

26

Opioid and Nonopioid Analgesics

Sandra P. Welch and Billy R. Martin



DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Nonopioid Analgesics			
Acetaminophen	314	Codeine	321
Aspirin	312	Dextromethorphan	327
Celecoxib	316	Dezocine	326
Diclofenac	316	Difenoxin	322
Etodolac	314	Dihydrocodeine	322
Fenoprofen	315	Diphenoxylate	322
Flurbiprofen	315	Fentanyl	323
Ibuprofen	315	Heroin	324
Indomethacin	314	Hydrocodone	322
Ketoprofen	315	Hydromorphone	322
Ketorolac	316	LAAM	323
Meclofenamate	315	Levopropoxyphene	327
Mefenamic acid	315	Levorphanol	323
Nabumetone	316	Loperamide	322
Naproxen	315	Meperidine	322
Oxaprozin	316	Methadone	323
Oxyphenbutazone	315	Morphine	320
Phenylbutazone	315	Nalbuphine	326
Piroxicam	316	Nalmefene	327
Rofecoxib	316	Naloxone	326
Sulindac	314	Naltrexone	327
Tolmetin	316	Noscapine	327
Opioid Analgesics		Oxycodone	322
Alfentanil	323	Oxymorphone	322
Benzonatate	327	Pentazocine	325
Buprenorphine	326	Propoxyphene	324
Butorphanol	325	Sufentanil	323

THE NATURE OF PAIN

Pain has been described by the International Association for the Study of Pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Although pain is a reaction of the body to harmful stimuli and is therefore a protective early warning system, the sensation of pain in postoperative patients, cancer patients, and other chronic pain patients has little positive effect. The stress response to pain can alter the healing process by evoking massive sympathetic discharge that in turn alters blood flow, tissue perfusion, and immune function. In addition, in certain painful conditions the patient has reduced respiratory function. Hence, the term *pain*, derived from the Latin *poena* for punishment, reflects the deleterious effects that can be inflicted upon the body. Since millions of Americans suffer from some form of pain each year, resulting in the expenditure of billions of dollars for various treatment modalities, pain and its underlying causes are a major public health problem.

The nature of pain is highly subjective. Pain has both sensory (somatic) and psychological (affective) components. One person may feel pain in response to noxious stimuli, while another person may disregard the stimuli. The affective (psychological) aspects of pain play a critical role in pain perception. A patient under external stress or other significant psychological problems often cannot handle the additional stress of pain. Anxiety exacerbates the perception of pain. Pain in turn exacerbates anxiety, decreases the comfort of the patient, and results in disturbances in sleeping, eating, and locomotion, creating a cycle of related medical problems. The drugs described in this chapter are used to interrupt such a cycle. *The nonopioid analgesics act to decrease the generation of the mediators of pain at the site of tissue damage, although several of the drugs also have some effects within the central nervous system (CNS). The opioid analgesics are unique in that they not only block the incoming nociceptive signals to the brain but also act at higher brain centers, controlling the affective components of the pain.* The drugs described in this chapter do not constitute the entirety of the armamentarium of therapies for pain relief. Many patients respond best to a combination of therapies. Therapeutic modalities in addition to the drugs described in this chapter include antidepressants, adrenergic agonists (e.g., clonidine), transcutaneous electrical nerve stimulation, physical therapy, massage therapy, acupuncture, meditation, and behavior modification. The treatment regimen is generally based upon the type of pain.

Cells in the substantia gelatinosa (lamina II contains highest levels of opioid binding) of the dorsal horn of the spinal cord respond to incoming nociceptive stimuli and regulate, or gate, the transmission of nociceptive impulses to other pathways within the CNS via the

spinothalamic tract. Opioids also can elicit analgesic effects by stimulating the release of norepinephrine from a descending noradrenergic pathway, which extends from the locus ceruleus to the dorsal horn of the spinal cord.

In general, pain can be described as either acute or chronic. *Acute pain*, which does not outlast the initiating painful stimulus, has three generally encountered origins. The most common type of acute pain is of superficial origin from wounds, chemical irritants, and thermal stimuli, such as burns. Acute pain of deep somatic origin usually arises from injection of chemical irritants or from ischemia, such as with myocardial infarction. Acute pain of visceral origin is most often associated with inflammation. *Chronic pain*, by contrast, outlasts the initiating stimulus, which in many cases is of unknown origin. Chronic pain is often associated with diseases such as cancer and arthritis. Treatment of chronic pain presents a challenge to the physician in that the underlying cause is often not readily apparent. Neuropathic pain, a type of chronic pain, responds poorly to opioids. Some causes of neuropathic pain include diabetic neuropathies, shingles (herpes zoster), ischemia following stroke, and phantom limb pain. Neuropathic pain responds well in many cases to therapies other than the use of opioids and nonsteroidal antiinflammatory drugs (NSAIDs).

Pain thus has several etiologies, and transmission of nociceptive inputs from diverse nociceptors occurs via different fiber bundles. A δ -fibers are the site for rapid transmission of sharp, painful stimuli. Such fibers are myelinated and enter the dorsal horn, from which point the ascending systems of the spinothalamic tract are activated. C-fibers, which also enter the dorsal horn and synapse on spinothalamic tract neurons, are responsible for the slower transmission (fibers are not myelinated) of nociceptive impulses, resulting in a dull, aching sensation. The A δ -fibers and C-fibers are activated by mechanoreceptors. A δ -fibers and C-fibers are also activated by other types of nociceptors, such as those responding to heat and chemicals. Current studies on the plasticity of pain-modulating systems that contribute to the chronic long-lasting nature of pain have been reviewed in detail by Julius and Basbaum (2001) and include alterations in numerous intracellular signaling systems beyond the scope of this chapter. However, what is becoming apparent is that novel analgesics may be designed in the future to target the modulation of intracellular targets in pain processing and neuronal plasticity.

The loss of quality of life for a patient with either acute or chronic pain has led to extensive development of various drugs to treat pain. Such drugs eliminate pain by either decreasing the underlying cause of the pain (as do the nonopioid analgesics described later) or decreasing the transmission of nociceptive impulses and

pain perception (as do the opioids). Both nonopioid and opioid drugs are described in detail in this chapter.

NONOPIOID ANALGESICS

In general, pain is first treated with the nonopioid analgesics. These drugs are useful for treatment of pain, fever, and inflammation and for reduction of platelet aggregation. Although the NSAIDs are less effective than the opioids in providing pain relief, they do not produce tolerance and physical dependence, as do the opioids. *The mechanism of action of traditional NSAIDs involves blockade of the production of prostaglandins by inhibition of the enzyme cyclooxygenase (COX) at the site of injury in the periphery, thus decreasing the formation of mediators of pain in the peripheral nervous system.* COX was originally thought to be a single enzyme that was responsible for the conversion of arachidonic acid to a variety of prostanoids. The prostanoids produced by COX activity include those that are involved in inflammatory responses in tissue leading to detrimental effects and those that are critical to the maintenance of the gastric mucosal lining and certain renal functions. Thus, inhibition of COX by the NSAIDs may be accompanied by ulceration of the stomach lining and renal damage. In 1991 it was discovered that the COX system consisted of two enzymes, COX-1 and COX-2. COX-1 appears to remain constitutively active and is the site of action of the NSAIDs used prior to the early 1990s. However, COX-2 is not constitutively active and is induced by traumatic tissue injury, although some evidence of low levels of COX-2 constitutive activity exists for certain regions, such as the brain. The discovery of COX-2 led to the hypothesis that the major therapeutic benefit of the COX inhibitors was due to the block of inducible COX-2, while the major problematic side effects of the NSAIDs were due to COX-1 inhibition. Although this hypothesis has undergone several iterations, it does appear that the COX-2 inhibitors can at the very least be described as gut sparing. The original NSAIDs appear to be nonselective for COX-1 and COX-2. Development of novel COX-2 inhibitors has led to the discovery of a class of NSAIDs largely devoid of the gastrointestinal (GI) and renal problems associated with the older NSAIDs. Although the COX-2 drugs are no more efficacious than the older nonselective COX inhibitors, the decrease in side effect profile has provided a new mechanism of long-term antiinflammatory treatment.

Aspirin is one of the most important NSAIDs because it decreases pain at predominantly peripheral sites with little cortical interaction and thus has few CNS effects. The prototypical COX-2 inhibitors are celecoxib (*Celebrex*) and its chemical cousin, rofecoxib (*Vioxx*). In addition to a role in inflammatory processes,

COX-2 seems to play a role in colon cancer and Alzheimer's disease, providing potential additional uses for COX-2-selective drugs.

Salicylates

Chemistry

Aspirin is a weak organic acid and is one of the oldest known drugs for the relief of fever and pain. Aspirin remains the standard to which most NSAIDs are compared for efficacy.

Pharmacokinetics

Aspirin itself is an acid with a pKa of 3.5 and is relatively insoluble in water, while its sodium or calcium salts have enhanced solubility. Aspirin and related salicylates are rapidly absorbed upon oral administration, with most absorption occurring in the small intestine. The pH of the stomach, a secondary site of drug absorption, along with the gastric emptying time of the stomach, determines the rate of absorption of the drug. Thus, food, which alters gastric emptying time and possibly the pH of the stomach, will alter absorption of the drug. Buffering of the drug decreases irritation in the stomach, increases drug solubility, and therefore may increase the rapidity of absorption. Enteric-coated aspirin tablets have a variable rate of dissolution depending on the preparation but are somewhat useful for prevention of stomach ulceration and gastric distress. Absorption of aspirin from rectal suppositories is slower and more variable than from oral administration. The peak plasma concentration of aspirin occurs 1 to 2 hours following oral administration. Aspirin is immediately hydrolyzed by various esterases in the stomach and in the liver to acetate and salicylic acid. Salicylic acid is glucuronidated, conjugated to glycine to form salicyluric acid (the major metabolic pathway), oxidized to gentisic acid (a minor metabolic pathway), or remains free as salicylic acid, which is secreted in the proximal tubule of the kidney. Diflunisal (*Dolobid*) differs from other salicylates in that it is not metabolized to salicylic acid but is rapidly glucuronidated. The conjugated metabolites of salicylates are inactive.

