**I. OVERVIEW**

Management of pain is one of clinical medicine’s greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the periph- eral and central nervous system (CNS). It is subjective, and the physician must rely on the patient’s perception and description of his or her pain. Alleviation of pain depends on the specific type of pain, nociceptive or neurogenic pain. In many cases, for example, with mild to moderate arthritic pain (nociceptive pain), nonsteroidal anti-inflammatory agents (NSAIDs, see Chapter 42) are effective. Neurogenic pain responds best to anticonvulsants (for example, pregabalin, see p. 188), tricyclic antidepres- sants (for example, amitriptyline, see p. 155), or serotonin/norepineph- rine reuptake inhibitors (for example, duloxetine, see p. 154) rather than NSAIDs or opioids. However, for severe or chronic malignant or nonma- lignant pain, opioids are usually the drugs of choice. Opioids are natu- ral or synthetic compounds that produce morphine-like effects. [Note: The term “opiate” is reserved for drugs, such as morphine and codeine, obtained from the juice of the opium poppy.] All drugs in this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain, wheth- er that pain is from surgery or a result of injury or disease such as cancer. However, their widespread availability has led to abuse of those opioids with euphoric properties. Antagonists that can reverse the actions of opi- oids are also very important clinically for use in cases of overdose. Figure 14.1 lists the opioid agonists and antagonists discussed in this chapter.

**II. OPIOID RECEPTORS**

Opioids interact stereospecifically with protein receptors on the mem- branes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal (GI) tract and other anatomic regions. The major effects of the opioids are mediated by three major receptor families. These are designated by the Greek letters µ (mu), κ (kappa), and δ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the µ receptors. However, the κ receptors in the dorsal horn also contribute (for example, butorphanol and nalbuphine) primarily owe their analgesic effect to κ-receptor activation. The enkephalins interact more selectively with the δ receptors in the periphery. All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase. The are also associated with ion channels, increasing postsynaptic K+ effl ux (hyperpolarization) or reducing presynaptic Ca2+ infl ux, thus impeding neu- ronal fi ring and transmitter release (Figure 14.2).

 **III. STRONG AGONISTS**

Morphine [MOR-feen] is the major analgesic drug contained in crude opi- um and is the prototype strong agonist. Codeine is present in crude opium in lower concentrations and is inherently less potent, making codeine the prototype of the weak opioid agonists. Morphine and several other opioids have high affi nity for µ receptors, whereas other agents have varying affi ni- ties for δ and κ receptors.

**A. Morphine**

**1. Mechanism of action**: Opioids exert their major eff ects by interact- ing with opioid receptors in the CNS and in other anatomic struc- tures, such as the GI tract and the urinary bladder. Opioids cause hyperpolarization of nerve cells, inhibition of nerve fi ring, and pre- synaptic inhibition of transmitter release. Morphine acts at κ recep- tors in laminae I and II of the dorsal horn of the spinal cord, and it decreases the release of substance P, which modulates pain percep- tion in the spinal cord. Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying noci- ceptive (painful) stimuli.

**2. Actions**:

 **a. Analgesia**: Morphine causes analgesia (relief of pain without the loss of consciousness). Opioids relieve pain both by raising the pain threshold at the spinal cord level and, what is more impor- tant, by altering the brain’s perception of pain. Patients treated with morphine are still aware of the presence of pain, but the sen- sation is not unpleasant. However, when given to an individual free of pain, its eff ects may be unpleasant and may cause nausea and vomiting. The maximum analgesic effi cacy for representa- tive agonists is shown in Figure 14.3.

**b. Euphoria**: Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmentum.

 **c. Respiration**: Morphine causes respiratory depression by reduc- tion of the sensitivity of respiratory center neurons to carbon di- oxide. This can occur with ordinary doses of morphine in patients who are opioid-naïve and can be accentuated as the dose is in- creased until, ultimately, respiration ceases. Respiratory depres- sion is the most common cause of death in acute opioid overdos- es. Tolerance to this eff ect does develop quickly with repeated dosing, which allows the safe use of morphine for the treatment of pain when the dose is correctly titrated.

