CHAPTER

10

Analgesic Agents

KEY CONCEPTS

1. The accumulation of morphine metabolites (morphine 3-glucuronide and morphine 6-glucuronide) in patients with kidney failure has been associated with narcosis and ventilatory depression lasting several days.
2. Rapid administration of larger doses of opioids (particularly fentanyl, sufentanil, remifentanil, and alfentanil) can induce chest wall rigidity severe enough to prevent adequate bag-and-mask ventilation.
3. Prolonged dosing of opioids can produce "opioid-induced hyperalgesia," in which patients become more sensitive to painful stimuli. Infusion of large doses of (in particular) remifentanil during general anesthesia can produce acute tolerance, in which much larger than usual doses of opioids are required for postoperative analgesia.
4. The neuroendocrine stress response to surgical stimulation is measured in terms of the secretion of specific hormones, including catecholamines, antidiuretic hormone, and cortisol. Large doses of opioids block the release of these hormones in response to surgery more completely than volatile anesthetics.
5. Aspirin is unique in that it irreversibly inhibits COX-1 by acetylating a serine residue in the enzyme. The irreversible nature of its inhibition underlies the nearly 1-week duration of its clinical effects (eg, return of platelet aggregation to normal) after drug discontinuation.

Regardless of how expertly surgical and anesthetic procedures are performed, appropriate prescription of analgesic drugs, especially opioids and cyclooxygenase (COX) inhibitors, can make the difference between a satisfied and an unsatisfied postoperative patient. Studies have shown that outcomes can be improved when analgesia is provided in a "multimodal" format (typically emphasizing COX inhibitors and local anesthetic techniques while minimizing opioid use) as one part of a well-defined and well-organized plan for postoperative care (see Chapter 48).

OPIOIDS

Mechanisms of Action

Opioids bind to specific receptors located throughout the central nervous system and other tissues. Four major opioid receptor types have been identified (Table 10–1): mu (μ, with subtypes μ_1 and μ_2), kappa (κ), delta (δ), and sigma (σ). All opioid receptors couple to G proteins; binding of an agonist to an opioid receptor causes membrane hyperpolarization. Acute opioid effects are mediated by inhibition of adenylyl cyclase (reductions in intracellular cyclic

TABLE 10–1 Classification of opioid receptors.[1]

Receptor	Clinical Effect	Agonists
μ	Supraspinal analgesia (μ_1) Respiratory depression (μ_2) Physical dependence Muscle rigidity	Morphine Met-enkephalin[2] β-Endorphin[2] Fentanyl
κ	Sedation Spinal analgesia	Morphine Nalbuphine Butorphanol Dynorphin[2] Oxycodone
δ	Analgesia Behavioral Epileptogenic	Leu-enkephalin[2] β-Endorphin[2]
σ	Dysphoria Hallucinations Respiratory stimulation	Pentazocine Nalorphine Ketamine

[1]Note: The relationships among receptor, clinical effect, and agonist are more complex than indicated in this table. For example, pentazocine is an antagonist at μ receptors, a partial agonist at κ receptors, and an agonist at σ receptors.

[2]Endogenous opioid.

adenosine monophosphate concentrations) and activation of phospholipase C. Opioids inhibit voltage-gated calcium channels and activate inwardly rectifying potassium channels. Opioid effects vary based on the duration of exposure, and opioid tolerance leads to changes in opioid responses.

Although opioids provide some degree of sedation and (in many species) can produce general anesthesia when given in large doses, they are principally used to provide analgesia. The properties of specific opioids depend on which receptor is bound (and in the case of spinal and epidural administration of opioids, the location in the neuraxis where the receptor is located) and the binding affinity of the drug. Agonist–antagonists (eg, nalbuphine, nalorphine, butorphanol, and pentazocine) have less efficacy than so-called full agonists (eg, fentanyl) and under some circumstances will antagonize the actions of full agonists. The pure opioid antagonists are discussed in Chapter 17.

The opioid drugs mimic endogenous compounds. Endorphins, enkephalins, and dynorphins are endogenous peptides that bind to opioid receptors. These three families of opioid peptides differ in their amino acid sequences, anatomic distributions, and receptor affinities.