Salicylic acid is highly plasma protein bound, an effect that alters the pharmacokinetics of other drugs taken in combination with aspirin. Salicylates passively diffuse to all tissues, including breast milk, fetal tissues, and the CNS. They tend to accumulate, since increases in dose decrease renal clearance and prolong the half-life of the drug. Clearance at high doses (>2–4 g/day) is via zero order kinetics, and the half-life can approach 15 hours. At lower doses (600–1000 mg/day), clearance depends on the concentration of glucuronide or glycine available for conjugation and is a first-order process (half-life of approximately 3–6 hours). However, renal clearance is

highly dependent on the pH of the urine; *the higher the pH of the urine, the greater the clearance of the drug*. Alkalinization of the urine is used to increase clearance of the salicylates in the case of toxicity or overdose.

Mechanism of Action and Pharmacological Effects

Aspirin and related salicylates produce their pharmacological effects predominantly by inhibiting the synthesis of prostaglandins and to a lesser extent synthesis of the thromboxanes (implicated in platelet aggregation). The prostanoids are mediators of inflammatory responses in many cell types. Aspirin is unique among NSAIDs in that it irreversibly acetylates COX-1 and COX-2, which are required for the synthesis of prostanoids from arachidonic acid. COX-2 is induced during inflammation and is therefore considered to mediate most inflammatory responses. Aspirin acetylation of COX-1 permanently inactivates the enzyme, while acetylated COX-2 is capable of producing 15-HETE. *New enzyme must be synthesized to overcome the effects of aspirin*, which in the case of platelets can take as long as 11 days. The metabolite of aspirin, salicylic acid, is a reversible inhibitor of COX. Other NSAIDs have reversible effects at different sites on COX-1 and on COX-2. In addition, aspirin interferes with kinin-induced modulation of the inflammatory response.

Clinical Uses

Aspirin and related salicylates are the primary treatment for mild to moderate pain, such as that associated with headache, joint and muscle pain, and dysmenorrhea. At higher doses aspirin is an effective analgesic in rheumatoid arthritis (see Chapter 36). The analgesic effects of salicylates are thought to be due to the inhibition of prostaglandin synthesis in the periphery and to a less well documented mechanism at cortical areas.

The salicylates are also potent antipyretic agents, with the exception of diflunisal, which is only weakly active. Aspirin acts at two distinct but related sites. It decreases prostaglandin-induced fever in response to pyrogens and induces a decrease in interleukin-1 modulation of the hypothalamic control of body temperature. Thus, the hypothalamic control of body temperature returns, vasodilation occurs, heat dissipates, and fever decreases. Other uses of aspirin include inhibition of platelet aggregation via inhibition of thromboxanes, which has been shown to decrease the incidence of blood clots, myocardial infarction, and transient ischemic attacks.

Overdose and Other Adverse Effects

The major consequence of aspirin overdose, which often occurs in children, results from actions on respira-

tory centers in the medulla. Salicylate-induced stimulation of respiration leads to hyperventilation. In addition, salicylates uncouple oxidative processes leading to increased carbon dioxide production and metabolic acidosis. The onset of acidosis, if not treated less than 1 hour after ingestion of aspirin, will lead to loss of rhythmicity of respiration and eventually loss of breathing. Treatments include alkalinization of the urine, fluid replacement, gastric lavage with activated charcoal, dialysis, and artificial ventilation.

Some patients exhibit hypersensitivity to aspirin in the form of *salicylism*, which is accompanied by ringing in the ears (tinnitus), vertigo, and bronchospasm (especially in asthmatics). The use of salicylate-containing preparations is not the only source of this drug. Those sensitive to salicylates should be aware of salicylates in a number of foods, such as curry powder, licorice, prunes, raisins, and paprika.

The use of aspirin in children and teenagers with either chickenpox or influenza is contraindicated, since there is evidence linking the use of the salicylates in such diseases to Reye's syndrome, a potentially fatal disease accompanied by liver damage and encephalopathy. The mechanism by which the use of salicylates increases the chances for development of Reye's syndrome is not known.

Other potential adverse effects of the drugs include the use of aspirin by patients who anticipate surgery or dental procedures. Such patients should be closely monitored and the salicylate stopped at least 1 week prior to surgery because of the possibility of increased clotting time and excessive bleeding. Similarly, the use of salicylates in pregnant women may increase bleeding upon delivery and prolong delivery. In addition, adverse fetal effects have been documented, such as low birth weight, fetal intracranial bleeding, and possible teratogenic effects. Due to the ulcerogenic effects of the drugs, patients with a history of ulcers or other GI disturbances should be carefully monitored for increased blood in the feces while taking salicylates.

Drug Interactions

The salicylates displace a number of drugs from plasma protein binding sites, thereby leading to potential adverse effects by these agents. Since aspirin is an over-the-counter medication, patients may fail to inform the doctor of their aspirin consumption. Anticoagulants are potentiated by aspirin by (1) displacement of the anticoagulants from plasma proteins and (2) the intrinsic anticoagulant effect of aspirin. Thus, the dosage of drugs such as coumarin and heparin should be reduced in patients taking aspirin. A similar effect is observed in patients taking oral sulfonylureas (*Orinase, DiaBeta*) for non-insulin-dependent diabetes or phenytoin (*Dilantin*) for seizures. Displacement of the sulfonylureas

or phenytoin from plasma binding necessitates a decrease in dosage to prevent an acute hypoglycemic event or sedation, respectively. Aspirin enhances the effects of insulin (leading to hypoglycemia), penicillins and sulfonamides (increasing acute toxicity), and corticosteroids. Aspirin increases the hypotensive effects of the cardiac drug nitroglycerin but decreases the effectiveness of the loop diuretics. In patients taking methotrexate for cancer chemotherapy, aspirin may increase retention of the drug, and severe toxicity may result.

Conversely, certain drugs modify the effectiveness or side effects of aspirin. Phenobarbital, occasionally used for seizures, induces liver enzymes that increase the metabolism and excretion of aspirin, β -adrenoceptor-blocking drugs, such as propranolol, and decrease the antiinflammatory effects of aspirin, whereas reserpine decreases its analgesic effects. Antacids decrease the absorption of aspirin. Alcohol consumption in combination with aspirin increases the latter's ulcerogenic effects.

***p*-Aminophenol Derivatives**

Acetaminophen (*Tylenol*) is the active metabolite of both phenacetin and acetanilide but has fewer toxic effects than either precursor. Phenacetin and acetanilide are no longer used therapeutically because they have been linked to methemoglobinemia.

Pharmacokinetics

Acetaminophen, with a pKa of 9.5, is rapidly absorbed from the GI tract following oral administration. Peak plasma concentrations are observed within 30 minutes to 2 hours. Absorption is nearly complete following oral administration but varies with suppository forms of the drug. Acetaminophen is less plasma protein bound than the salicylates, although the amount bound varies from 20 to 50%. Following the use of normal therapeutic doses of acetaminophen, metabolism and conjugation to sulfate or glucuronides occurs, and clearance of these metabolites occurs in the kidney. A minor toxic metabolite is generated by the metabolism of acetaminophen via the P450 mixed-function oxidase system. This toxic metabolite is normally conjugated to glutathione in the liver and excreted via the kidney as conjugated cysteine and mercapturic acid. However, with the depletion of glutathione in certain disease states, such as liver cirrhosis and necrosis, and following chronic use of high doses of acetaminophen, this toxic reactive metabolite can accumulate and induce liver damage.

Mechanism of Action

Acetaminophen is a weak inhibitor of peripheral COX. Its analgesic effects may arise from inhibition of prostanoid synthesis in the CNS or other centrally mediated effects yet to be elucidated. The antipyretic ef-

fects of acetaminophen are similar to those of aspirin in that it acts at the level of the hypothalamus to reduce pyrogen-initiated alterations in body temperature by inhibiting prostaglandin synthesis.

Pharmacological Effects and Clinical Uses

Acetaminophen is similar to salicylates in that it is a useful analgesic for mild to moderate pain, with equal efficacy to aspirin, and like aspirin, it is antipyretic. However, *acetaminophen exerts little if any effects on platelet aggregation and is not antiinflammatory*. Thus, it is not useful for patients with arthritis or other inflammatory diseases. It is also not useful as an antithrombotic agent in the prevention of myocardial infarction or transient ischemic attacks. Acetaminophen does not produce the gastric ulceration that can occur with aspirin and is useful in patients who are salicylate sensitive or who have a history of ulcers or other gastric ulcerations.

Adverse Effects, Contraindications, and Drug Interactions

Toxicity from overdose with acetaminophen differs in time course and mechanism from that observed with the salicylates. The onset of toxicity may not occur for several days, and the predominant damage is to the liver. The initial signs of toxicity occur within 12 to 24 hours and include nausea and vomiting. Signs of hepatotoxicity occur within 72 hours. In addition to hepatotoxic effects, renal necrosis and myocardial damage may occur. Oral *N*-acetylcysteine is used to treat acetaminophen toxicity, although many patients are hypersensitive to such treatment. In addition, gastric lavage with activated charcoal can be used immediately after ingestion of the drug to decrease acetaminophen absorption from the stomach.

Acetaminophen is contraindicated in late-stage alcoholism, since chronic alcohol consumption can induce the P450 system, leading to increased production of the toxic metabolite of acetaminophen, hence to liver necrosis. In addition, barbiturates and phenytoin induce the liver P450 system and may decrease the effectiveness of acetaminophen. Acetaminophen crosses the placenta but is nonetheless used in pregnant women with few side effects for the mother or the fetus. Although the drug has been shown to be present in breast milk, no conclusive evidence links the drug to abnormalities associated with consumption of breast milk by the newborn.

Indoles (indomethacin) and Related Compounds

Chemistry and Mechanism of Action

Indomethacin (*Indocin*) is an acetic acid derivative related functionally to sulindac (*Clinoril*), a prodrug with a long half-life, and etodolac (*Lodine*). They are metabolized in the liver and excreted as metabolites in the

bile and via the kidney. They are potent inhibitors of COX and thus extremely effective antiinflammatory agents (see Chapter 36).

