

CHAPTER 3

OVERVIEW OF CLINICAL PHARMACOLOGY

The opioid analgesics can be divided into agonists, agonist-antagonists, and antagonists on the basis of their interaction with opioid receptors (table 4).

Pure agonists

Pure μ -agonists are generally preferred over agonist-antagonist drugs for management of moderate to severe pain. With no ceiling effect for analgesia and the availability of multiple formulations (table 5), they offer great flexibility to prescribers. Clinical experience with these medications throughout the ages for treatment of acute and chronic pain is extensive.

Clinical pharmacology

Although there is great intraindividual variation in the response to the different pure μ -agonists, the pharmacodynamic profile is similar across them. For analgesia, there is a concentration-response relationship that continues to slope upward until the patient becomes unconscious. Side effects are very common, and the clinical challenge is to identify a dose associated with a favorable balance between analgesia and side effects.

The concept of relative potency has important implications for the clinical use of opioid analgesics. All the opioids differ in potency, which is defined as the dose required to generate a given effect. If the doses of 2 opioids are appropriately adjusted, the same level of effect should be obtainable. In this context, therefore, potency does not mean strength of effect or efficacy. The efficacy of 2 opioids, one more potent than the other, is the same if the doses used are equianalgesic.

Numerous controlled trials have been done in populations with relatively little opioid exposure, to calculate the relative potencies between different opioids and between the same opioids given by different routes of administration. These studies have allowed the construction of an equianalgesic dose table (see table 5). The table describes relative potencies by listing the doses of different drugs and the administration routes that are equianalgesic to a standard, usually 10 mg of morphine given intravenously or intramuscularly. The equianalgesic dose table represents the best science but was developed from studies in selected populations.

Guidelines for switching opioids and routes of administration have been developed and are based on use of the table as a starting point for dose selection (see chapter 5, page 40).

Adverse effects. The most important potential adverse effect from use of the pure agonists is respiratory depression. These

Continued on page 20

Table 4. Classification of opioid analgesics for pain management in the United States

Opioid type	Medications	Notes about therapy
Pure agonists	Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Levorphanol Meperidine Methadone Morphine Oxycodone Oxymorphone Propoxyphene	<ul style="list-style-type: none"> • No clinically relevant ceiling effect to analgesia; as dose is raised, analgesic effects increase until analgesia is achieved or dose-limiting side effects supervene • Most commonly used for moderate to severe pain
Agonist-antagonists	<p>Partial agonists</p> Buprenorphine	<ul style="list-style-type: none"> • μ-Agonist with lower intrinsic efficacy (partial agonists) or agents that produce agonist effects at one receptor and antagonist effects at another (mixed agonist-antagonists) • Ceiling effect for analgesia • Some produce psychotomimetic side effects more readily than do pure agonist opioids • Potential to induce acute abstinence in patients with physical dependency to agonist opioids • In general, less preferred by patients with opioid addiction disorder
	<p>Mixed agonist-antagonists</p> Butorphanol Dezocine Nalbuphine Pentazocine	
Pure antagonists	Alvimopan* Methylnaltrexone* Naloxone Naltrexone	<ul style="list-style-type: none"> • Compete with endogenous and exogenous opioids at μ receptor sites • Administered for prevention or reversal of opioid effects
Other	Tramadol	<ul style="list-style-type: none"> • μ-Agonist distinguished by a mechanism of action that includes effects on monoamines, such as serotonin

* Not yet commercially available; minimal systemic absorption by enteral route.

Table 5. Pure μ -agonists used for pain in the United States

Opioid analgesic	Equianalgesic doses*† (mg)	Half-life (hr)	Peak effect (hr)	Duration (hr)
Morphine	10 IM/IV/SQ 20-30 PO†	2-3 2-3	0.5-1 1-2	3-4 3-6
Controlled-release morphine	20-30 PO†	2-3	NA	8-12
Sustained-release morphine	20-30 PO†	2-3	NA	12-24
Hydromorphone	1.5 IM/IV/SQ 7.5 PO	2-3 2-3	0.5-1 1-2	3-4 3-6
Oxycodone	20-30 PO	2-3	1-2	3-6
Controlled-release oxycodone	20-30 PO	NA	3-4	8-12
Oxymorphone	1 IM/IV/SQ 10 PR 15 PO	NA NA	0.5-1 1.5-3	3-6 4-6
Levorphanol	2 IM/IV/SQ 4 PO	12-15 12-15	0.5-1 1-2	3-6 3-6
Methadone	Variable	12-150	1-2	6-8
Hydrocodone	30 PO	2-4	1-2	3-6
Fentanyl	50-100 μ g IV/SQ	7-12	<10 min	1-2
Fentanyl transdermal system	NA	NA	12-24	48-72 per patch
Oral transmucosal fentanyl citrate	NA	7-12	15-30 min	1-2

FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; NA, not applicable; PO, by mouth; PR, per rectum; SQ, subcutaneous.

