bind to opioid receptors and possesses little or no analgesic activity. 656, 657 However, M6G accounts for nearly 10 percent of morphine's metabolism and is a more potent ?- receptor agonist than morphine with a similar duration of action. It is now clear the M6G contributes substantially to morphine's analgesic effects even in patients with normal renal function. 658 Interestingly, M6G appears to have a more favorable side effect profile than morphine. 659 *N*-demethylation metabolites of morphine also represent a small percent of its metabolism.

Because of morphine's high hepatic extraction ratio, the bioavailability of orally administered morphine is significantly lower (20–30%) than after IM or subcutaneous injection. 650 As demonstrated in Figure 10–22, in contrast to IV administration, the hepatic first-pass effect on an orally administered dose of morphine results in substantial levels of M6G. It appears that M6G is in fact the primary active compound when morphine is administered orally. 660
FIGURE 10–22 Mean plasma concentrations of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after intravenous and oral administration. Note the high concentrations of morphine-6-glucuronide after oral administration. (From Osborne et al660 )

*Meperidine*

The plasma concentration versus time decay curve of meperidine is best characterized by a two-compartment model. 661, 662, 663, 664, 665, 666 Unlike morphine, after IV injection, first-pass uptake of meperidine by the lungs is approximately 65 percent. 644 The volume of distribution of meperidine is similar to that of morphine (4±1 L•kg– 1 ), 661, 662, 663, 664, 665 as is its clearance (8–18 mL •kg– 1 •min– 1 ). 661, 662

Meperidine's physicochemical properties are similar to those of the fentanyl congeners. Meperidine is more highly bound to plasma proteins than morphine, principally (70%) to ?1 -acid glycoprotein. In contrast to morphine, meperidine binds only to a minor extent to plasma albumin. Meperidine is even less un-ionized (<10%) than morphine at physiologic pH, but it is significantly more lipid soluble.

As with morphine, a relatively high hepatic extraction ratio results in biotransformation that is dependent on hepatic blood flow. The principal metabolic pathways of meperidine are *N*-demethylation and diesterification,

which produces normeperidine, meperidinic acid, and normeperidinic acid as the major metabolites. Little meperidine (<5%) is excreted unchanged in the urine. Normeperidine has analgesic activity and is roughly twice as potent as the parent compound in producing seizures in animals. 667 The greater epileptogenic properties of meperidine cause its therapeutic index to be less than one-tenth that of morphine (5 versus 70).

Normeperidine is dependent on renal clearance mechanisms for elimination. The elimination half-life of normeperidine is considerably greater than that of meperidine, and thus repeated doses can easily produce accumulation of this toxic metabolite in patients with renal disease, potentially producing seizures (see later). 668

*Fentanyl*

A three-compartment model is typically used to describe plasma fentanyl concentration decay. 339, 366, 669, 670 The lungs exert a significant first-pass effect and transiently take up approximately 75 percent of an injected dose of fentanyl. 644, 671 As is typical of the fentanyl congeners, at steady state fentanyl's volume of distribution (3–6 L•kg– 1 ) and clearance (10–20 mL•kg– 1 •min– 1 ) are both high.

Approximately 80 percent of fentanyl is bound to plasma proteins, and significant amounts (40%) are taken up by red blood cells. 672 Because the pKa of fentanyl is high (8.4) at physiologic pH, it exists mostly in the ionized form (>90%). Fentanyl's lipid solubility is also high (see Table 10–12), a finding that explains in part its large volume of distribution. Björkman et al 673 found the tissue/blood partition coefficients of fentanyl to be 2- to 30-fold higher than those of alfentanil. Because fentanyl is distributed so widely in the body, it must ultimately be returned to the blood to be metabolized in the liver. Fentanyl is relatively long acting, in large part because of this widespread distribution in body tissues.

TABLE 10–12. Physicochemical and Pharmacokinetic Data of Commonly Used Opioid Agonists

Fentanyl is primarily metabolized in the liver by *N*-dealkylation and hydroxylation. 674 Fentanyl has a high hepatic clearance (approaching hepatic blood flow) and a high hepatic extraction ratio (approaching 1.0). 370 Metabolites begin to appear in the plasma as early as 1.5 minutes after injection. 675 Norfentanyl, the primary metabolite, is detectable in the urine for up to 48 hours after IV fentanyl in humans. 676 The activity of fentanyl's metabolites is unclear, but it is thought to be minimal. Little fentanyl is excreted in the urine unchanged. 366

*Alfentanil*

Perhaps more than any other opioid, the pharmacokinetics of alfentanil has been extensively evaluated 370, 677, 678, 679, 680, 681 and discussed. 17, 682, 683, 684 Following IV injection, alfentanil plasma concentrations are described by either two-compartment 370, 677, 678, 681 or three-compartment models. 679, 680 Alfentanil's clearance (4–9 mL•min– 1 •kg– 1 ) is less than that of fentanyl. A small volume of distribution at steady state (0.4–1.0 L•kg– 1 ) limits drug distribution and tissue drug accumulation and is largely responsible for the short elimination half-life of alfentanil in spite of a lower clearance than fentanyl.

