

Pharmacokinetics and Pharmacodynamics of Selected Opioids*

Charles E. Inturrisi, PhD[†]

ABSTRACT

Choosing the right opioid for the right patient at the right time can be challenging. Many factors can affect the analgesic response to an opioid. The drug's half-life, bioavailability, and the potential for biotransformation to active metabolites are all important considerations for drug selection. The drug's pharmacodynamic properties—the effects of active metabolites, opioid receptor mediated effects as well effects mediated at other receptors, and incomplete cross-tolerance—also need to be considered. Finally, each patient's response to a particular analgesic also must be factored into pain treatment. This article identifies many of the key pharmacokinetic and pharmacodynamic characteristics of some of the commonly used opioids and discusses their implications for drug selection, dose titration, and individualized pain management.

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Opioid drugs are commonly used for pain management. Knowledge surrounding the sites and mechanisms of opioid action has increased significantly in recent years while pharmacokinetic studies have provided new insights about some of the factors influencing interindividual variation in opioid response.^{1,2} The clinician interview of Ann Berger, RN, MD, presented later in this publication, provides vivid insights into the extent to which an individual patient's response to opioids can be highly variable and illustrates the fact that many patients do not fit simple fixed dosing regimens. Rarely is the pharmacokinetic half-life of a drug measured as part of the examination of a patient with pain, thus we need to rely on average population data, which do not provide an estimate of the often wide range of values that characterize the population. The intensity of pain and the extent of tolerance before opioid therapy are key considerations in choosing an opioid, as are the patient's age and organ function. Emergent research is uncovering genetic polymorphisms that are expressed by both the genes associated with pain responsiveness and those that influence the response of opioid receptors to opioid analgesics.³ Research in these areas should provide a mechanism-based approach to the diagnosis of pain states and improved scientifically based guidelines that will be used in the selection of analgesic drugs. But until that time, it is important to have an understanding of current clinical pharmacologic properties of the opioids, even though much of this information is not based on level 1 evidence. This information, along with

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[†]Professor of Pharmacology, Weill Cornell Medical College, New York, New York.

Address correspondence to: Charles E. Inturrisi, PhD, Professor of Pharmacology, Weill Cornell Medical College, 1300 York Avenue, Room LC-524, New York, NY 10021. E-mail: ceintur@med.cornell.edu.

Table. Plasma Half-Lives for Opioids

Opioids with short plasma half-lives	
	Average half-life, <i>h</i>
Morphine	3
Hydromorphone	2.5
Fentanyl	4
Opioids with longer plasma half-lives	
	Average half-life, <i>h</i>
Methadone	24
Levorphanol	13

adherence to the principle of individualization of dose by titration to effect, are the mainstays of opioid selection.

PHARMACOKINETIC PROPERTIES OF OPIOIDS

Several opioids have relatively short plasma half-lives; morphine, hydromorphone, and fentanyl are a few examples. Two opioids, levorphanol and methadone, have considerably longer plasma half-lives (Table).

As a consequence of this difference and the recognition that approximate steady state will be reached after completion of 4 half-lives, some useful predictions can be made. With regular dosing, short half-life opioids rapidly reach their steady-state plasma levels. For example, a constant dose of morphine results in maximum plasma levels and effects that should occur at approximately 12 hours on this dosing regimen. In contrast, methadone has a relatively long half-life thus corresponding steady-state plasma levels are, on average, achieved over the course of several days. This longer half-life can lead to accumulation of methadone when a dose is administered on a regular schedule that is based on the initial analgesic duration of action of 4 to 6 hours. As discussed in upcoming sections, the consequences of these very different pharmacokinetic profiles are one of the key considerations to the appropriate dosing of these opioids.

MORPHINE

When taken orally, the bioavailability of morphine ranges from 35% to 75%.¹ However, this

interindividual variation in bioavailability can be compensated by titration of dose to an analgesic endpoint. As discussed previously the relative short half-life of morphine tends to limit drug accumulation during this titration period. It should also be emphasized that the plasma profile of the extended-release formulations of morphine discussed in the next section are the result in plasma profiles of longer duration and these formulations are intended for dosing at intervals of 8, 12, or 24 hours as described in the labeling. An important aspect of morphine's pharmacokinetic profile is that it appears to be linear. There is no evidence of autoinduction of biotransformation during chronic dosing.⁴ Therefore, when the dose is doubled, the plasma levels also will double, and the pharmacokinetics will not change with continued use in individuals with normal organ function. This allows for both predictability and flexibility in morphine dosing.