Opioid receptor activation inhibits the presynaptic release and postsynaptic response to excitatory neurotransmitters (eg, acetylcholine, substance P) from nociceptive neurons. The cellular mechanism for this action was described at the beginning of this chapter. Transmission of pain impulses can be *selectively* modified at the level of the dorsal horn of the spinal cord with intrathecal or epidural administration of opioids. Opioid receptors also respond to systemically administered opioids. Modulation through a descending inhibitory pathway from the periaqueductal gray matter to the dorsal horn of the spinal cord may also play a role in opioid analgesia. Although opioids exert their greatest effect within the central nervous system, opiate receptors have also been identified on somatic and sympathetic peripheral nerves. Certain opioid side effects (eg, depression of gastrointestinal motility) are the result of opioid binding to receptors in peripheral tissues (eg, the wall of the gastrointestinal tract), and there are now selective antagonists for opioid actions outside the central nervous system (alvimopan and oral naltrexone). The distribution of opioid receptors on axons of primary sensory nerves and the clinical importance of these receptors (if present) remains speculative, despite the persisting practice of compounding of opioids in local anesthetic solutions applied to peripheral nerves.

Structure–Activity Relationships

Opioid receptor binding is a property shared by a chemically diverse group of compounds. Nonetheless, there are common structural characteristics, which are shown in Figure 10–1. As is true for most classes of drugs, small molecular changes can convert an agonist into an antagonist. The levorotatory isomers are generally more potent than the dextrorotatory opioid isomers.