Alfentanil's physicochemical properties make it unique compared with the other fentanyl congeners. Alfentanil is lipid soluble but significantly less so than fentanyl. 682, 685 Alfentanil is also bound to plasma proteins (mostly glycoproteins) in higher proportions (90%) than fentanyl. 370, 678, 680 Alfentanil's most unique physicochemical feature is that at physiologic pH, it is mostly (90%) un-ionized because of its relatively low pKa (6.5). 686 Thus, despite more intense protein binding, the diffusible fraction of alfentanil is higher than fentanyl. This explains, in part, its short latency to peak effect after IV injection. Although not proven, it may be that alfentanil's lower lipid solubility compared with fentanyl makes for less uptake of alfentanil by lipid-rich brain tissue. This may also contribute to alfentanil's rapid onset and offset of effect. 141, 682, 687

The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative *N*-dealkylation and *O*-demethylation, aromatic hydroxylation, and ether glucuronide formation. 688 Reported hepatic extraction ratios vary from 0.3 to 0.5. 370, 680, 689 Oxidative- *N*-dealkylation of alfentanil produces its major metabolite, noralfentanil. Other metabolites include desmethylalfentanil, desmethylnoralfentanil, and a number of other products. 690, 691 The degradation products of alfentanil have little, if any, opioid

activity. Little alfentanil (<1%) appears in the urine unchanged due to its protein binding, renal tubular reabsorption and hepatic metabolism.

Patients deficient in the cytochrome P-450 form involved in debrisoquin metabolism do not have an altered disposition of alfentanil. 690, 691 This is consistent with the finding that human alfentanil metabolism may be predominantly, if not exclusively, by cytochrome P-450 3A3/4. 692 Cytochrome P-450 3A3/4 is one of a family of cytochrome P-450 isoenzymes that have distinct but overlapping substrate specificities. 693 This enzyme is known to display at least an 8-fold difference in activity in humans. This may be why patients are occasionally found to have a very low alfentanil clearance and unexpected prolonged effects.

*Sufentanil*

Until recently, the pharmacokinetics of sufentanil had been inadequately characterized because of poor assay sensitivity. For example, in carefully designed and conducted studies, Bovill et al 694 and Hudson et al 695 reported sufentanil pharmacokinetic parameter sets that had a similar central clearance but a 5-fold difference in steady-state distribution volumes. This difference likely reflected that it is difficult to estimate accurately the distribution and elimination properties of a drug unless it can be detected at the low levels present during the later stages of the concentration decay.

Sufentanil's potency is so great that it continues to exert its effects when the concentrations in the plasma are at very low levels. In order to estimate pharmacokinetic parameters that are meaningful, it was necessary to develop an assay that could measure sufentanil at the low levels observed during the elimination phase. A radioimmunoassay was developed that made adequate characterization of sufentanil's pharmacokinetics possible. 696

As was suggested by the earlier work of Bovill and Hudson and their colleagues, the pharmacokinetics of sufentanil is adequately described by a three-compartment model. 697 After IV injection, first-pass pulmonary extraction, retention, and release are similar to those of fentanyl. 651 Representative pharmacokinetic parameters include an apparent steady-state distribution volume of 262 L and a central clearance of 0.92 L•min– 1 in a typical adult. 697

The pKa of sufentanil at physiologic pH is the same as that of morphine (8.0), and, therefore, only a small amount (20%) exists in the un-ionized form. Sufentanil is twice as lipid soluble as fentanyl and is highly bound (93%) to plasma proteins including ?1 -acid glycoprotein. This combination of physicochemical properties means that sufentanil has a diffusible fraction that is very similar to that of fentanyl.

Sufentanil's hepatic extraction ratio is very high (0.8), and thus changes in liver blood flow can significantly alter its elimination. The major metabolic pathways of sufentanil include *N*-dealkylation, oxidative *N*-dealthylation, oxidative *O*-demethylation, and aromatic hydroxylation. 698 Major metabolites include *N*-phenylpropanamide. Extensive renal tubular reabsorption leads to little unchanged sufentanil in the urine.