Clinical Uses, Adverse Effects, and Contraindications

All of these drugs produce analgesic effects, antipyresis, and antiinflammatory effects. Due to the high incidence of gastric irritation, headache, nausea, and other side effects, including hematological effects and coronary vasoconstriction, *they are not useful as an initial treatment for pain*. GI irritation and ulceration occur to a lesser extent with etodolac. Indomethacin is useful in the treatment of acute gout, osteoarthritis, ankylosing spondylitis, and acceleration of the closure of the ductus arteriosus in premature infants. The tocolytic effects of indomethacin to prevent preterm labor are the result of its effects on prostaglandin synthesis. However, the toxicity of the drug limits such application, since it increases fetal morbidity. Indomethacin is contraindicated in pregnancy, in asthmatics, and in those with gastric ulcers or other ulceration of the GI tract. Indomethacin may increase the symptoms associated with depression or other psychiatric disturbances and those associated with epilepsy and Parkinson's disease. The drug should be used with caution in such patients.

Fenamates

Meclofenamate (*Meclomen*) and mefenamic acid (*Ponstel*) exhibit potency and side effects similar to those of other nonsalicylate NSAIDs. However, both drugs produce serious side effects, have a short duration of action, and are not safe for children. Their use is limited to patients who fail to respond to other treatments. They are analgesic, antipyretic, and antiinflammatory agents indicated for mild to moderate pain, treatment of dysmenorrhea, rheumatoid arthritis, and osteoarthritis. These drugs are metabolized via glucuronidation in the liver and excreted via the kidney. Thus, fenamates require normal liver and kidney function for excretion and are contraindicated in patients with either liver or renal failure. Overdose with fenamates leads to seizures that are sometimes insensitive to traditional treatment with benzodiazepines. In cases of overdose with meclofenamate dialysis may be required to restore fluid and electrolyte balance.

Arylpropionic Acid Derivatives Chemistry and Mechanism of Action

Ibuprofen (*Advil*), flurbiprofen (*Ansaid*), fenoprofen (*Nalfon*), ketoprofen (*Orudis*), and naproxen (*Naprosyn*) are all 2-substituted propionic acid derivatives. They block the production of prostaglandins via inhibition of COX and therefore are similar to the salicylates in that

they produce analgesia, antipyresis, and antiinflammatory effects. However, they are more potent than aspirin, with a decreased incidence of side effects such as gastric irritation. Ketoprofen inhibits lipoxygenase and COX, thus decreasing the production of both leukotrienes and prostaglandins. It also decreases lysosomal release of enzymes in inflammatory diseases. *The principal differences among these drugs lie in the time to onset and duration of action*. Naproxen has a long half-life, whereas fenoprofen and ketoprofen have short half-lives. All of the drugs are extensively metabolized in the liver and require adequate kidney function for clearance of the metabolites. The drugs vary in plasma protein binding, but clearly all are bound to a relatively high degree and can interfere with the binding of other drugs that compete for plasma protein binding (as described for aspirin). The one exception is ketoprofen, which although highly bound to plasma proteins, does not appear to alter the binding of other drugs.

Clinical Uses, Adverse Effects, and Contraindications

The arylpropionic acid derivatives are useful for the treatment of rheumatoid arthritis and osteoarthritis, for reduction of mild to moderate pain and fever, and for pain associated with dysmenorrhea. Side effects of the drugs are similar to but less severe than those described for the salicylates. Those who are sensitive to salicylates also may be sensitive to and have adverse reactions when taking ibuprofen and related drugs. Acute hypersensitivity to ibuprofen has been reported in patients with lupus. The hypersensitivity reaction to sulindac can be fatal. The use of sulindac has also been linked to cases of acute pancreatitis. The use of dimethylsulfoxide (DMSO) topically in combination with sulindac has been reported to induce severe neuropathies. The concurrent use of ibuprofen with aspirin reduces the antiinflammatory effects of both drugs. Ibuprofen is contraindicated in patients with aspirin sensitivity leading to bronchiolar constriction and in patients with angioedema. As with all NSAIDs, renal and liver function should be normal for adequate clearance of the drugs.

Pyrazolone Derivatives

Phenylbutazone (*Butazolidin*) is metabolized to oxyphenbutazone (*Phlogistol*), and both compounds have all of the activities associated with the NSAIDs. Their use is accompanied by serious adverse reactions, such as anemia, nephritis, renal failure or necrosis, and liver damage. Because of their toxicity, they are prescribed only for the treatment of pain associated with gout or phlebitis or as a last resort for other painful inflammatory diseases resistant to newer and less toxic treatments. Interactions with a large number of other drugs

(similar to those described for aspirin) occur, since phenylbutazone displaces several drugs from plasma protein binding sites. The drug is contraindicated in children and in the elderly with diminished renal function. The consequences of overdose occur slowly and can include liver damage, renal failure, and shock. There is no antidote for overdose. Supportive measures include ventilation, dialysis, and gastric lavage with activated charcoal, as well as the use of benzodiazepines to control convulsions.

Oxicam Derivatives

Piroxicam (*Feldene*) is the prototypical oxicam derivative, with analgesic, antipyretic, and antiinflammatory properties. Its long half-life (45 hours) favors compliance, since only one dose per day is given. Side effects are similar to those encountered with other NSAIDs: gastric disturbances, tinnitus, and headache. Piroxicam is indicated for inflammatory and rheumatoid conditions.

Acetic Acid Derivatives

Diclofenac (*Voltaren*) is a phenylacetic acid derivative that is a potent inhibitor of COX and that has analgesic, antiinflammatory, and antipyretic effects. Its use is accompanied by side effects similar to those of other NSAIDs. Indications for the drug include rheumatoid arthritis, osteoarthritis, and ophthalmic inflammation (use of an ophthalmic preparation).

Ketorolac (*Toradol*) is an NSAID with very mild antiinflammatory and antipyretic activity. It is a potent analgesic for postoperative pain. Its efficacy is equivalent to that of low doses of morphine in the control of pain. For this reason it is often combined with opioids to reduce opioid dose and related side effects while providing adequate pain relief. It is also used to replace the opioids in some patients with opioid sensitivity. The mechanism of action of ketorolac involves the inhibition of COX and decreased formation of prostaglandins. However, some evidence exists that ketorolac may stimulate the release of endogenous opioids as a part of its analgesic activity.

Tolmetin (*Tolectin*) is an antiinflammatory, analgesic, and antipyretic agent that produces the usual gastric distress and ulceration observed with NSAIDs. However, tolmetin is better tolerated than aspirin and produces less tinnitus and vertigo. Tolmetin is a substitute for indomethacin in indomethacin-sensitive patients and is unique among such drugs in that it can be used to treat juvenile arthritis.

Miscellaneous Agents

Oxaprozin (*Daypro*) has pharmacological properties that are similar to those of other propionic acid derivatives. However, it has a very long half-life (more than 40 hours) and therefore can be effective with once-a-day treatment.

Nabumetone (*Relafen*) has antiinflammatory, antipyretic, and analgesic properties. It is converted by liver enzymes to an active metabolite that is a potent COX inhibitor. Although nabumetone shares many of the adverse effects of other NSAIDs, it appears to produce a lower incidence of GI ulceration.

COX-2 Inhibitors

Chemistry

Celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are the two available COX-2 inhibitors. Both lack a carboxylic group present in most NSAIDs and therefore are able to orient into the COX-2 enzyme in a selective manner that differs from that of other NSAIDs. They have low aqueous solubility that prevents parenteral administration.

Mechanism of Action

As previously discussed, the COX-2 inhibitors have selectivity for inhibition of the COX-2 enzyme, which has low constitutive activity but is highly inducible at sites of tissue injury. In addition to the peripheral role of COX-2 in inflammation, COX-2 may play an important role in the CNS. COX-2 is expressed constitutively in some excitatory neurons in the brain and spinal cord and is induced in traumatic brain injury such as that induced by ischemia and seizures. It has been hypothesized that COX-2 may also be involved in neurodegenerative diseases, since COX-2 inhibitors have shown some positive effects in Alzheimer's disease. Thus, the mechanism of action of COX-2 inhibitors may involve brain and spinal cord sites as well as local sites of injury.

Pharmacological Effects and Clinical Uses

Celecoxib has been approved for the treatment of osteoarthritis and rheumatoid arthritis, and rofecoxib has been approved for the treatment of osteoarthritis, acute pain and primary dysmenorrhea. Celecoxib and rofecoxib do not appear to differ in efficacy for the treatment of osteoarthritis. However, neither drug has efficacy greater than that of the non-selective NSAIDs. Since the COX-2 enzyme appears to play an important role in colon cancer the COX-2 inhibitors may find future uses in the treatment or prevention of colorectal cancer.

Adverse Effects, Contraindications

The major advantage of the COX-2 inhibitors is their decreased GI effects and formation of gastric ulcerations compared with the COX nonselective agents. However, once an ulcer is present, COX-2 is induced in response, and the COX-2 enzyme is essential for wound healing. Therefore, celecoxib and rofecoxib can delay in wound healing and increase the time for ulcer repair and tissue regeneration. Patients with gastric ulcers

should be switched if possible to another antiinflammatory to allow ulcers to heal.

Celecoxib is contraindicated during pregnancy, since COX-2 levels must be maintained for ovulation and onset of labor. COX-2 seems to be involved into the regulation of the renin-angiotensin system, and both celecoxib and rofecoxib use are associated with transient sodium retention.

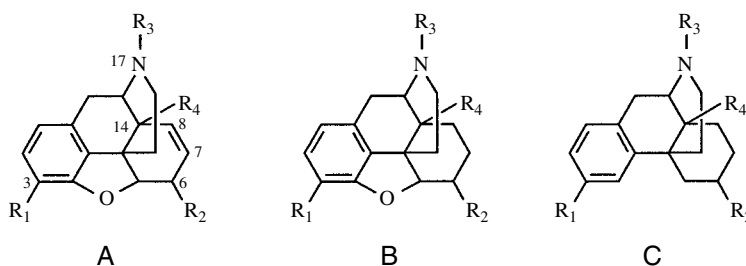
OPIOID ANALGESICS

Chemistry

The basic structure of morphine (Fig. 26.1) can be altered in rather minor ways that drastically change the effects of the drug. Acetylation of the hydroxyl groups leads to the synthesis of heroin (diacetylmorphine),

which has a much greater ability to pass the blood-brain barrier. In the brain, however, heroin is converted to morphine and monoacetyl morphine. Some researchers attribute heroin's potent analgesic effects and rapid onset of action solely to its conversion to morphine. Others contend that heroin produces analgesic effects distinct from the conversion to morphine and thus should be considered as a therapeutically useful analgesic. Heroin is not approved for medical use in the United States, although it is used therapeutically in other nations.