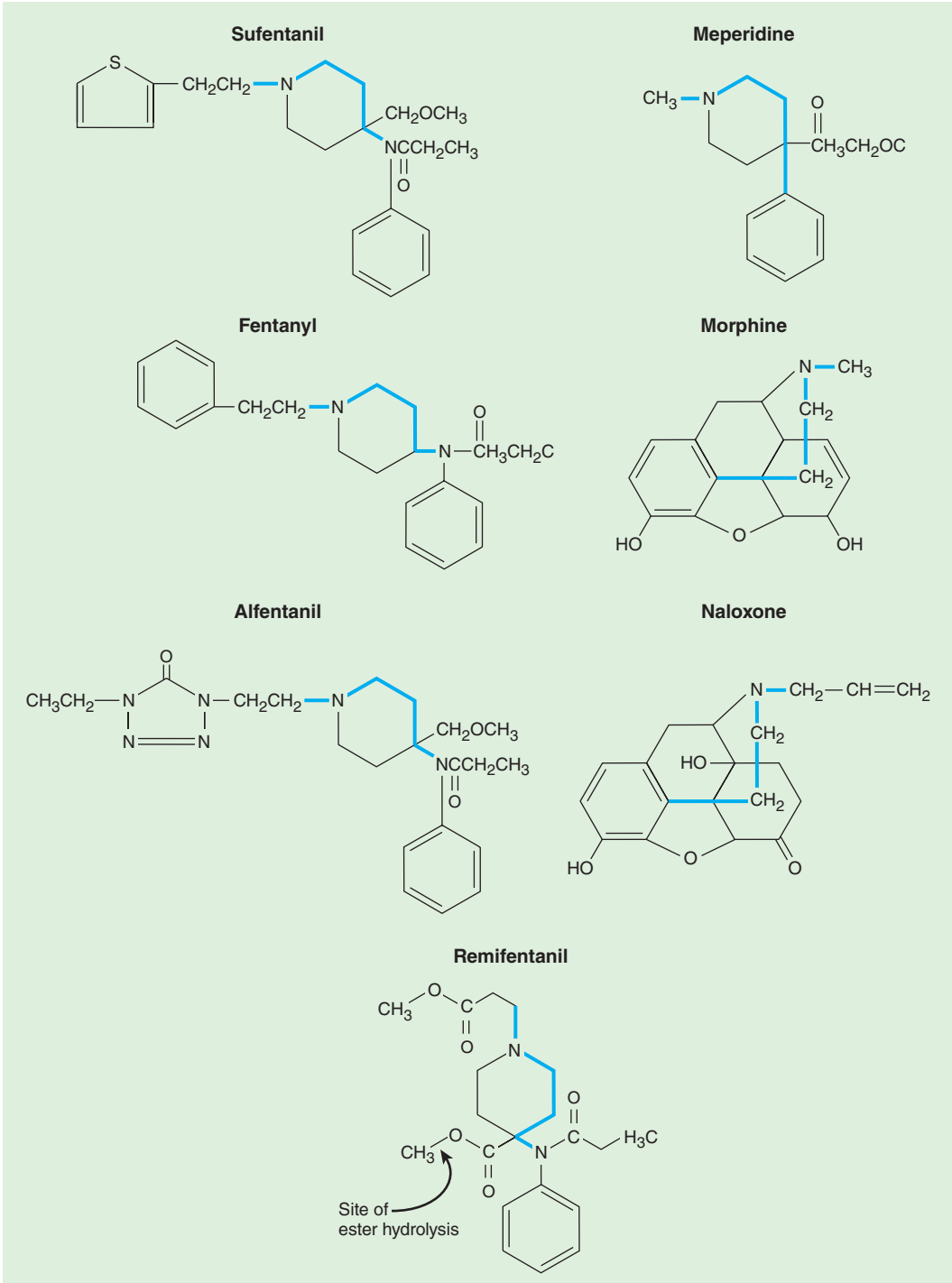

FIGURE 10–1 Opioid agonists and antagonists share part of their chemical structure, which is outlined in cyan.

Pharmacokinetics

A. Absorption

Rapid and complete absorption follows the intramuscular injection of hydromorphone, morphine, or meperidine, with peak plasma levels usually reached after 20–60 min. Oral transmucosal fentanyl citrate absorption (fentanyl "lollipop") provides rapid onset of analgesia and sedation in patients who are not good candidates for conventional oral, intravenous, or intramuscular dosing of opioids.

The low molecular weight and high lipid solubility of fentanyl also favor transdermal absorption (the transdermal fentanyl "patch"). The amount of fentanyl absorbed per unit of time depends on the surface area of skin covered by the patch and also on local skin conditions (eg, blood flow). The time required to establish a reservoir of drug in the upper dermis delays by several hours the achievement of effective blood concentrations. Serum concentrations of fentanyl reach a plateau within 14–24 h of application (with peak levels occurring after a longer delay in elderly than in younger patients) and remain constant for up to 72 h. Continued absorption from the dermal reservoir accounts for persisting measurable serum levels many hours after patch removal. Fentanyl patches are most often used for outpatient management of chronic pain and are particularly appropriate for patients who require continuous opioid dosing but cannot take the much less expensive, but equally efficacious, oral agents such as methadone.

A wide variety of opioids are effective by oral administration, including oxycodone, hydrocodone (most often in combination with acetaminophen), codeine, tramadol, morphine, hydromorphone, and methadone. These agents are much used for outpatient pain management.

Fentanyl is often administered in small doses (10–25 mcg) with local anesthetics for spinal anesthesia, and adds to the analgesia when included with local anesthetics in epidural infusions. Morphine in doses between 0.1 and 0.5 mg and hydromorphone in doses between 0.05 and 0.2 mg provide 12–18 hours of analgesia after intrathecal administration. Morphine and hydromorphone are commonly included in local anesthetic solutions infused for postoperative epidural analgesia. Extended-release epidural morphine (DepoDur) is administered as a single epidural dose (5–15 mg), the effects of which persist for 48 h.

TABLE 10–2 Physical characteristics of opioids that determine distribution.[1]

Agent	Nonionized Fraction	Protein Binding	Lipid Solubility
Morphine	++	++	+
Meperidine	+	+++	++
Fentanyl	+	+++	++++
Sufentanil	++	++++	++++
Alfentanil	++++	++++	+++
Remifentanil	+++	+++	++

[1]+, very low; ++, low; +++, high; ++++, very high.