*Remifentanil*

Remifentanil is a synthetic opioid that has been approved for clinical use in the United States and Europe. 699 Although chemically related to the fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases, resulting in rapid metabolism. Remifentanil thus constitutes the first "ultrashort"-acting opioid for use as a supplement to general anesthesia.

Remifentanil's pharmacokinetics is best described by a three-compartment model. It appears that the lungs do not represent a site of significant remifentanil metabolism or sequestration. 700 Its clearance is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic metabolism. Several high-resolution studies in both volunteers and patients have confirmed its very short-acting pharmacokinetic profile. 701, 702, 703 Figure 10–23 contrasts the fall in blood concentrations when remifentanil and alfentanil are given in a crossover fashion to a group of adult male volunteers in doses sufficient to produce profound slowing of the EEG during a 10-minute infusion. 703 Remifentanil concentrations fall very rapidly after termination of an infusion.

FIGURE 10–23 The raw concentration versus time data when a group of ten volunteers received (in a cross-over trial) remifentanil and alfentanil in doses sufficient to produce profound slowing of the electroencephalogram. (From Egan et al703 )

Remifentanil's physicochemical properties are characteristic of drugs in the fentanyl family. 704 It is a weak base with a pKa of 7.07. It is highly lipid soluble with an octanol/water partition coefficient of 19.9 at pH 7.4. Like the other fentanyl congeners, remifentanil is highly bound (?70%) to plasma proteins (mostly ?1 -acid glycoprotein). The remifentanil free base is formulated with glycine. Because glycine has been shown to act as an inhibitory neurotransmitter that causes a reversible motor weakness when injected intrathecally in rodents, remifentanil is not approved for spinal or epidural use. 705 In addition, because remifentanil is unstable in solution for long periods of time, the lyophilized powder must be reconstituted within 24 hours prior to use.

After IV injection, remifentanil undergoes widespread extrahepatic hydrolysis by nonspecific blood and tissue esterases. As depicted in Figure 10–24, the primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite, GI-90291. 699 GI-90291 is dependent on renal clearance mechanisms. *N*-dealkylation of remifentanil to GI-94219 is a minor metabolic pathway. Almost 90 percent of the drug is recovered in the urine in the form of the acid metabolite. Although specific human data are not available, evidence from dogs suggests that the remifentanil metabolites are, for practical purposes, completely inactive, even in the face of renal failure. 706 A unique feature of remifentanil metabolism is that its pharmacokinetics is not appreciably influenced by renal or hepatic failure. 707, 708
FIGURE 10–24 Remifentanil's metabolic pathway. De-esterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GI-90291) is the primary metabolic pathway. *N*-dealkylation of remifentanil to GI-94219 is a minor metabolic pathway. (From Egan699 )

Remifentanil metabolism is mediated by nonspecific esterases in blood and tissue. In blood, remifentanil is metabolized primarily by enzymes within the red cell. 709 Remifentanil is not a good substrate for pseudocholinesterase and, therefore, is not influenced by pseudocholinesterase deficiency. 710

## NEW PHARMACOKINETIC-DYNAMIC CONCEPTS IN OPIOID PHARMACOLOGY

### *Irrelevance of the Terminal Half-Life*

Half-life, perhaps the most familiar and widely used concept in pharmacokinetics, is the parameter employed to describe the rate at which drug concentrations decline. However, unlike clearance and volume of distribution, half-life is not a fundamental pharmacokinetic parameter. It is, instead, a derived or calculated parameter. Because the value of half-life is dependent on the primary pharmacokinetic parameters volume of distribution and clearance, half-life is not independently influenced by changes in patient physiology. 643 Alterations in volume of distribution, clearance, or both these parameters that come about as a result of changes in patient physiology affect the value of half-life secondarily.

The clinical relevance of half-life is even more obscure when dealing with opioid multicompartmental models because there are as many half-lives as there are compartments. Although the terminal half-life from multicompartmental models has traditionally been the pharmacokinetic parameter relied on for predictions regarding the duration of opioid effect, it can be grossly misleading. Distribution volumes and clearances can be similarly confusing to apply clinically. This confusion relates to the complex way in which these multiple pharmacokinetic parameters interact.