Multiple formulations are available, including immediate- and extended-release oral, parenteral (intravenous [IV] or subcutaneous), spinal (epidural or intrathecal), and rectal. Thus, morphine may be administered through many different routes that can be tailored to the individual patient.

For dosing using the opioids discussed in this paper, see the guidelines published by the American Pain Society.⁵

MORPHINE-6-GLUCURONIDE

Morphine-6-glucuronide (M-6-G) is an active metabolite of morphine that appears to contribute to the analgesic activity of morphine.⁶ Because morphine is converted to a glucuronide and is excreted primarily by the kidney, M-6-G will accumulate relative to morphine in patients with renal insufficiency.⁷ The degree to which this accumulation of M-6-G contributes to the incidence and severity of adverse effects experienced by these patients has not been conclusively demonstrated.^{7,8} However, in some studies prolonged respiratory depression has been associated with persistent M-6-G levels.⁸ In a survey that measured steady-state morphine and M-6-G levels and adverse effects in 109 patients with cancer, the presence of myoclonus or cognitive impairment was not associated with M-6-G

accumulation.⁷ For a subset of the 20 patients with the highest M-6-G levels (>2000 ng/mL), the M-6-G level and concurrent organ failure was associated with the most severe toxicity (respiratory depression and/or obtundation).⁷ It is appropriate to consider an alternate opioid for a patient receiving morphine who experiences a decrease in renal function and a concomitant increase in undesirable effects. Morphine-3-glucuronide (M-3-G), the predominate metabolite of morphine in humans, is devoid of opioid activity but has excitatory effects in animals after direct injection into the central nervous system (CNS). This has led to the suggestion that M-3-G may be responsible for the neuroexcitatory effects sometimes seen with high chronic morphine dosing.⁹ Although M-3-G and M-6-G accumulate in patients with renal failure, these patients exhibit CNS depression characteristic of morphine and M-6-G rather than the excitatory antioioid effects expected of M-3-G.⁸

HYDROMORPHONE

Hydromorphone is a short half-life opioid and, therefore, is a useful alternative to morphine by the oral and parenteral routes. It is more soluble than morphine and available in a concentrated dosage form at 10 mg/mL. This preparation is intended for parenteral administration to the opioid-tolerant patient with cachexia where the volume of the opioid solution to be injected must be limited. Similar to morphine, hydromorphone is converted to a 3-glucuronide metabolite. However, the clinical relevance of the metabolite remains to be determined.⁸

FENTANYL

When administered parenterally, fentanyl is a highly lipophilic, short half-life drug that is 80 to 100 times more potent than morphine.¹⁰ It is available in a transdermal patch (TTS) for persistent pain, a transmucosal dosage form used for breakthrough pain in opioid-tolerant patients, and a new patient-controlled transdermal system. The TTS-fentanyl system demonstrates the principle that a delivery system can be designed that alters the rate of drug absorption, resulting in an absorption-limited system significantly altering the pharmacokinetic profile of the drug. Thus, fentanyl, a drug with a short half-life following parenteral adminis-

tration, exhibits the pharmacokinetic properties of an extended-release depot formulation. The transdermal patch results in sustained serum fentanyl levels and a long duration of action with dosing intervals from to 48 to 72 hours.¹¹ The transmucosal dosage form avoids injections and localizes drug absorption to the buccal mucosal, which allows more rapid absorption than after oral administration and avoids the first-pass metabolism seen when drugs are given orally. Fentanyl is biotransformed almost entirely to an inactive metabolite, norfentanyl. This has led to the recommendation that fentanyl may be relatively safe for patients with renal failure and on dialysis.¹² However, as Dean points out,¹² fentanyl is a highly protein-bound, lipid-soluble drug with a large distribution volume and, therefore, not likely to be dialyzable. Whether, the parent drug, fentanyl, accumulates over time in patients on dialysis is unknown.