* Dose provides analgesia equivalent to 10 mg of morphine given by IM route. These ratios are useful guides when switching drugs or routes of administration. In clinical practice, the potency of the IM route is considered to be identical to IV and SQ routes.

† When switching from one opioid to another, incomplete cross-tolerance requires a reduction in the dose of the new drug by 25% to 50%, to prevent excessive opioid effects. Provision of "rescue" medication during the conversion period (a few days) prevents breakthrough pain

Toxicity	Comments
Constipation, nausea, sedation are most common; respiratory depression is rare when titrated to effect	Standard for comparison of opioids; multiple routes available
Typical opioid effects	Once-a-day morphine recently approved in United States
Typical opioid effects	Potency and high solubility may be beneficial for patients requiring high opioid doses and for SQ administration
Typical opioid effects	Available as single entity or combined with aspirin or acetaminophen
Typical opioid effects	Oral immediate release and extended release formulations are currently under FDA review
Typical opioid effects	With long half-life, accumulation possible after beginning or increasing dose
Typical opioid effects	Highly variable half-life and potential for accumulation require increased vigilance for development of opioid toxicity; can prolong QTc interval
Typical opioid effects	Available only in combination with acetaminophen or aspirin
Typical opioid effects	Can be administered as continuous IV or SQ infusion
Typical opioid effects	Refer to package insert for equianalgesic dosing guidelines for oral and parenteral medication; currently available doses not usually recommended for opioid-naïve patients; not recommended for acute pain
Typical opioid effects	Not recommended for opioid-naïve patients; recommended starting dose for breakthrough pain is 200-400 µg, even with high “baseline” opioid

that might result from relative underdosing. When switching to methadone from another drug, the reduction in the equianalgesic dose should be greater, usually 75% to 90%.

‡ Extensive survey data suggest that the relative potency ratio of IM to PO morphine, which has been shown to be 1:6 in an acute dosing study, is 1:2 to 1:3 with chronic dosing.

opioids produce a concentration-dependent shift in the carbon dioxide response curve. At clinically appropriate doses, compensation for the shift occurs and respiratory rate typically does not decline. Tolerance to the respiratory effects usually develops quickly, and doses can be steadily increased without risk. If some other cardiopulmonary insult occurs, however, the patient's response may be greater than it would have been without the opioid present.

Clinical evidence of this phenomenon is observed when patients receiving long-term therapy experience respiratory compromise associated with a new insult, such as pneumonia, and show improvement after administration of naloxone. The response to the opioid antagonist in this situation does not mean that the opioid was the primary driver for the respiratory problem, but it does show that there is some ongoing effect on respiratory reserve even after opioid therapy has continued for a time.

Other side effects more commonly have clinical impact (see chapter 6, page 53). Nausea and mental clouding or sedation are common, but tolerance to these effects usually develops within days to weeks. Constipation is also very common, and adaptation to this effect occurs much less reliably. Many patients require ongoing laxative therapy during long-term treatment.

Some patients experience fatigue, confusion, or other psychotomimetic effects (such as nightmares or hallucinations), myoclonus, other gastrointestinal effects (such as bloating, symptoms of reflux, or anorexia), dysphoria or other mood effects (such as mood lability), headache, urinary retention, or sexual dysfunction. Itch is relatively common during acute administration and rarely reflects a true allergic response. Many factors may predispose to adverse effects, including advanced age, medical comorbidities, and concurrent administration of other drugs. Successful management of side effects increases the likelihood of a favorable outcome and potentially allows the use of a more efficacious opioid dose over time.