 **d. Depression of cough refl ex:** Both morphine and codeine have an- titussive properties. In general, cough suppression does not cor- relate closely with the analgesic and respiratory depressant prop- erties of opioid drugs. The receptors involved in the antitussive action appear to be diff erent from those involved in analgesia.

**e. Miosis**: The pinpoint pupil, characteristic of morphine use, re- sults from stimulation of µ and κ receptors. Morphine excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye (Figure 14.4). There is little tolerance to the effect, and all morphine abus- ers demonstrate pinpoint pupils. [Note: This is important diag- nostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

**f. Emesis**: Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

 **g. GI tract**: Morphine relieves diarrhea and dysentery by decreas- ing the motility and increasing the tone of the intestinal circu- lar smooth muscle. Morphine also increases the tone of the anal sphincter. Overall, morphine and other narcotics produce con- stipation, with little tolerance developing. [Note: A nonprescrip- tion laxative combination of the stool softener docusate with the stimulant laxative senna has been used successfully to treat this opioid-induced constipation.] Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constric- tion of the biliary sphincter.

**h. Cardiovascular**: Morphine has no major effects on the blood pressure or heart rate except at large doses, at which hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid (CSF) pressure. Therefore, morphine is usually contraindicated in individuals with head or severe brain injury.

**i. Histamine release**: Morphine releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug.

**j. Hormonal actions:** Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hor- mone and, thus, leads to urinary retention. [Note: Because it also can inhibit the urinary bladder voiding reflex, catheterization may be required.]

**k. Labor:** Morphine may prolong the second stage of labor by tran- siently decreasing the strength, duration, and frequency of uter- ine contractions.

 **3. Therapeutic uses:**

**a. Analgesia**: Despite intensive research, few other drugs have been developed that are as effective as morphine in the relief of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supple- ment the sleep-inducing properties of benzodiazepines such as temazepam. [Note: The sedative-hypnotic drugs are not usually analgesic, and they may have diminished sedative effect in the presence of pain.]

b. **Treatment of diarrhea:** Morphine decreases the motility and in- creases the tone of intestinal circular smooth muscle. [Note: This can cause constipation. Morphine products such as tincture of opium and camphorated tincture of opium (paregoric) have been used to treat diarrhea.]

**c. Relief of cough**: Although morphine suppresses the cough re- fl ex, codeine or dextromethorphan are more widely used for this purpose. Codeine has greater antitussive action than morphine.

**d. Treatment of acute pulmonary edema**: Intravenous (IV) mor- phine dramatically relieves dyspnea caused by pulmonary ede- ma associated with left ventricular failure, possibly by its vasodi- latory eff ect.

**4. Pharmacokinetics**:

**a. Administration**: Because signifi cant fi rst-pass metabolism of morphine occurs in the liver, intramuscular, subcutaneous, and IV injections produce the most reliable responses. Absorption of morphine from the GI tract is slow and erratic. When used oral- ly, morphine is commonly administered in an extended-release form to provide more consistent plasma levels. It is important to note that morphine has a linear pharmacokinetic profi le. This pharmacokinetic trait allows dosing to be more predictable and more fl exible. [Note: In cases of chronic pain associated with neo- plastic disease, it has become common practice to use either the extended-release tablets orally or pumps that allow the patient to control the pain through self-administration.]

**b. Distribution**: Morphine rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for anal- gesia during labor. Infants born of addicted mothers show physi- cal dependence on opiates and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of mor- phine crosses the blood-brain barrier, because morphine is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as fentanyl and methadone, which readily penetrate into the brain.