METHADONE

Methadone's bioavailability is 85%, and its plasma half-life averages 24 hours but may range from 13 to 50 hours, whereas the duration of analgesia is often only 4 to 8 hours. Repetitive analgesic doses of methadone lead to drug accumulation because of the discrepancy between its plasma half-life and the duration of analgesia. Sedation, confusion, and even death can occur when patients are not carefully monitored and dosage is adjusted during the accumulation period, which can last from 5 to 10 days. The considerable interindividual variation in the pharmacokinetics of methadone appears to be partially related to the variability of intestinal transporters (P-glycoprotein) and hepatic enzymes (CYP3A4 and CYP2B6). Human P-glycoprotein, CYP3A4, and CYP2B6 are subject to induction or inhibition by several compounds.¹³ The metabolites of methadone are devoid of pharmacologic activity and are not dependent on renal function for elimination. Pharmacodynamic variability also is seen in the analgesic response to methadone, even when determined at apparent steady-state plasma levels.¹⁴ More recently, case reports have raised concerns about the potential for methadone to prolong the QTc interval (QT corrected for heart rate) and predispose patients to torsade de pointes, a life-threatening arrhythmia.^{15,16} The issue is discussed elsewhere in this monograph.

Methadone is still considered a useful alternative to morphine because in some patients it may provide a larger therapeutic window than other opioids. Unfortunately, this potential advantage cannot be determined without an individual trial and/or opioid rotation. The safety considerations related to the dosing of methadone, as discussed previously, necessitate greater sophistication in dose selection and monitoring during dose titration as compared with morphine. Initial doses should be titrated carefully using the as-needed mode of dosing during the titration period thus the dosing interval can be increased if accumulation does occur.¹⁷⁻¹⁹

Opioid rotation to methadone requires pharmacokinetic (elimination half-life) and pharmacodynamic (incomplete cross-tolerance) considerations. Ripamonti et al²⁰ reported a prospective study of 38 consecutive cancer patients who were switched from morphine to oral methadone and titrated to effect so the equianalgesic dose ratio (morphine/methadone) could be estimated. The dose ratio increased as a function of the prior morphine dose, thus no single dose ratio was appropriate for naïve patients or patients who were receiving various doses of morphine at the time they were switched to methadone. The data indicate that those patients who were receiving the highest doses of morphine were relatively more sensitive to the analgesic effects of methadone (ie, they had the highest dose ratio). This unidirectional variability in the dose ratio may reflect incomplete cross-tolerance between morphine and methadone and further emphasizes the need for individualization of dose and careful titration to effect when switching to methadone.¹⁷⁻¹⁹

Some clinical experience suggests that rotating from methadone to other opioids is not bidirectional. Moryl et al reported on 13 consecutive prospective rotations from methadone to a different opioid.²¹ The opioid rotation was followed by escalation of pain and/or severe dysphoria that remained uncontrolled by a rapid increase in the dose of the second opioid.

The dosage form of methadone that is used clinically in most countries, including the United States, is a racemic mixture of

equal amounts of the l-isomer, an opioid, and the d-isomer, which lacks opioid activity.²² However, both the l- and the d-isomers of methadone bind to the N-methyl-D-aspartic acid (NMDA) receptor, and the d-isomer has functional NMDA receptor antagonist activity in animals, including antihyperalgesic activity and the ability to prevent the development of morphine tolerance.^{1,22} Due caution should be exercised in attempting to extrapolate these preclinical observations until controlled clinical studies are available that determine whether the d-isomer of methadone alone or in combination with an opioid has any clinical efficacy for pain.

DISCUSSION

Dr Davis: I am surprised that fentanyl is typically referred to as having a short half-life. In fact, fentanyl's half-life is context related. In the intensive care unit (ICU), if you achieve a steady state with continuous infusion, then stop administering fentanyl, the sedative effects are prolonged. This is also true with other lipophilic opioids, such as buprenorphine, but not sufentanil, alfentanil, or remifentanil.