Outcomes generally considered under the rubric of chemical dependency or drug abuse should also be considered potential adverse effects of opioid use. All opioids that have agonist effects interact with deep brain structures that subservise "reinforcement and reward" mechanisms. It has been estimated that at least 5% to 10% of people have variants of this system that predispose to addiction to opioids or other drugs with potentially reinforcing effects (see chapter 9, page 67). Presumably, these individuals represent a group that is more likely to experience euphoric effects when an opioid is first taken. The likelihood of

addiction is thought to increase if this biologic predisposition occurs in tandem with a complex and poorly understood set of psychologic, social, and situational factors.

In most patients, the disease of addiction presents at an early age. A patient who has reached middle age without developing compulsive use behaviors to potentially abusable drugs, including alcohol and nicotine, appears to be at very low risk. This is particularly true if there is also no family history of addiction. Patients who may be at relatively increased risk must be identified so that opioid administration can be structured in a manner that lessens the liability.

Development of true addiction is not the only concern during long-term opioid administration and it indeed appears to be far less common than problems related to misuse and abuse. Drug diversion, a criminal act, also is rarely encountered but must be considered among the risks of therapy. To date, there are very few empirical data to help define the patterns of these behaviors or their clinical meaning. However, acute short-term administration is clearly less likely than long-term administration to be associated with any of these potential outcomes. Healthcare providers, patients, and families require reassurance about these concerns, but at the same time, prescribers must be aware of the need for careful monitoring for nontherapeutic outcomes.

Members of the drug class

Morphine. Morphine is often considered the prototype pure μ -agonist. It is available in multiple formulations and has been extensively used in management of both acute and chronic pain.

Morphine has 2 biologically active metabolites, morphine-6-glucuronide and morphine-3-glucuronide. Morphine-6-glucuronide binds to the opioid receptor and is believed to contribute to the effects of the parent compound. Morphine-3-glucuronide does not bind to the receptor and is believed to contribute in some cases to adverse effects such as myoclonus and confusion. Usually, the metabolites are considered a clinical issue only when their concentrations in the blood are likely to fluctuate differently than the concentration of the parent compound. This can occur during renal insufficiency, in which concentrations of the renally cleared metabolites relative to the parent compound can become very high. Patients with fluctuating renal insufficiency are, on theoretical grounds, the most likely patients to be at risk for unpredictable morphine effects because of a changing ratio between metabolite and parent compound.

Morphine is available in immediate-release and modified-release formulations. The latter formulations have an 8- to

24-hour duration of effect, depending on the specific drug and individual variation.

Hydromorphone. Hydromorphone is significantly more potent than morphine, permitting smaller volumes to be used when injecting equianalgesic doses. Like morphine, it can be administered through oral, parenteral (subcutaneous, intramuscular, and intravenous), rectal, or intraspinal (epidural and intrathecal) routes. Its relatively short half-life of elimination (2 to 3 hours) facilitates dose titration but complicates efforts to use hydromorphone for chronic pain. Modified-release formulations, which will increase the convenience of oral therapy for chronic pain, are in development and are currently being reviewed by the US Food and Drug Administration (FDA).

Because hydromorphone is very soluble in water, high-concentration solutions can be made and are particularly suitable for subcutaneous administration, including continuous subcutaneous infusion. A high-potency preparation (10 mg/mL) is commercially available. Side effects associated with hydromorphone are qualitatively similar to those associated with opioids in general, and most often include constipation, nausea, and sedation. Hydromorphone may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulation.

Oxycodone. Oxycodone is available in both an immediate-release and a modified-release (8- to 12-hour duration) preparation. The immediate-release formulation is available as a single entity and in combination with acetaminophen or aspirin. Lower doses of oxycodone (eg, 2.5 mg, 5 mg, 7.5 mg, 10 mg) in combination with a nonopioid coanalgesic are frequently used for management of acute pain in patients with limited prior opioid exposure. When these drugs are used, care must be taken not to exceed the recommended maximal dose of the coanalgesic (for example, 4 g or less of acetaminophen per day). The modified-release formulation of oxycodone is now widely used for management of chronic pain.

Oxymorphone. Oxymorphone has a short half-life and is both a potent congener of morphine and an active metabolite of oxycodone. It is presently available in suppository and injectable forms. Although an oral form is not yet available, immediate-release and modified-release formulations are in development and are currently under review by the FDA. Oxymorphone may have particular utility for patients subject to drug-drug interactions since it does not affect the CYP2D6 or CYP3A4 enzymes.