Morphine is glucuronidated in the liver at the phenolic hydroxyl group (C_3). Protection of that group with a methyl group, as occurs in codeine and other codeine derivatives such as oxycodone, renders the molecule less susceptible to glucuronidation and decreases the first-pass effect in the liver. It is for this reason that codeine and its derivatives retain activity following oral



Generic name	Template	R ₁	R ₂	R ₃	R ₄
Morphine	A	—OH	—OH	—CH ₃	—H
Codeine	A	—OCH ₃	—OH	—CH ₃	—H
Heroin	A	—OCOCH ₃	—OCOCH ₃	—CH ₃	—H
Hydrocodone	B	—OCH ₃	=O	—CH ₃	—H
Oxycodone	B	—OCH ₃	=O	—CH ₃	—OH
Dihydrocodeine	B	—OCH ₃	—OH	—CH ₃	—H
Hydromorphone	B	—OH	=O	—CH ₃	—H
Oxymorphone	B	—OH	=O	—CH ₃	—OH
Levorphanol	C	—OH	—H	—CH ₃	—H
Butorphanol	C	—OH	—H	—CH ₂	—OH
Nalbuphine	B	—OH	—OH	—CH ₂	—OH
Buprenorphine	B ¹	—OH	—OCH ₃	—CH ₂	—OH
Naloxone	B	—OH	=O	—CH ₂ CH=CH ₂	—OH
Naltrexone	B	—OH	=O	—CH ₂	—OH
Nalmefene	B	—OH	=CH ₂	—CH ₂	—OH

FIGURE 26.1

Opioid agonists, mixed agonist-antagonists, and antagonists.

administration to a greater degree than does morphine. However, the glucuronidation of morphine at the hydroxyl moiety on C₆ leads to an active metabolite, morphine-6-glucuronide, which contributes to the activity of morphine and extends its duration of action.

Endogenous Opioids

The *endogenous opioids* are naturally occurring peptides that are the products of four known gene families. The gene responsible for the production of the *endomorphins*, a new class of endogenous opioids, has yet to be identified. The enkephalins, the first opioid peptides identified, were first discovered in the brain and were therefore given the name *enkephalin*, which means from the head. The *dynorphins* were so named because they were thought to be dynamic endorphins, having a wide range of activities in the body, a hypothesis that has proved to be accurate.

The endogenous opioids have been implicated in the modulation of most of the critical functions of the body, including hormonal fluctuations, thermoregulation, mediation of stress and anxiety, production of analgesia, and development of opioid tolerance and dependence. The endogenous opioids maintain homeostasis, amplify signals from the periphery to the brain, and serve as neuromodulators of the body's response to external stimuli. As such, the endogenous opioids are critical to the maintenance of health and a sense of well-being.

Opioid Receptors

Given the diversity of opioid effects, William R. Martin hypothesized that multiple opioid receptors existed. Recently, a number of previously hypothesized opioid receptors have been cloned (μ , δ , and κ). The σ -receptor, once thought to be an opioid receptor, is a nonopioid receptor that mediates some of the dysphoric effects of the opioids. *The cloned opioid receptors are members of the large superfamily of G protein-coupled receptors.* Subtypes of the receptors have been proposed. It has been shown that μ_1 -receptors mediate the analgesic and euphoric effects of the opioids and physical dependence on them, whereas μ_2 -receptors mediate the bradycardiac and respiratory depressant effects. δ -Receptors, of which at least two subtypes have been identified pharmacologically, mediate spinal analgesic effects and have been implicated in the modulation of tolerance to μ -opioids. Three κ -opioid receptors have been identified and are thought to mediate spinal analgesia, miosis, sedation, and diuresis. The existence of the ϵ -receptor is hypothetical pending cloning of the receptor.

Opioid receptors and their precursor mRNAs are distributed throughout the brain and spinal cord. High levels of opioid binding have been found in the ascending pathways for nociceptive transmission, including the

dorsal horn of the spinal cord and in particular the substantia gelatinosa lamina II. Other ascending tracts with high levels of binding include the spinothalamic tracts to the subcortical regions and limbic areas of the brain responsible for the discriminative and sensory aspects of pain and the euphoric effects of the drugs. Limbic areas, including cortical sites and the amygdala, are involved in the anxiolytic effects of the drugs. Binding in the thalamus and hypothalamus is also very high. Binding in the hypothalamus is linked to the modulation of hormone release and to thermoregulation by the opioids and opioid peptides. Some descending pathways possess high levels of opioid receptors believed to be linked to the analgesic effects of the drugs. In addition, the receptor binding in medullary pathways has been linked to inhibitory neurotransmitter release in the dorsal horn.

Opioid binding at medullary sites is consistent with the respiratory depressant effects of the drugs. *Binding in the nucleus accumbens and the resultant release of dopamine by the μ - and δ -opioids is linked to the development of physical dependence.* However, the κ -opioids, which also bind extensively in the nucleus accumbens, are linked to a decrease in dopamine release, possibly explaining their lower abuse liability. The localization of different receptor subtypes within different-size fiber pathways has been established. The μ - and δ -receptors appear associated with the large-diameter fibers, while the κ -receptors appear to be located in the small to medium-size fiber bundles of the dorsal root ganglia. Such differences may explain the modulation of specific types of nociceptive stimuli by the different opioid agonists and opioid peptides.

Pharmacokinetics

Most of the opioids are well absorbed from the GI tract in addition to being absorbed following transcutaneous administration. As described previously, the first-pass effect on drugs like morphine, which have a free hydroxyl group in position 3, is glucuronidation by the liver. In the case of morphine, the conjugation to glucuronide decreases the oral bioavailability of the drug. Following absorption, the drugs distribute rapidly to all tissues, although the distribution is limited by their lipophilicity. Fentanyl (highly lipophilic) distributes to the brain rapidly but also remains in fat, which serves as a slow-releasing pool of the drug. Certain of the drugs, notably methadone and fentanyl, have long half-lives inconsistent with their duration of action. This discrepancy is due to accumulation in various tissue and plasma reservoirs and redistribution from the brain to these reservoirs. Heroin passes readily into the brain. Codeine passes into the brain more readily than morphine, which is slow in crossing the blood-brain barrier. The drugs cross readily into fetal tissues across the pla-

centa and therefore should be used with care during pregnancy and delivery. Moreover, glucuronidation by the fetus is slow, increasing buildup of the drugs and increasing their half-life in the fetus.

The majority of their metabolites are inactive with a few notable exceptions, such as morphine-6-glucuronide, which produces an analgesic effect; normeperidine and norpropoxyphene, which produce excitatory but not analgesic effects; and 6- β -naltexol, which is less active than naltrexone as an antagonist but prolongs the action of naltrexone. Excretion of the metabolites requires adequate renal function, since excretion by routes other than the urine are of minor importance.

Cellular Mechanisms of Action

Opioid receptors are members of the G protein superfamily of receptors. Drug-induced interaction with these receptors is associated with a decrease in activation of the enzyme adenylyl cyclase and a subsequent decrease in cyclic adenosine monophosphate (cAMP) levels in the cell. Binding of opioids to their receptors produces a decrease in calcium entry to cells by decreasing the phosphorylation of the voltage operating calcium channels and allows for increased time for the channels to remain closed. In addition, activation of opioid receptors leads to potassium efflux, and the resultant hyperpolarization limits the entry of calcium to the cell by increasing the negative charge of the membrane to levels at which these calcium channels fail to activate. *The net result of the cellular decrease in calcium is a decrease in the release of dopamine, serotonin, and nociceptive peptides, such as substance P, resulting in blockade of nociceptive transmission.*

Pharmacological Effects Analgesia

Opioid agonists interact with receptors in the brain and in the spinal cord. The initial binding of opioids in the brain causes the release of the inhibitory neurotransmitter serotonin, which in turn induces inhibition of the dorsal horn neurons. Both the brain and the spinal cord are required for the production of a maximal analgesic effect following systemic administration of opioids, although analgesia can be elicited by spinal administration only. In the spinal cord, morphine inhibits the release of most nociceptive peptides. Morphine also affects descending noradrenergic pathways. Norepinephrine release in response to opioid administration results in an analgesic effect at the spinal level.

Opioids have profound effects upon the cerebrocortical regions that control the somatosensory and discriminative aspects of pain. Thus, the *opioids suppress the perception of pain by eliminating or altering the emotional aspects of pain and inducing euphoria and sleep*

with higher doses. Patients become inattentive to the painful stimuli, less anxious, and more relaxed. Disruption of normal REM sleep occurs with opioid administration. In addition, opioids depress polysynaptic responses but can increase monosynaptic responses and lead to convulsant effects in high doses. In patients with chronic pain, the euphoric effect of opioids, mediated by the μ -receptor, is usually blunted. Some patients feel a dysphoric effect upon the administration of opioids, which is most likely mediated by the σ -receptor.

Medullary Effects

Opioids depress respiration via the μ_2 -receptor at the level of the medulla and thereby increase PCO_2 . Opioids reduce respiration, an effect that is fatal in the case of overdose, by a dual action. *The opioids decrease both the sensitivity of the medulla to carbon dioxide concentrations and the respiratory rate.* Cardiovascular function and the response to hypoxia are not compromised. By contrast, *tolerance to the respiratory depressant effects of the opioids does not appear to occur*, while tolerance to the emetic effects of the opioids occurs upon repeated administration. The area postrema chemoreceptor trigger zone of the medulla mediates opioid-induced vomiting.

Miosis

Miosis, or the pinpoint pupillary response to the opioids, is diagnostic of the use and abuse of the opioids. No tolerance to such an effect is observed. Miosis is due to disinhibition of the Edinger-Westphal nucleus in the cortex resulting in increased pupillary constrictor tone.

Hypothalamic Effects

The opioids have pronounced effects on the release of hormones from both the pituitary and the hypothalamus. Stimulation of some of the opioid receptors in hypothalamic nuclei decrease the release of dopamine, thus increasing release of prolactin. Opioids bind in the supraoptic nuclei of the hypothalamus and increase the release of antidiuretic hormone (vasopressin).