Dr Inturrisi: Several studies have demonstrated that when certain drugs are discontinued, the duration of effect is not always predictable. The observations with fentanyl relate to a postoperative situation where the administration of fentanyl intraoperatively results in a relatively slow emergence from the sedative effects, and this also would apply to its use by continuous infusion in the ICU. This lag has been attributed to the high lipid solubility of fentanyl resulting in a large distribution volume of the drug in brain tissue and slow redistribution out of the CNS as blood fentanyl levels fall over time. The point I was making is that without the absorption-limited kinetics imposed by the TTS-fentanyl system, 48 to 72 hours of sustained plasma fentanyl levels and the corresponding duration of analgesia would not occur.

Dr Bruera: Many studies of the highly liposoluble drugs—the transmucosal studies, studies of the new rapid-onset opioids, and even

some of the transdermal iontophoretic studies—report no relationship between the regular dose and the dose needed to treat breakthrough pain. I do not understand how that conclusion is possible. Perhaps it can be attributed to the variable behavior of the highly liposoluble drugs and their ability to achieve a rapid brain level that is dissociated from the blood level. Can you comment on that?

Dr Inturrisi: The pharmacokinetic studies of the oral transmucosal fentanyl citrate (OTFC) preparations indicate that the analgesic effects are initiated during the rapid distribution phase of drug uptake. A recent analysis of 3 clinical studies of OTFC in patients with cancer and breakthrough pain found, as Dr Bruera indicates, that not only was there no relationship between the effective OTFC dose and the daily scheduled opioid dose but also the effective OTFC dose did not correlate with other clinical variables (eg, gender, pain pathophysiology, or pain intensity). Only age predicted a decrease in effective dose.²³ The authors conclude that breakthrough medication should be individualized by patient response. Until we understand more about the relationships between the scheduled dose and the breakthrough dose as well as other variables, individualization beginning with a safe starting dose is a reasonable approach.

Dr Davis: Incident pain is kinetically resistant to opioids because pain onset is quick and subsides before opioid analgesia takes effect. We found that the dose needed for incident pain is much higher than what is needed for nonincident breakthrough pain. Lipophilic drugs sequestered in buccal fat have a prolonged half-life relative to intranasal administration. Some studies suggest a quicker onset to analgesia with intranasal opioids. It may be related to regional differences in absorption that influence opioid kinetics.

Dr Bruera: I think Dr Davis' points support the potential need for using more drug in a given patient. However, I do not understand how the studies support the converse idea that less drug should be used. Why would you report an extremely high variable response rate, then conclude that you should titrate independently as opposed to titrating based on previously established levels of opiate tolerance? The data may be too limited to explain this adequately.

Dr Shaiova: A double-blinded, placebo-controlled study of 18 opioid-tolerant patients with can-

cer with stage III or IV mucositis reported on the use of transmucosal fentanyl for acute pain. At a dose of 200 µg administered for 4 consecutive days, the drug was well tolerated, but its efficacy was limited. Patients had been given approximately 60 mg of morphine for a week before treatment for breakthrough pain. Following treatment with transmucosal fentanyl, analgesia was not significantly reduced from baseline. In the titration phase of the study, fentanyl administered transbuccally or transmucosal was titrated to an average dose of 800 µg, which correlated with the dosing for the long-acting drug previously taken. Patients who were on methadone maintenance treatment programs and took subsequent methadone for their long-acting drug needed 3200 µg of transmucosal or buccal fentanyl. Thus I agree we cannot correlate any type of breakthrough pain medication based on long-term treatment. I think it is clinically incorrect.

Dr Bruera: Manufacturers are producing extremely potent opiates and recommend you dose each patient as if he was opiate naïve. I am concerned about patients suffering needlessly while the correct dose is being established. I think we should refrain from using these drugs until the manufacturers have done their homework and dosing can be established with greater certainty.

Dr Shaiova: And then when you change opiates, dosing becomes even more complex. If someone is on methadone and you need to rescue them with another opiate, and then you return to methadone's incomplete cross-tolerance, how do you dose with any degree of certainty?

Dr Davis: The breakthrough dose gives you the safe dose in the equation, but very few studies have prospectively assessed breakthrough dosing in relationship to the chronic dose. I agree with Dr Bruera that the homework has not been done.