Meperidine. Meperidine is not preferred for long-term use because of the risk of toxicity associated with accumulation of

the metabolite normeperidine. Normeperidine can cause dysphoria, tremulousness, hyperreflexia, and seizures. It is renally cleared, and use of meperidine in patients with kidney disease is not recommended.

Methadone. In the United States, methadone is commercially available as a racemic mixture. The *l*-isomer is the opioid compound; the *d*-isomer does not bind to the opioid receptor but instead blocks the *N*-methyl-D-aspartate (NMDA) receptor. This pharmacology has been adduced to explain methadone's apparent increased potency when it is administered to a patient who is already receiving another opioid. There are anecdotal observations suggesting particularly good efficacy against some pains that were otherwise poorly responsive to opioids.

The unique pharmacology of methadone, its potential efficacy, and its low cost have combined to increase interest in the drug. This is appropriate as long as the challenges inherent in dosing a medication with an uncertain potency and a long and variable half-life (from 12 to more than 150 hours, with the usual half-life approximating 24 hours) are appreciated. It is recommended that a switch to methadone be accompanied by a large (75% to 90%) decrease in the calculated equianalgesic dose, to account for the potential for high potency. Because the plasma concentration of methadone rises to steady-state levels over 4 to 5 half-lives, rapid titration to an effective dose can subsequently be followed by continued escalation of the plasma concentration, ultimately leading to toxicity (known as accumulation).

Finally, there are recent reports linking methadone to prolongation of the QTc interval. At a critical point, this prolongation can predispose to life-threatening cardiac arrhythmia. In short, methadone dosing requires close monitoring, use of low starting doses, an adequate interval between dose changes, and caution in patients who have heart disease or medications with concurrent effects on the QTc interval.

Levorphanol. Levorphanol is another opioid with a long half-life (usually 12 to 15 hours). It generally can be administered at an interval of 6 hours and may be useful particularly in patients who are unable to tolerate, or access, modified-release opioids.

Codeine. Codeine is the most commonly used opioid for mild or moderate acute pain. It is typically used in combination with aspirin or acetaminophen. Clinical experience suggests that nausea and constipation are more commonly encountered with codeine than with equianalgesic doses of other opioids.

Propoxyphene. Propoxyphene is a weak opioid agonist that, when administered at typical doses, has an efficacy similar to that of aspirin or acetaminophen. Like meperidine, propoxyphene

has an excitotoxic metabolite that can accumulate, particularly in the setting of renal insufficiency. It is not preferred for management of chronic pain or for use in older patients.

Hydrocodone, dihydrocodeine. The oral analgesic potency of hydrocodone and dihydro-codeine is approximately 50% to 100% that of oral morphine. In the United States, they are available only in combination with acetaminophen or aspirin. The doses provided in these combination products are such that these medications typically are used for treatment of acute moderate to severe pain in patients with limited opioid exposure.

Fentanyl. Fentanyl is a synthetic opioid that is characterized by both high potency and comparatively high lipid solubility. A transdermal fentanyl patch is available for continuous opioid analgesia, and an oral transmucosal formulation is available for relief of brief, episodic severe pain (eg, breakthrough pain). Each transdermal fentanyl patch provides 48 to 72 hours of pain relief at steady state. Some patients consider the patch delivery form and the long dosing interval to be favorable characteristics. The fentanyl patch is particularly useful for patients who are unable to swallow or absorb an orally administered opioid, and studies that suggest a lesser potential for constipation provide support for a trial treatment with fentanyl when this symptom is especially problematic.

The pharmacokinetics of the transdermal system are complex and may be variable across patients. The formulation produces a subcutaneous depot, resulting in a slow onset of effect after a dose change and in a prolonged apparent elimination half-life (usually 24 hours) after the patch is removed. Steady-state concentrations are not approached for 1 to 3 days and sometimes longer. Oral transmucosal fentanyl is approved for treatment of cancer-related breakthrough pain but has been used for other types of episodic severe pains in opioid-tolerant patients. This formulation incorporates fentanyl into a lozenge that is sucked, allowing partial absorption through the buccal mucosa. The formulation has been shown to be effective and well tolerated and has an onset of effect faster than comparable doses of “immediate-release” oral opioids.