An opioid whose pharmacokinetics is described by a three-compartment model, for example, has three half-lives, three clearances, and four distribution volumes (the steady-state distribution volume is the sum of the three compartment volumes). Which of these multiple parameters is important? How do they interact? To the dismay of clinicians and pharmacokineticists alike, the interaction of these parameters is not easily predicted. In fact, in most cases, it is virtually impossible to predict without the aid of computers. 643

No single parameter from a multicompartmental model can be relied on to make predictions about the overall opioid pharmacokinetic profile. The terminal elimination half-life is often used clinically as if it constituted the only pharmacokinetic parameter of importance in predicting the duration of opioid effect. 711 In fact, for drugs described by multicompartmental models, there are numerous half-lives that must be considered, along with a host of other parameters. Each half-life, or other parameter, contributes variably to

the prediction of drug concentration at a given time after drug administration. 712 For most opioids, the terminal elimination half-life has very minimal impact on the overall decline in drug concentration within the range of clinical significance because most of the concentration decrease is accounted for by other components of the model. The popularity of the terminal elimination half-life as an indicator of duration of drug effect, given its lack of usefulness, is a clinical tradition that requires reexamination. 701

The primary shortcoming of half-lives in opioid pharmacology is that they fail to account for the important influence of distribution processes on drug disposition. 713 Distribution processes refer to the net transfer of drug between the central compartment and the peripheral compartments. Depending on the size of the peripheral compartment and the rate at which drug transfer occurs, distribution into or out of the peripheral compartments can have a major impact on the concentration versus time profile.

Figure 10–25 is a hydraulic representation of a pharmacokinetic model for a drug such as sufentanil that illustrates how distribution processes influence the concentration versus time profile. For sufentanil, the volume of one of the peripheral compartments is large, and the rate of transfer into it from the central compartment is slow. Thus, the concentrations in the two compartments come to equilibrium very slowly. If equilibrium has not been reached when a sufentanil infusion is terminated, both elimination from the central compartment and distribution into the slowly equilibrating peripheral compartment can combine to lower central drug concentration. Conversely, if the two compartments have come to equilibrium, the peripheral compartment serves as a reservoir of sufentanil that reenters the central compartment after termination of an infusion, thus impeding the decrease in sufentanil concentration produced by elimination from the central compartment.

*Context-Sensitive Half-Time*

Computer simulation techniques predict the time necessary to achieve a 50 percent decrease in drug concentration after termination of a variable length continuous infusion to a steady-state drug level (Fig. 10–26). Using concepts developed by Shafer and Varvel, these simulations are an attempt to provide “context-sensitive half-times” as proposed by Hughes et al. 713 In this case, the “context” is the duration of a continuous infusion. The context-sensitive half-time has also been referred to as the 50 percent decrement time. 714 Such simulations are intended to provide more clinically relevant meaning to pharmacokinetic parameters.
FIGURE 10–26 A graphic representation of the context-sensitive half-times for the fentanyl congeners. It simulates the time required for a 50 percent decrease in plasma concentration after termination of a continuous infusion. (From Egan et al701 )

For example, and perhaps contrary to contemporary established notions, alfentanil does not exhibit a more rapid 50 percent decrease in plasma concentration compared with sufentanil after termination of a continuous infusion until after approximately 8 hours of infusion, despite its short terminal elimination half-life. Thus, sufentanil appears to have more favorable pharmacokinetics for infusions lasting less than 8 hours when the goal is to achieve a rapid 50 percent decrease in concentration. As noted previously, in terms of pharmacokinetic theory, this surprising difference between alfentanil and sufentanil can be explained by the fact that sufentanil‘s pharmacokinetic model has a large, slowly equil-ibrating peripheral compartment that continues to fill after termination of an infusion, thus contributing to the faster decrease in sufentanil‘s central compartment concentration.

Remifentanil has a context-sensitive half-time that is markedly shorter than those of the other fentanyl congeners. 701 Remifentanil‘s context-sensitive half-time is also independent of infusion duration. Hence, despite very long infusions, remifentanil concentrations decrease by 50 percent within 3 to 5 minutes of stopping drug administration. Clinically, when rapid offset of opioid effect is important, or when the need for opioid effect is highly variable, remifentanil‘s unique pharmacokinetic profile can be exploited.

Interestingly, for cases of very brief duration, the context-sensitive half-times for sufentanil, alfentanil, and fentanyl are nearly identical. Thus, for brief cases, when the opioid is administered by infusion, there would not be any substantial differences among the three drugs in the time to a 50 percent drop in concentration after stopping a continuous infusion. It should be noted that the shapes and relationships of these curves vary depending on the percentage decrease in concentration required. For some anesthetic techniques, a 50 percent decrease in concentration is not sufficient to permit spontaneous ventilation at the end of the

operation (e.g., “high dose” opioid anesthesia for cardiac surgery). In such cases, the 80 percent decrement time (or some other percentage) may be more clinically useful. 714

*Biophase and Latency to Peak Effect*

Equilibration delay between peak drug concentration in the blood or plasma and peak drug effect must also be considered in understanding the implications of opioid pharmacokinetic simulations. For many opioids, there is a significant time lag between peak concentration in the plasma and peak drug effect. This time lag, or hysteresis, is a function of drug movement into and action within the effect site, or biophase. 715, 716 The hysteresis is a summation of all the events that can conceivably affect the onset of pharmacologic effect such as drug diffusion to the effect site and receptor binding. Because effect site concentrations lag behind plasma or blood concentrations, pharmacologic effect also lags behind plasma or blood concentrations.