GI Effects

Morphine and most other opioids produce some degree of constipation by increasing sphincter tone and decreasing gastric motility. Such an effect is uncomfortable for patients required to take opioids chronically. Tolerance to the constipative effects of the opioids does not generally occur. In addition, the decrease in gastric motility increases gastric emptying time and reduces absorption of other drugs. The constriction of sphincters, especially the bile duct, may result in increased pain in certain patients with biliary colic or other GI distress. Constriction of the urinary sphincter can lead

to painful urine retention in some patients. The effects of opioids on the GI tract are largely mediated by the parasympathetic release of acetylcholine. All of the opioid receptors have been shown to mediate such GI effects.

Immune Function and Histamine

Opioids induce the release of histamine, which leads to the itching sensation associated with use and abuse of opioids. Bronchiolar constriction is possible. Opioids are also immunosuppressive, having effects on the T-helper and T-suppressor cells.

Antitussive Effects

The opioids block cough by a mechanism that is not yet understood. No stereoselectivity of the opioids for blockade of the cough reflex has been shown. Thus, the isomers of opioids, such as dextroprhan, are as efficacious as the L-isomers as antitussives. *This lack of stereoselectivity prompted the development of the D-isomers of opioids as antitussives since they are devoid of the dependence liability of L-isomers.* Drugs with predominantly antitussive effects are described later in this chapter. Certain of the opioids, such as propoxyphene and meperidine, are relatively devoid of antitussive effects.

Tolerance and Physical Dependence

All of the opioid agonists produce some degree of tolerance and physical dependence. The biochemical mechanisms underlying tolerance and physical dependence are unclear. It is known, however, that intracellular mechanisms of tolerance to opioids include increases in calcium levels in the cells, increased production of cAMP, decreased potassium efflux, alterations in the phosphorylation of intracellular and intranuclear proteins, and the resultant return to normal levels of release of most neurotransmitters and neuromodulators. Tolerance to the analgesic effects of opioids occurs rapidly, especially when large doses of the drugs are used at short intervals. However, tolerance to the respiratory depressant and emetic effects of the opioids occurs more slowly. The miotic and constipative effects of the opioids rarely show tolerance.

Tolerance to one opioid usually renders a patient cross-tolerant to other opioids but not to drugs of other classes. Within the opioid class of drugs, certain drugs with high intrinsic activity (e.g., fentanyl) appear to lack cross-tolerance to opioids of lower intrinsic activity (e.g., morphine), an effect thought to be related to the change in receptor number induced by the chronic opioid administration. Theoretically, a drug with high intrinsic activity would need to occupy fewer receptors to exert an effect and would be less affected by changes in

receptor number, which occurs upon chronic administration of drugs with lower intrinsic activity.

The cessation of opioid drug administration leads to an observable abstinence syndrome. In the case of the opioids, signs of withdrawal include chills, fever, sweating, yawning, vomiting, diarrhea, nausea, dizziness, and hypertension. The onset of symptoms occurs 6 to 12 hours after the last drug dose (depending on the kinetics of the drug) and continues for several days, with most of the signs of withdrawal ending by 72 hours after the last dose of the drug. However, signs of withdrawal, including restlessness, anxiety, and drug craving, may be detectable for 6 months to 1 year after cessation of drug use.

In general, the effects observed upon withdrawal from a drug are opposite to those observed when the person is taking the drug, and such is the case with the opioids. The degree of dependence is generally reflected by the severity of withdrawal signs. In addition, drugs with long half-lives, such as methadone, produce a gradual and prolonged withdrawal. The use of methadone replacement for heroin is based upon the pharmacokinetics of methadone. The longer onset and duration of action and the oral bioavailability render the drug useful for the treatment of opioid addiction by decreasing the rapid highs and lows associated with fast-onset, short-duration drugs such as heroin. Drugs with a short duration of action produce a more rapid onset of withdrawal signs.

A derivative of methadone, L- α -acetyl-methadol (LAAM) has been approved for the treatment of opioid addiction. In some addicts whose degree of tolerance is not known, the patient is first given methadone to stabilize the withdrawal signs and is then switched to LAAM. LAAM has an advantage over methadone in that it has a longer duration of action. Dosing is required only three times per week in most addicts to prevent withdrawal.

Babies born to opioid-addicted women also exhibit withdrawal signs, but because of the slower metabolism of opioids in the newborn, the withdrawal signs are more protracted. The babies are often treated with the opium preparation paregoric to reduce withdrawal signs.

Other treatments for opioid addiction are described in detail in Chapter 35.

Morphine Clinical Uses

Morphine remains the standard by which other analgesic drugs are compared. The predominant effects of morphine are at the μ -opioid receptor, although it interacts with other opioid receptors as well. Morphine is indicated for the treatment of moderate to severe and chronic pain. It is useful preoperatively for sedation,

anxiolytic effects, and to reduce the dose of anesthetics. Morphine is the drug of choice for the treatment of myocardial infarction because of its bradycardiac and vasodilatory effects. In addition, morphine is the most commonly used drug for the treatment of dyspnea-associated pulmonary edema. It is thought that morphine reduces the anxiety associated with shortness of breath in these patients along with the cardiac preload and afterload.

The use of morphine via the oral route has drawbacks because of its first-pass effect; however, oral morphine has been recommended for use in cancer patients for its ease of administration. In particular, the long-acting preparations of morphine, such as *MS-Contin* and *Ora-Morph*, are described as the cornerstone of pain treatment in cancer patients, either alone or in combination with nonopioids.

Morphine is the most commonly used analgesic drug administered via the epidural route because it is potent, efficacious, and hydrophilic. The more hydrophilic the drug, the slower the onset and the longer the duration of action following epidural administration. Single-dose or continuous infusion of morphine is used to provide pain relief in thoracic and abdominal surgical patients and in cancer patients at high risk for developing side effects associated with systemic opioids. Since morphine does not produce anesthesia via the epidural route, the patient is able to move about normally; motor function is preserved. The drawback to epidural use of morphine is that certain types of pain are relatively unresponsive, such as that associated with visceral stimuli, as in pancreatitis, and neuropathic pain from nerve deafferentation. In addition, patients can develop respiratory depression and nausea from the rostral flow of the drug to medullary centers, although the effects are much less severe than those observed following the systemic administration of the drug, and can be alleviated by elevation of the head of the patient at a 30-degree angle. Patients may also itch because of histamine release.

Patient-controlled analgesia (PCA) is an alternative method of administration of morphine. The use of an indwelling catheter allows the patient to administer the drug at frequent intervals for pain relief. PCA systems allow patients the freedom to assess the need for their own analgesia and to titrate a dose tailored to their needs. Dependence is rarely observed in patients using PCA for acute pain management.

Adverse Effects and Contraindications

The opioids generally have a high level of safety when used in therapeutic dosages. However, there are several notable exceptions. Morphine and other opioids are contraindicated in patients with hypersensitivity reactions to the opioids. In addition, morphine should not be used in patients with acute bronchial asthma and should

not be given as the drug of first choice in patients with pulmonary disease, because it has antitussive effects that prevent the patient from clearing any buildup of mucus in the lungs. Opioids with less antitussive effects, such as meperidine, are better for such situations.

When used via the epidural route, the site for injection must be free of infection. In addition, the use of corticosteroids by the patient should be halted for at least 2 weeks prior to the insertion of the catheter to prevent infection, since morphine increases the immunosuppressive effects of the steroids.

Opioids are contraindicated in head trauma because of the risk of a rise in intracranial pressure from vasodilation and increased cerebrospinal fluid volume. In addition, in such patients the onset of miosis following opioid administration can mask the pupillary responses used diagnostically for determination of concussion.

The clearance of morphine and its active metabolite, morphine-6-glucuronide depends on adequate renal function. The elderly are particularly susceptible to accumulation of the drugs, hence respiratory depression and sedation. Morphine, like all opioids, passes through the placenta rapidly and has been associated with prolongation of labor in pregnant women and respiratory depression in the newborn.

Morphine and other opioids exhibit intense sedative effects and increased respiratory depression when combined with other sedatives, such as alcohol or barbiturates. Increased sedation and toxicity are observed when morphine is administered in combination with the psychotropic drugs, such as chlorpromazine and monoamine oxidase inhibitors, or the anxiolytics, such as diazepam.

Respiratory depression, miosis, hypotension, and coma are signs of morphine overdose. While the IV administration of naloxone reverses the toxic effects of morphine, naloxone has a short duration of action and must be administered repeatedly at 30- to 45-minute intervals until morphine is cleared from the body.

Codeine and Other Phenanthrene Derivatives

Like morphine, codeine is a naturally occurring opioid found in the poppy plant. Codeine is indicated for the treatment of mild to moderate pain and for its antitussive effects. It is widely used as an opioid antitussive because at antitussive doses it has few side effects and has excellent oral bioavailability. *Codeine is metabolized in part to morphine, which is believed to account for its analgesic effect.* It is one of the most commonly used opioids in combination with nonopioids for the relief of pain. The administration of 30 mg of codeine in combination with aspirin is equivalent in analgesic effect to the administration of 65 mg of codeine. The combination of the drugs has the advantage of reducing the

amount of opioid required for pain relief and abolition of the pain via two distinct mechanisms, inhibition of prostanoid synthesis and opioid inhibition of nociceptive transmission. When given alone, orally administered codeine has about one-tenth to one-fifth the potency of morphine for the relief of pain. In addition, IV codeine has a greater tendency to release histamine and produce vasodilation and hypotension than does morphine. Thus, the use of IV codeine is rare. Codeine is rarely addictive and produces little euphoria.

Adverse effects and drug interactions with codeine are similar to those reported for morphine, although they are less intense. Overdose in children results in the same effects as overdose of morphine, such as respiratory depression, miosis, and coma; these symptoms are treated with naloxone administration.

Hydrocodone (*Hycodan*), oxycodone (*Roxicodone*), dihydrocodeine, hydromorphone (*Dilaudid*), and oxymorphone (*Numorphan*) are derivatives of codeine and morphine. All are indicated for the relief of mild to severe pain or for their antipyretic effects; they are often used in combination with nonopioid analgesics. The drugs vary in potency, but their pharmacological effects do not differ significantly from those of codeine or morphine.