**c. Fate**: Morphine is conjugated with glucuronic acid in the liver. Morphine-6-glucuronide is a very potent analgesic, whereas the conjugate at position 3 (morphine-3-glucuronide) has been found not to have opioid activity, but is believed to cause the neuro-excitatory eff ects seen with high doses of morphine. The conjugates are excreted primarily in urine, with small quantities appearing in bile. The duration of action of morphine is 4 to 6 hours when administered systemically to morphine-naïve indi- viduals but considerably longer when injected epidurally, be- cause its low lipophilicity prevents redistribution from the epi- dural space. [Note: A patient’s age can infl uence the response to morphine. Elderly patients are more sensitive to the analgesic ef- fects of the drug, possibly due to decreased metabolism or other factors, such as decreased lean body mass, renal function, etc. They should be treated with lower doses. Neonates should not receive morphine because of their low conjugating capacity.]

**5. Adverse eff ects**: Severe respiratory depression can occur and result in death from acute opioid poisoning. A serious eff ect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale. [Note: If used in such individuals, respiration must be carefully monitored.] Other eff ects include vomiting, dysphoria, and histamine-enhanced hypotensive eff ects (Figure 14.5). The ele vation of intracranial pressure, particularly in head injury, can be serious. Morphine enhances cerebral and spinal ischemia. In benign prostatic hyperplasia, morphine may cause acute urinary retention. Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids. Morphine should be used cautiously in patients with bronchial asthma, liver failure, or impaired renal function.

**6. Tolerance and physical dependence**: Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychological dependence readily occur with morphine and with some of the other agonists (see Figure 14.3). Withdrawal produces a series of autonomic, motor, and psycho- logical responses that incapacitate the individual and cause seri- ous (almost unbearable) symptoms. However, it is very rare that the effects are so profound as to cause death. [Note: Detoxification of morphine-dependent individuals is usually accomplished through the oral administration of methadone, buprenorphine (see below), or clonidine.]

**7. Drug interactions**: Drug interactions with morphine appear to be rare, although the depressant actions of morphine are enhanced by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricy- clic antidepressants (Figure 14.6).

**B. Meperidine**

Meperidine [me-PER-i-deen] is a synthetic opioid structurally unrelated to morphine. It is used for acute pain. 1. Mechanism of action: Meperidine binds to opioid receptors, partic- ularly µ receptors. It also binds well to κ receptors.

**2. Actions**: Meperidine causes a depression of respiration similar to that of morphine, but it has no significant cardiovascular action when given orally. On IV administration, meperidine produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate. As with morphine, mep- eridine dilates cerebral vessels, increases CSF pressure, and contracts smooth muscle (the latter to a lesser extent than does morphine). Meperidine does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an anticholinergic action.

**3. Therapeutic uses**: Meperidine provides analgesia but is not recom- mended for long-term use due to its active metabolite, normeperi- dine, which has significant neurotoxic properties. Unlike morphine, meperidine is not clinically useful in the treatment of diarrhea or cough. Meperidine produces less of an increase in urinary retention than does morphine.

**4. Pharmacokinetics:** Meperidine is well absorbed from the GI tract, and is available for oral administration. However, meperidine is most often administered parenterally. The drug has a duration of action of 2 to 4 hours, which is shorter than that of morphine (Figure 14.7). Meperidine is N-demethylated to normeperidine in the liver and is excreted in urine.

**5. Adverse eff ects:** Large or repetitive doses of meperidine can cause anxiety, tremors, muscle twitches, and, rarely, convulsions, due to the accumulation of normeperidine. The drug diff ers from opioids in that, when given in large doses, it dilates the pupil and causes hyperactive refl exes. Severe hypotension can occur when the drug is administered postoperatively. Due to its antimuscarinic (antich- olinergic) action, patients may experience dry mouth and blurred vision. When used with major antipsychotic drugs, depression is greatly enhanced. Administration to patients taking MAOIs or dex- tromethorphan can provoke severe reactions, such as convulsions and hyperthermia. Meperidine is considered to be inappropriate for use in geriatric patients and patients with impaired renal function, due to the accumulation of normeperidine. Due to toxicities asso- ciated with meperidine use in elderly populations, this medication has been included on the Beers list, which was developed to iden- tify those medications that should be avoided in elderly patients. Adverse eff ects associated with normeperidine are not reversible by administration of naloxone.