Dr Berger: Regarding the discussion of titration to effect, I would very much caution against prescribing methadone as needed. We frequently prescribe methadone, but some of our patients do not experience side effects and, therefore, would continue to titrate until they may become sedated. I would be extremely uncomfortable about having them self-medicate. There have been multiple reports of prescription drug abuse with prescribed pain medications, with resultant overdosing.

Dr Shaiova: Often, the patients who use methadone inappropriately are those who use illic-

it drugs. Very few patients with cancer overdose on prescribed methadone, and I do not consider them to be a high-risk population.

Dr Berger: We are very cautious. We prescribe methadone on a fixed dosing schedule and prescribe a short-acting drug as needed.

Dr Inturrisi: For physicians who are not highly experienced with prescribing methadone or who do not have the resources for ongoing patient monitoring, use of a regular dosing schedule without supervision can be very dangerous. When we prescribe methadone as needed, the expectation is that the patient will titrate the dose to reduce his pain and the interval may increase over time as the drug accumulates. Clearly, the patient must be monitored to be sure that signs of toxicity associated with accumulation (eg, sedation) are not occurring.

Ms Derby: Patients who are on chronic opioids, either oral methadone or IV patient-controlled analgesia of methadone, require constant contact with their clinicians. The healthcare providers must be meticulously involved and instruct the patient and family during the titration phase. The dose conversion can take several days. But you must differentiate between an opioid-tolerant patient and the opioid-naïve patient because they are entirely different.

Dr Bruera: I think there should be a healthy debate about rescue dosing patients with noncancer pain who will need opiates for the long-term. There are interesting reports from Scandinavian clinics that have eliminated rescue dosing almost entirely and instead only titrate regular dosing. It is an interesting concept that should be studied further.

Dr Davis: There are 2 populations to consider. One is the chronic pain population whom you prescribe doses at every 12 hours and then schedule for follow-up. The other is the cancer population with rapidly escalating pain that requires a different dosing strategy. In chronic noncancer pain, the desired outcome is function, thus we use a longer titration period, establish specific goals, and reduce medication when necessary. In the cancer setting, the desired outcome is comfort.

Dr Bruera: This is a very interesting point because frequently in community medical practice, patients treated with opioids are rarely titrated down. Patients will urinate less frequently,

M-6-G circulation levels will increase, and patients become progressively toxic. The strategy of titrating down is useful not only for patients stabilized on methadone, but also those treated with morphine and other opiates. I would suggest that if your patient is doing very, very well or if he has no pain, consider titrating down.

Dr Perlov: There are many variables, which would require different dosing strategies based on a particular clinical situation. To name a few, such variables are prior opiate exposure, pain severity, availability of close supervision of treatment, home versus a healthcare facility, patient's age, prognosis of the painful condition, and the risk and history of addiction. For example, treating an opioid-naïve patient may require a low initial dose with careful titration. On the other hand, emergency department care for a person with a malignant pain crisis would allow for a rapid dose escalation. Treating a chronic non-malignant condition may warrant a stable around-the-clock dosing with emphasis on function, whereas management of an acute or unstable pain may require generous breakthrough dosing. A useful protocol should be adaptable to various clinical scenarios.

Dr Bruera: My suggestion is that the appropriate patient assessment needs to take place before pain medication is prescribed. The days when the patient's self-rating of pain intensity was interpreted as purely an expression of nociception are fortunately over. The prescriber must understand that patients frequently somatize and turn to chemical coping. By increasing opiate titration, we may hurt the patient. The fundamentals of pain assessment must go beyond the use of a simple 0 to 10 pain scale rating to include precise characterization of the individual patient.

Dr Kalman: Most providers are not going to have the support systems in place to allow for frequent patient phone calls and monitoring. The palliative care community must establish basic guidelines for initiation of a drug that is dangerous yet incredibly helpful. If you provide me with those guidelines, as a cardiologist I feel comfortable prescribing methadone to patients who have been under the care of a palliative care physician and then returned to me for ongoing management.

Dr Davis: In situations where the patient's pain is not relieved before 24 hours and the physician increases the dose before steady state, there is the potential for respiratory arrest in 4 to 6 days from methadone accumulation. The problem is not the drug, it is the naïve prescriber.

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