Hydromorphone is eight times as potent as morphine but has less bioavailability following oral administration. Its side effects do not differ from those of morphine but are more intense. Hydromorphone is indicated for use in severe pain and in high doses for relief of pain in opioid-addicted patients.

Oxycodone is nearly 10 times as strong as codeine, with absorption equal to that of orally administered morphine. Neither hydromorphone nor oxycodone is approved for use in children, and hydromorphone is contraindicated in obstetrical analgesia and in asthmatics.

Oxymorphone is 10 times as potent as morphine, with actions similar to those of hydromorphone. Oxymorphone, however, has little antitussive activity, and as such is a useful analgesic in patients with pulmonary disease who need to retain the ability to cough.

Meperidine and Related Phenylpiperidine Derivatives

Clinical Uses and Adverse Effects

Meperidine (*Demerol*) is a phenylpiperidine derivative of morphine that was developed in the late 1930s as a potential anticholinergic agent. It has some anticholinergic side effects that lead to tachycardia, blurred vision, and dry mouth. Meperidine is approximately one-fifth as potent as morphine and is absorbed only half as well when administered orally as parenterally. It has a rapid onset and short duration of action (2 hours), that is, approximately one-fourth that of morphine.

Like morphine, meperidine has an active metabolite, normeperidine, formed by *N*-demethylation of meperidine. Normeperidine is not analgesic but is a proconvulsant and a hallucinogenic agent. For this reason, meperidine use in patients with renal or liver insufficiency is contraindicated because of the decreased clearance of the drug and its metabolite. Convulsant activity has been documented in elderly patients given meperidine and in patients using PCA who have decreased renal function.

Meperidine differs from morphine in that it has far less antitussive effect and little constipative effect. The drug is particularly useful in cancer patients and in pulmonary patients, in whom the cough reflex must remain intact. However, it does have more seizure-inducing activity than morphine. Although meperidine produces spasms of the biliary tract and colon, such spasms are of shorter duration than those produced by morphine.

Meperidine readily passes the placenta into the fetus. However, respiratory depression in the newborn has not been observed, and meperidine clearance in the newborn is rapid in that it does not rely upon conjugation to glucuronides. Meperidine, unlike morphine, has not been associated with prolongation of labor; conversely, it increases uterine contractions.

Symptoms of overdose with meperidine are qualitatively different from those of morphine in that seizures rather than sedation are common. Respiratory depression and miosis are present. While naloxone reverses overdose-associated toxicity, its use in patients who have received large, frequent doses of meperidine may precipitate seizures.

Diphenoxylate (*Lomotil*) is a meperidine derivative used as an antidiarrheal. It exhibits no morphinelike effects at low doses, but it produces mild opioid effects, such as sedation, euphoria, and dependence, at higher doses. Its salts are highly insoluble in water, which reduces recreational use. Preparations often include atropine.

Difenoxin is a metabolite of diphenoxylate with antidiarrheal effects similar to the parent drug. Loperamide (*Imodium*) is a piperidine derivative of diphenoxylate, which acts both at the level of the gut and also in the CNS to reduce GI motility. Its use as an antidiarrheal and its potency are similar to those of diphenoxylate.

Contraindications

Contraindications are similar to those of morphine. In addition, because normeperidine accumulates in renal dysfunction and meperidine accumulates in hepatic dysfunction, meperidine is contraindicated in such patients because of convulsant effects. Similarly, the use of meperidine is contraindicated in patients who have a

history of seizures or who are taking medication to prevent seizures. Phenytoin administered for seizures may reduce the effectiveness of meperidine by increasing the metabolism of the drug in the liver. Meperidine is not generally used in patients with cardiac dysfunction, since its anticholinergic effects can increase both heart rate and ectopic beats.

Fentanyl, Sufentanil, and Alfentanil Clinical Uses and Pharmacological Effects

Fentanyl (*Sublimaze*) and its related phenylpiperidine derivatives are extremely potent drugs. They are used as adjuncts to anesthesia, and fentanyl may be given transdermally as an analgesic and as an oral lozenge for the induction of anesthesia, especially in children who may become anxious if given IV anesthesia.

Fentanyl is 80 to 100 times as potent as morphine. Sufentanil (*Sufenta*) is 500- to 1,000-fold more potent than morphine, while alfentanil (*Alfenta*) is approximately 20 times more potent than morphine. Their onset of action is usually less than 20 minutes after administration. Dosage is determined by the lean body mass of the patient, since the drugs are lipophilic and tend to get trapped in body fat, which acts as a reservoir, prolonging their half-life. In addition, redistribution of the drugs from the brain to fat stores leads to a rapid offset of action. Droperidol, a neuroleptic agent, is generally administered in combination with fentanyl for IV anesthesia.

Fentanyl transdermal patches are available for analgesia in chronic pain and for postsurgical patients. The use of the patch is contraindicated, however, for patients immediately after surgery because of the profound respiratory depression associated with its use. The patches must be removed and replaced every 3 days. The onset of action of transdermal fentanyl is slower than that of oral morphine. Thus, patients may require the use of oral analgesics until therapeutic levels of fentanyl are achieved. Fentanyl lozenges have been used to induce anesthesia in children and to reduce pain associated with diagnostic tests or cancer in adult patients. However, all of the adverse side effects associated with morphine are produced with far greater intensity, but shorter duration, by fentanyl in the patch, the lozenge, or IV administration. Given the abuse liability of fentanyl, controversy exists as to the ethics of marketing a lollipop lozenge form.

Sufentanil is much more potent than fentanyl and is indicated specifically for long neurosurgical procedures. In such patients, sufentanil maintains anesthesia over a long period when myocardial and cerebral oxygen balance are critical.

Fentanyl is commonly used to relieve pain from intubation of premature infants, although the safety of the

drug in infants has not been established. Sufentanil has been studied to a limited extent in newborns, and reports indicate that it can be used safely. Tolerance and physical dependence have been demonstrated after prolonged use of fentanyl in the newborn.

Adverse Effects and Contraindications

In addition to all of the adverse effects and contraindications previously described for morphine, the following contraindications apply specifically to these drugs. They are contraindicated in pregnant women because of their potential teratogenic effects. They also can cause respiratory depression in the mother, which reduces oxygenation of fetal blood, and in the newborn; the incidence of sudden infant death syndrome (SIDS) in the newborn is also increased.

Cardiac patients need to be monitored closely when receiving these drugs because of their bradycardiac effects (which can lead to ectopic arrhythmias), and hypotensive effects resulting from prolonged vasodilation. In addition, the drugs stiffen the chest wall musculature, an effect reversed by naloxone.

Levorphanol

Levorphanol (*Levo-Dromoran*) is an L-isomer morphinan derivative of morphine that is five to seven times more potent than morphine. It produces all of the side effects associated with morphine but less nausea. It is indicated for moderate to severe pain as a preoperative anxiolytic. It is often used in combination with thiopental to reduce the latter drug's anesthetic dose and to decrease postoperative recovery time. The D-isomer of levorphanol, dextrorphan, does not possess opioid analgesic activity but is a useful antitussive.

Methadone

Methadone (*Dolophine*) has an analgesic profile and potency similar to that of morphine but a longer duration of action and better oral bioavailability. The kinetic properties of methadone and its derivative, LAAM, have been shown to be useful in the treatment of opioid addiction, as discussed in Chapter 35.

Methadone is a useful analgesic drug for the treatment of moderate to severe pain. Unlike morphine, it is generally not used epidurally because of its long duration of action. It is also rarely or never used in PCA systems or in pregnant women during labor. The side effects and signs of overdose following methadone administration are similar to those observed with morphine. Overdose is treated with naloxone. Clearance of methadone is via the urine and bile as the cyclic *N*-demethylated drug. The ability to *N*-demethylate the drug decreases in elderly patients, prolonging the action

of methadone. In such patients, dosing intervals should be longer than in younger patients. In addition, the pH of the urine has a major effect on clearance of the drug. Alkalinization of the urine or renal insufficiency decreases excretion of the drug.

Drug interactions and precautions for the use of methadone are similar to those of morphine. In addition, rifampicin and hydantoin markedly increase the metabolism of methadone and can precipitate withdrawal from methadone. Conversely, the tricyclic antidepressants and certain benzodiazepines can inhibit metabolism of methadone, thereby increasing accumulation of the drug, prolonging its half-life, and intensifying its side effects. Continuous dosing with methadone may lead to drug accumulation and to an increased incidence of side effects; methadone is generally not used for PCA. In pregnant heroin-addicted women, substitution of methadone for heroin has been shown to be associated with fewer low-birth-weight newborns and fewer learning and cognition problems later in the life of the child.

Propoxyphene

Propoxyphene (dextropropoxyphene; *Darvon*) is structurally related to methadone but is much less potent as an analgesic. Compared with codeine, propoxyphene is approximately half as potent and is indicated for the treatment of mild pain. *It is not antipyretic or antiinflammatory like aspirin and is less useful than aspirin in most cases of mild pain.* Toxicity from propoxyphene, especially in combination with other sedatives, such as alcohol, has led to a decrease in its use. Death following ingestion of alcohol in combination with propoxyphene can occur rapidly (within 20 minutes to 1 hour). The drug is not indicated for those with histories of suicide or depressive illnesses.

Like meperidine, propoxyphene has an active metabolite, norpropoxyphene, that is not analgesic but has excitatory and local anesthetic effects on the heart similar to those of quinidine. Use of the drug during pregnancy is not safe. Teratogenic effects have been observed in newborns, as have withdrawal signs at birth. As with morphine, propoxyphene requires adequate hepatic and renal clearance to prevent toxicity and drug accumulation. It is thus contraindicated in the elderly patient and those with renal or liver disease.

Propoxyphene interacts with several drugs. The use of sedatives in combination with propoxyphene can be fatal. In addition, the metabolism of the drug is increased in smokers due to induction of liver enzymes. Thus, smokers may require a higher dose of the drug for pain relief. Propoxyphene enhances the effects of both warfarin and carbamazepine and may increase the toxicity associated with both drugs, such as bleeding and sedation, respectively.