Agonist-antagonists

Use of agonist-antagonists for persistent pain generally is not preferred because of their ceiling dose for analgesia and the potential for inducing an acute abstinence syndrome in patients taking opioid agonists. Some of these medications, such as pentazocine and butorphanol, also have a higher likelihood of psychotomimetic side effects than the pure agonists. Studies sug-

gest that these opioids have a lower abuse potential than the pure opioid agonists in the known addict population, but this property has limited relevance in the general patient population. Buprenorphine, a partial agonist, is now available in the United States for office-based substitution treatment of opioid addiction.

Pure antagonists

Opioid antagonists exert their pharmacologic effect by competing with endogenous and exogenous opioids at μ receptor sites. Their role in pain management is primarily to prevent or reverse opioid-induced adverse effects. Low doses of oral naloxone have been shown to reverse opioid-induced bowel dysmotility without reversing analgesia. Use of naloxone, however, is not without risk, because some patients experience uncomfortable signs of systemic opioid withdrawal. Methylnaltrexone and alvimopan, opioid antagonists whose activity is restricted to peripheral receptors when ingested orally, are currently undergoing investigation for prevention or reversal of opioid-induced bowel effects without reversal of analgesia or precipitation of withdrawal symptoms. Some studies suggest that ultra-low doses of opioid antagonist drugs have analgesic effects (see chapter 2, page 9). The clinical utility of this observation is currently under study.

Drug metabolism and potential interactions

Most opioids are metabolized through the liver microsomal cytochrome P-450 (CYP) system. The enzymes CYP2D6 and CYP3A4, which are responsible for metabolism of a wide variety of drugs, are the most important enzymes for opioid metabolism. Patients may lack normal levels of enzymatic activity to metabolize opioids at expected rates because of genetic factors, severe liver disease, or competition with other medications.

The potential importance of enzyme activity is illustrated by codeine. Codeine is actually a prodrug that requires metabolic transformation to morphine. Patients who are slow metabolizers at the CYP2D6 isozyme produce little morphine from codeine and are unlikely to benefit after codeine administration.

Concomitant treatment with an inducer of a particular enzyme may lead to decreased levels of medications that are metabolized by that enzyme; treatment with an inhibitor may lead to increased levels. There are many potential interactions (table 6). It is likely that these interactions can produce clinically relevant effects, warranting closer monitoring, but further research is necessary to clarify their clinical implications.

Table 6. Potential drug interactions for major cytochrome P-450 enzymes CYP2D6 and CYP3A4

Enzyme	Substrates	Inhibitors	Inducers
CYP2D6	Amitriptyline, bupropion, clomipramine, clozapine, clonazepam, codeine, clonazepam, codeine, desipramine, dextromethorphan, doxepin, fluoxetine, haloperidol, hydrocodone, imipramine, methadone, modafinil, morphine, nortriptyline, olanzapine, oxycodone, paroxetine, sertraline, tiagabine, tramadol, venlafaxine	Citalopram (weak), desipramine, fluoxetine, olanzapine (weak), paroxetine, sertraline, venlafaxine (weak)	Carbamazepine, phenobarbital, phenytoin
CYP3A4	Alfentanil, alprazolam, amitriptyline, bupropion, citalopram, clozapine, cyclosporin, dexamethasone, dextromethorphan, etoposide, fentanyl, fluoxetine, ifosfamide, imipramine, ketamine, lidocaine, meperidine, modafinil, paclitaxel, prednisone, sertraline, tamoxifen, tiagabine, venlafaxine, vincristine	Dexamethasone, dextromethorphan, fluoxetine, paroxetine (weak), sertraline, venlafaxine	Carbamazepine, dexamethasone, erythromycin, modafinil, phenobarbital, phenytoin

Conclusion

There is an ever-enlarging pharmacopeia of opioid analgesics in a variety of formulations and delivery systems. A fundamental understanding of the clinical pharmacology of opioids can inform drug selection and assist in anticipating, and managing, both favorable and adverse opioid effects.

Suggested readings

Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage* 2002;24:71-90

Gammaitoni AR, Fine P, Alvarez N, et al. Clinical application of opioid equianalgesic data. *Clin J Pain* 2003;19:286-97

Gazelle G, Fine PG. Methadone for the treatment of pain. *J Palliat Med* 2003;6:621-2

Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002;18:S3-13

Liu M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. *J Pain Symptom Manage* 2002;23:48-53

Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* 1999;79:303-12