In short, opioids do not act in the plasma or blood. Thus, this lag time must be considered when using plasma or blood simulations of drug concentration in forecasting drug effect. The time lag is particularly important when giving opioids by bolus administration such as during patientcontrolled analgesia (PCA) therapy, whereas for long infusions, the time lag assumes less importance because the biophase and plasma are generally much closer to equilibrium.

For many of the opioids in widespread clinical use, the equilibration delay between peak concentration in the plasma and peak effect has been characterized. Flow of drug to the effect compartment is a first-order process and can be elucidated by estimating keo, a first-order rate constant for elimination of drug from the effect compartment. When the keo parameter is available for an opioid, theoretic effect compartment concentrations can be simulated along with plasma or blood concentrations, thus making the implications of the time lag easily appreciated.

Figure 10–27 is a simulation of fentanyl administration, showing both the plasma and effect site concentrations based on parameters from the literature. Recognizing that drug effect best correlates with effect site concentration, the simulation is quite revealing, illustrating that the time course of drug concentration in the effect site is much smoother than in the plasma. In general, the fentanyl congeners (especially alfentanil and remifentanil) have a short keo half-life (t1/2 keo ), whereas morphine‘s blood-brain equilibration time is much longer. 717 Hence, when administered in “equipotent” doses, the fentanyl congeners reach peak effect considerably faster than morphine.
FIGURE 10–27 A simulation of plasma and effect site concentrations after intravenous fentanyl administration during typical anesthesia. Plasma concentrations are indicated by the solid line and are designated Cp. The effect site concentrations are represented by the dotted line and are labeled Ce. The effect site concentrations lag behind the plasma concentrations. (Reprinted with permission from Egan,643 St. Louis, Mosby)

Figure 10–28 contrasts the implications of plasma effect site equilibration delay on the achievement of peak concentrations in the effect site for the fentanyl congeners. Note that alfentanil and remifentanil reach peak concentrations very shortly after bolus administration, whereas fentanyl and sufentanil are slower to reach peak concentration in the effect site. 718 When equipotent doses are given, this simulation is a general guide to the speed of onset of the fentanyl congeners. Alfentanil and remifentanil can be regarded as very rapid-onset opioids (i.e., short latency to peak effect). Interestingly, after single bolus administration, alfentanil and remifentanil also exhibit a rapid speed of offset because effect site concentrations begin to fall immediately after the rapid peak. 18 Note that gross overdosage of any of these drugs renders these simulations irrelevant because opioid receptor saturation may occur before peak effect site levels are reached.
FIGURE 10–28 A computer simulation of the time required to reach peak effect site concentration after bolus administration of fentanyl, alfentanil, sufentanil, and remifentanil using pharmacokinetic parameters from the literature. This is a graphic illustration of the plasma-biophase equilibration process for these drugs. Ce is the effect site concentration; a bolus injection was made at time 0. (From Egan718 )

Remifentanyl
-unique because of ester linkage
-metabolized by tissue and blood non specific esterases
-highly lipid sol. / weak base
-unstable in soln. lyophilized powder must be reconstituted within 24 hrs prior to use

-bolus 1 mcg/kg with propofol for induction
-maintenance 0.1-1.0 mcg/kg/min
(0.1mcg/kg/min allows spont. ventil.)

Sufentanil
-induction =-0.25-1 mcg/kg
-bolus as maintenance=0.1-0.25mcg/kg
-cont. infusion =0.25-1.5mcg/kg/hr

Opioid Dosages for TIVA
drug/load dose (mcg/kg)/maintenance/addit. bolus
-Alfenta/25-100//0.5-2mcg/kg/min//5-10mcg/kg
-Sufenta/0.25-2//0.5-1.5mcg/kg/hr//2.5-10mcg
-Fenta/4-20//2-10mcg/kg/hr//25-100mcg
-Remifent/1-2//0.1-1.0mcg/kg/min//0.1-1.0mcg/kg

Range of target plasma concent for TIVA (whole blood for remifent )
(ng/ml) sufenta/remifenta
main agent/5-10//--
major surg/1-3//2-4
minor surg/0.25-1//1-3
spont vent/<0.4//0.3-0.6
analgesia/0.2-0.4//0.2-0.4