The abuse liability of propoxyphene is low because of the extreme irritation it causes at the site of injection. Oral use is the preferred route of administration for this reason.

Opium-Containing Preparations

The use of opium dates to 4,000 B.C. At that time it was used for medicinal and recreational purposes mainly via inhalation. Today few opium-containing preparations are used, since the activity of opium is largely attributed to its morphine content. The preparations in use today are those that have constipative effects useful for the treatment of diarrhea. Preparations include pantopon, an injectable hydrochloride of opium alkaloids, and paregoric, a camphorated tincture of opium. Paregoric can be used to treat infants with opioid withdrawal signs following in utero exposure to opioids.

Heroin

Heroin is the diacetyl derivative of morphine. It is not available in the United States for therapeutic use, although its use as a recreational drug is again on the rise. It is either injected or snorted (taken intranasally). It is most often cut, or diluted, with substances such as quinine, which contribute to the flash, or high. Injection of the drug leads to the eventual collapse of the vessels into which it is injected, leading to the appearance of track marks under the skin. Heroin passes rapidly into the brain and thus has a rapid onset of action. It is then metabolized to morphine. The rapid onset contributes to the abuse liability of the drug. Heroin use in pregnant women can lead to low-birth-weight babies, babies born addicted to heroin, immunosuppression, and an increased incidence of infections in both the mother and newborn; an increased incidence of AIDS also occurs.

Mixed Opioid Agonist–Antagonists or Partial Agonists

The mixed opioid agonist–antagonists are potent analgesics in opioid-naïve patients but precipitate withdrawal in patients who are physically dependent on opioids. They are useful for the treatment of mild to moderate pain. They were developed to reduce the addiction potential of the opioids while retaining the analgesic potency of the drugs. Their analgesic effect is generally attributed to an interaction at the κ - and to a lesser extent the μ -opioid receptor.

Interaction at the κ -receptor increases the sedative effects of the drugs. The euphoric effects are due to interaction with the μ -receptor. The dysphoric and psychotomimetic side effects of the drugs are attributed to interaction at the σ -receptor.

The mixed agonist–antagonists and partial agonists differ from morphine in that they (1) produce excita-

tory and hallucinogenic effects, (2) produce a low degree of physical dependence, (3) induce withdrawal signs that differ from those of morphine, and (4) produce excitatory effects related to the sympathetic discharge of norepinephrine and therefore are positive inotropic agents in the heart.

Pentazocine

Pharmacological Effects

Pentazocine (*Talwin*) is a potent analgesic with antagonistic activity in opioid-addicted patients. It incompletely blocks the effects of morphine in such patients but will precipitate withdrawal. To eliminate abuse of the drug via IV administration, pentazocine is combined with naloxone (*Talwin-NX*). IV administration of *Talwin-NX* will produce no analgesic or euphoric effects because naloxone blocks the pentazocine moiety. However, the drug will retain its analgesic potency when administered orally, since naloxone is not active orally. Pentazocine produces as much respiratory depression as morphine but does not produce the same degree of constipation or the biliary constriction observed with morphine. Pentazocine may increase GI motility if used in high doses. Unlike morphine, pentazocine increases heart rate and blood pressure by releasing norepinephrine. Pentazocine also may increase uterine contractions in pregnancy.

Pharmacokinetics

Absorption of pentazocine following oral administration is rapid. The onset of action occurs within approximately 15 minutes, and the half-life is 2 to 3 hours. Pentazocine is extensively metabolized in the liver and thus has a high first-pass effect following oral administration; its half-life differs considerably from patient to patient. Oxidation of the methyl groups followed by conjugation to glucuronides in the liver terminates the effects of pentazocine. Excretion occurs through the kidney.

Clinical Uses

Pentazocine is indicated for relief of moderate pain in patients not receiving large doses of opioids. It is also used as premedication for anesthesia and as a supplement to surgical anesthesia.

Adverse Effects

The most common side effect of pentazocine is sedation resulting from an interaction with the κ -receptor. Also observed are sweating, dizziness, psychotomimetic effects, anxiety, nightmares, and headache. Nausea and vomiting are less frequent than with morphine. Respiratory depression and increased heart rate, body temperature, and blood pressure accompany overdose. Naloxone is effective in reducing the respiratory depression but requires the use of higher doses than for morphine overdose.

Contraindications

Most of the contraindications specific to pentazocine stem from its excitatory effects. Other contraindications are similar to those for morphine. Pentazocine is contraindicated in patients with myocardial infarction because it increases heart rate and cardiac load. Similarly, it is contraindicated in epileptic patients because it decreases seizure threshold. In addition, in head trauma patients, it can increase intracranial pressure and brain injury. Pentazocine use in patients with psychoses is contraindicated because of its psychotomimetic side effects.

Drug Interactions

The combination of pentazocine with the antihistamine tripeleminamine results in a combination known to drug abusers as T's and blues. This combination produces heroinlike subjective effects, and heroin addicts use it in the absence of heroin. In addition, the use of pentazocine in combination with alcohol or barbiturates greatly enhances its sedative and respiratory depressant effects.

Tolerance and Dependence

Tolerance to the analgesic effects of pentazocine develops. Withdrawal signs are milder than those seen with morphine, and they produce more excitatory effects.

Butorphanol

Butorphanol (*Stadol*) is chemically related to levorphanol but pharmacologically similar in action to pentazocine. As an opioid antagonist it is nearly 30 times as potent as pentazocine and has one-fortieth the potency of naloxone. It is a potent opioid analgesic indicated for the relief of moderate to severe pain. Its potency is 7 times that of morphine and 20 times that of pentazocine as an analgesic. Its onset of action is similar to that of morphine. The side effects and signs of toxicity are similar to those produced by pentazocine. It produces excitatory effects and sedation and precipitates withdrawal in opioid-dependent patients. Although generally administered parenterally because of its low bioavailability following oral administration, it is also unique in that a nasal spray formulation is available. The nasal spray is indicated for the relief of postoperative pain and migraine headache. The low molecular weight of butorphanol, its high lipophilicity, and its lack of vasoconstrictor effects make it particularly suitable for nasal administration.

Nasal administration of butorphanol decreases the onset of action to 15 minutes and decreases the first-pass effect of the drug, which increases bioavailability. Generally the patient sprays a set dose of 1 mg per hour for 2 hours. The duration of action is 4 to 5 hours. The convenience of such administration is a major

advantage to patients requiring repeat dosing. The abuse potential following such administration has not been extensively studied, although it is thought to be small. Butorphanol is not a federally controlled (“scheduled”) drug, so physicians are not required to obtain the licenses and security safeguards required for other opioid analgesics.

Adverse effects, contraindications, and drug interactions are similar to those for pentazocine and morphine.

Nalbuphine

Nalbuphine (*Nubain*) is a mixed agonist–antagonist that is similar in structure to both the antagonist naloxone and the agonist oxymorphone. It is administered parenterally and is equipotent to morphine and 5 times as potent as pentazocine. Although the pharmacological effects (analgesia, respiratory depression, sedation, and so on) are similar to those produced by pentazocine, nalbuphine produces fewer psychotomimetic effects. It differs from pentazocine in that it has far greater antagonist than agonist effect. Thus, its use is likely to precipitate severe withdrawal in opioid-dependent patients. It is used much as pentazocine is, that is, for moderate to severe pain, postsurgical anesthesia, and obstetrical analgesia. Nalbuphine’s abuse potential is less than that of codeine and propoxyphene, although tolerance and dependence have been shown following chronic administration. High doses are perceived by addicts as being like those of the barbiturates. Drug interactions and contraindications are similar to those for pentazocine and morphine.

Buprenorphine

Buprenorphine (*Temgesic*) is a mixed agonist–antagonist and a derivative of the naturally occurring opioid thebaine. Buprenorphine is highly lipophilic and is 25 to 50 times more potent than morphine as an analgesic. The sedation and respiratory depression it causes are more intense and longer lasting than those produced by morphine. Its respiratory depressant effects are not readily reversed by naloxone. It binds to the μ -receptor with high affinity and only slowly dissociates from the receptor, which may explain the lack of naloxone reversal of respiratory depression.

Buprenorphine has more agonist than antagonist effects and is often considered a partial agonist rather than a mixed agonist–antagonist, although it precipitates withdrawal in opioid-dependent patients. Its pharmacological effects are similar to those produced by both morphine and pentazocine. Indications for its use are similar to those of pentazocine, that is, for moderate to severe pain. Sublingual preparations are available, but have a slow onset and erratic absorption.

The abuse potential of buprenorphine is low. While high doses of the drug are perceived by addicts as being

morphinelike, it does reduce the craving for morphine and for the stimulant cocaine. Thus, buprenorphine is a potential new therapy for the treatment of addiction to both classes of drugs.

Drug interactions and contraindications are similar to those described for pentazocine and morphine.

Dezocine

Dezocine (*Dalgan*) is a synthetic aminotetralin derivative with potent agonist–antagonist effects. The onset of activity and potency as an analgesic are comparable to those of morphine. Although the drug requires glucuronidation during metabolism, patients with hepatic insufficiency clear it normally. The main route for clearance is the kidney. Thus, patients with renal dysfunction are prone to buildup of dezocine over time. As an antagonist, dezocine is more potent than pentazocine. As an agonist, dezocine produces analgesia and respiratory depression (which is readily reversed by naloxone), but unlike pentazocine, it has little if any effect on the cardiovascular system.

Dezocine is indicated as an analgesic for moderate to severe pain. In addition, it shows promise in chronic pain states, such as with victims of severe burns. Contraindications and adverse effects of the drug are similar to those described for morphine. No tendency toward abuse has been demonstrated thus far.

Opioid Antagonists

Naloxone and naltrexone are pure opioid antagonists synthesized by relatively minor changes in the morphine structure. Alteration of the substituent on the piperidine nitrogen from a methyl group to a longer side chain changes the drug from an agonist to an antagonist.

Opioid antagonists bind to the opioid receptor with high affinity and have low efficacy. The pure antagonists block the effects of opioids at all opioid receptors. However, as previously discussed, the dose required for naloxone blockade of the μ -receptor versus the κ -opioid receptor is several times as much. All opioid antagonists will precipitate withdrawal in opioid-dependent patients.

Naloxone

Because of its fast onset (minutes), naloxone (*Narcan*) administered IV is used most frequently for the reversal of opioid overdose. However, it fails to block some side effects of the opioids that are mediated by the σ -receptor, such as hallucinations. The rapid offset of naloxone makes it necessary to administer the drug repeatedly until the opioid agonist has cleared the system to prevent relapse into overdose. The half-life of naloxone in plasma is 1 hour. It is rapidly metabolized via

glucuronidation in the liver and cleared by the kidney. Naloxone given orally has a large first-pass effect, which reduces its potency significantly. Often an overshoot will follow the administration of naloxone for overdose. The heart rate and blood pressure of the patient may rise significantly. The overshoot is thought to be due to precipitation of acute withdrawal signs by naloxone. Given alone to nonaddicts, naloxone produces no pharmacological effects.

Naloxone is approved for use in neonates to reverse respiratory depression induced by maternal opioid use. In addition, naloxone has been used to improve circulation in patients in shock, an effect related to blockade of endogenous opioids. Other experimental and less well documented uses for naloxone include reversal of coma in alcohol overdose, appetite suppression, and alleviation of dementia from schizophrenia. Side effects of naloxone are minor.

Naltrexone

Naltrexone (*Trexan*) is three to five times as potent as naloxone and has a duration of action of 24 to 72 hours, depending on the dose. It is used orally in the treatment of opioid abstinence. Naltrexone exhibits a large first-pass effect in the liver. However, the major metabolite, 6- β -naltrexol, is also a pure opioid antagonist and contributes to the potency and duration of action of naltrexone. Administration of naltrexone orally blocks the subjective effects of abused opioids and is used to decrease the craving for opioids in highly motivated recovering addicts. However, high doses of the opioids can overcome the naltrexone blockade and lead to seizures or respiratory depression and death. In addition, it has been reported recently that naltrexone can reduce the craving for alcohol in alcoholic patients. Naltrexone also has been used with success in treating apneic episodes in children, an effect hypothesized to be due to blockade of β -endorphin-induced respiratory depression.

Naltrexone can induce hepatotoxicity at doses only five times the therapeutic dose and should be used with care in patients with poor hepatic function or liver damage. Side effects of the use of naltrexone are more frequently observed than following naloxone administration. Such side effects include headache, difficulty sleeping, lethargy, increased blood pressure, nausea, sneezing, delayed ejaculation, blurred vision, and increased appetite.

Nalmefene

Nalmefene (*Revex*) is a long-acting injectable pure opioid antagonist recently introduced in the United States. It binds all opioid receptors and reverses the effects of opioid agonists at those receptors. The onset of action is

2 minutes after IV administration. Hepatic metabolism is slow and occurs via glucuronide conjugation to inactive metabolites. Its half-life of 11 hours is about 5 times that of naloxone. Indications include use in postoperative settings to reverse respiratory depression and in opioid overdose. Due to the long duration of action of nalmefene, however, naloxone may be preferred for treatment of overdose because it produces a shorter duration of withdrawal effects.

Drugs Used Predominantly as Antitussives

Certain opioids are used mainly for their antitussive effects. Such drugs generally are those with substituents on the phenolic hydroxyl group of the morphine structure. The larger the substituent, the greater the antitussive versus analgesic selectivity of the drugs.

Dextromethorphan

Dextromethorphan hydrobromide is the D-isomer of levorphanol. It lacks CNS activity but acts at the cough center in the medulla to produce an antitussive effect. It is half as potent as codeine as an antitussive. Anecdotal reports of abuse exist, but studies of abuse potential are lacking. It has few side effects but does potentiate the activity of monoamine oxidase inhibitors, leading to hypotension and infrequently coma. Dextromethorphan is often combined in lozenges with the local anesthetic benzocaine, which blocks pain from throat irritation due to coughing.

Levopropoxyphene

Levopropoxyphene is the L-isomer of the analgesic agonist dextropropoxyphene. Levopropoxyphene is only mildly antitussive and is rarely used. It has no CNS effects. Side effects include dizziness and nausea. It is available as the napsylate derivative (*Novrad*) and is taken orally in the form of a liquid or less frequently as a capsule.

Noscapine

Noscapine is a naturally occurring product of the opium poppy. It is a benzyloisoquinoline with no analgesic or other CNS effects. Its antitussive effects are weak, but it is used in combination with other agents in mixtures for cough relief.

Benzonatate

Benzonatate (*Tessalon*) is related to the local anesthetic tetracaine. It anesthetizes the stretch receptors in the lungs, thereby reducing coughing. Adverse reactions include hypersensitivity, sedation, dizziness, and nausea.

Study QUESTIONS

- Which of the following opioids has an analgesically active metabolite?
 - Naloxone
 - Meperidine
 - Propoxyphene
 - Codeine
 - Nalmefene
- Which of the following statements about celecoxib is true?
 - It irreversibly acetylates the COX-2 enzyme.
 - It inhibits both the inducible and constitutive COX-2 enzyme.
 - It produces no GI bleeding.
 - It is indicated only for the disease, osteoarthritis.
 - It increases healing of GI ulcers.
- Morphine produces an analgesic effect due to
 - A block of potassium efflux from a neuron
 - An increase in c-AMP accumulation in a neuron
 - A decrease in intracellular calcium in a neuron
 - Interaction with a G_s protein in the neuron
 - An increase in calcium channel phosphorylation in the neuron
- κ-Opioid receptor activation is required to observe
 - Respiratory depression
 - Bradycardia
 - Miosis
 - Mydriasis
 - Hypocapnia
- Which of the following statements about fentanyl patches is true?
 - They produce no respiratory depression.
 - They produce anesthesia and analgesia.
 - They produce no constipation.
 - They can be used during pregnancy.
 - They cannot be used in nonambulatory patients.

ANSWERS

- D.** The purpose of this question is to identify first opioids that produce analgesia and then those with a metabolite that compounds the analgesic effects of the drug by being an active analgesic. Naloxone and nalmefene are not analgesics but opioid antagonists. Codeine is metabolized to an active analgesic metabolite, morphine. Meperidine and propoxyphene have nonanalgesic, excitatory, and proconvulsant metabolites.
- B.** The purpose of this question is to clarify the uses and limitations of use of the COX-2 selective inhibitor celecoxib. Celecoxib, by inhibiting COX-2 reversibly, will block the activity of both injury-

inducible COX-2 and the small amount of constitutive COX-2. COX-2 inhibition has been shown to produce some GI bleeding, albeit less than with the nonselective COX inhibitors. If a patient has ulcerations and bleeding, COX-2 inhibitors will prolong healing by blocking the protective effects of COX-2 in the GI tract. Celecoxib is indicated for both osteoarthritis and rheumatoid arthritis.

- C.** The purpose of this question is to clarify the cellular mechanism of analgesia produced by morphine. First, morphine blocks the transmission of nociceptive impulses. In that case, the relevant question is how nociceptive impulses are transmitted via the release of pronociceptive neurotransmitters. The question then is to determine which intracellular process favors a block of release of neurotransmitters. The correct answer is C because calcium is required for neurotransmitter release. Blocking potassium efflux and increasing calcium channel phosphorylation produce functional depolarization and neurotransmitter release. Opioids are coupled to G_i (inhibitory proteins) that decrease cAMP.
- C.** The purpose of this question is to clarify the functional significance of the activation of opioid receptor types. Respiratory depression and bradycardia are associated with the μ₂-opioid receptor. Mydriasis is associated with the σ-receptor, which is no longer thought of as opioid. Opioids, via respiratory depression, induce hypercapnia, a build-up of carbon dioxide. The clinically relevant sign of opioid overdose and opioid use is miosis, pinpoint pupils, mediated by κ-receptor activation.
- E.** Fentanyl patches have the same effect as fentanyl, only in a time-release manner. Thus, the purpose of the question is delineation of opioid effects—respiratory depression and constipation. The respiratory depression is life-threatening when the patch is used in nonambulatory patients, and it is therefore contraindicated for that purpose. Similarly, fentanyl is a teratogenic drug contraindicated for use during pregnancy. The fentanyl patch does not induce anesthesia (loss of consciousness) but does produce analgesia.

SUPPLEMENTAL READING

- Darland T et al. Orphanin FQ/nociceptin: A role in pain and analgesia, but so much more. *Trends Neurosci* 1998;21:215–221.
- Devi LA. Heterodimerization of G-protein-coupled receptors: Pharmacology, signaling and trafficking. *Trends Pharmacol Sci* 2001;22:532–537.

- Julius D and Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001;413:203–210.
- Marnett LJ and Kalutkar M. Cyclooxygenase 2 inhibitors: Discovery, selectivity and the future. *Trends Pharmacol Sci* 1999;20:465–469.
- Moran TD et al. Cellular neurophysiological actions of nociceptin/orphanin FQ. *Peptides* 2000;21:969–976.
- Tseng, L. Evidence for ϵ -opioid receptor-mediated β -endorphin-induced analgesia. *Trends Pharmacol Sci* 2001;22:623–630.
- Wallace JL. Selective COX-2 inhibitors: Is the water becoming muddy? *Trends Pharmacol Sci*. 1999;20: 4–6.
- Zadina JE et al. Endomorphins: novel endogenous mu-opiate receptor agonists in regions of high mu-receptor density. *Ann NY Acad Sci* 1999;897: 136–144.

CASE Study Opioids and Head Trauma

A 45-year-old woman is found outside her car after hitting a tree. The car appears severely damaged. There is no evidence as to how the woman escaped from the car. It is thought that she was able to open her door and then fell from the car. When she is discovered, she is conscious but disoriented and complaining of severe pain of multiple origins. While in route to the emergency department, her pain increases in intensity. Which opioid might be used to ease her pain immediately upon her arrival at the hospital?

ANSWER: No opioid should be used immediately. The use of an opioid at this stage will block the pupillary responses in her eyes due to miosis, which will detract from immediate diagnosis of a concussion. In addition, opioids will induce hypercapnia due to respiratory depression, vasodilation, bradycardia, and hypotension and make a patient in shock less stable. Such effects will be intensified if the woman was drinking prior to the accident. In addition, opioids increase intracranial pressure via hypercapnia and vasodilation, possibly increasing any damage to the brain. In general a patient in severe pain may be given a general anesthetic agent.