B. Distribution

Table 10–2 summarizes the physical characteristics that determine distribution and tissue binding of opioid analgesics. After intravenous administration, the distribution half-lives of all of the opioids are fairly rapid (5–20 min). The low fat solubility of morphine slows passage across the blood–brain barrier, however, so that its onset of action is slow and its duration of action is prolonged. This contrasts with the increased lipid solubility of fentanyl and sufentanil, which are associated with a faster onset and shorter duration of action **when administered in small doses**. Interestingly, alfentanil has a more rapid onset of action and shorter duration of action than fentanyl following a bolus injection, even though it is less lipid soluble than fentanyl. The high nonionized fraction of alfentanil at physiological pH and its small volume of distribution (V_d) increase the amount of drug (as a percentage of the administered dose) available for binding in the brain.

Significant amounts of lipid-soluble opioids can be retained by the lungs (first-pass uptake); as systemic concentrations fall they will return to the bloodstream. The amount of pulmonary uptake is reduced by prior accumulation of other drugs, increased by a history of tobacco use, and decreased by concurrent inhalation anesthetic administration.

Unbinding of opioid receptors and redistribution (of drug from effect sites) terminate the clinical effects of all opioids. After smaller doses of the lipid-soluble drugs (eg, fentanyl or sufentanil), redistribution alone is the driver for reducing blood concentrations, whereas after larger doses biotransformation becomes an important driver in reducing plasma levels below those that have clinical effects. Thus, the time required for fentanyl or sufentanil concentrations to decrease by half is *context sensitive;* in other words, the half-time depends on the total dose of drug and duration of exposure (see Chapter 7).

C. Biotransformation

With the exception of remifentanil, all opioids depend primarily on the liver for biotransformation and are metabolized by the cytochrome P (CYP) system, conjugated in the liver, or both. Because of the high hepatic extraction ratio of opioids, their clearance depends on liver blood flow. The small V_d of alfentanil contributes to a short elimination half-life (1.5 h). Morphine and hydromorphone undergo conjugation with glucuronic acid to form, in the former case, morphine 3-glucuronide and morphine 6-glucuronide, and in the latter case, hydromorphone 3-glucuronide. Meperidine is *N*-demethylated to normeperidine, an active metabolite associated with seizure activity, particularly after very large meperidine doses. The end products of fentanyl, sufentanil, and alfentanil are inactive. Norfentanyl, the metabolite of fentanyl, can be measured in urine long after the native compound is no longer detectable in blood to determine chronic fentanyl ingestion. This has its greatest importance in diagnosing fentanyl abuse.

Codeine is a prodrug that becomes active after it is metabolized by CYP to morphine. Tramadol similarly must be metabolized by CYP to *O*-desmethyltramadol to be active. Oxycodone is metabolized by CYP to series of active compounds that are less potent than the parent one.

The ester structure of remifentanil makes it susceptible to hydrolysis (in a manner similar to esmolol) by nonspecific esterases in red blood cells and tissue (see Figure 10–1), yielding a terminal elimination half-life of less than 10 min. Remifentanil biotransformation is rapid and the duration of a

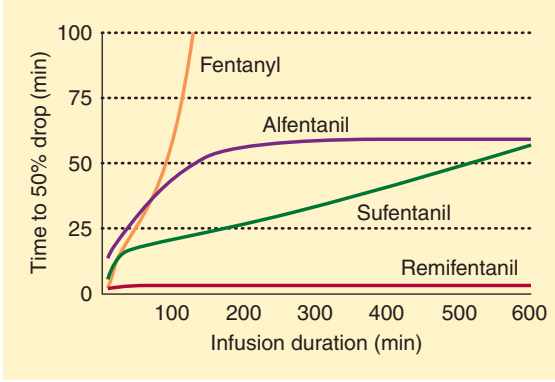

FIGURE 10–2 In contrast to other opioids, the time necessary to achieve a 50% decrease in the plasma concentration of remifentanil (its **context-sensitive half-time**) is very short and is not influenced by the duration of the infusion. (Reproduced, with permission, from Egan TD: The pharmacokinetics of the new short-acting opioid remifentanil [GI87084B] in healthy adult male volunteers. Anesthesiology 1993;79:881.)

remifentanil infusion has little effect on wake-up time (Figure 10–2). The context-sensitive half-time of remifentanil remains approximately 3 min regardless of the dose or duration of infusion. In its lack of accumulation remifentanil differs from other currently available opioids. Hepatic dysfunction requires no adjustment in remifentanil dosing. Finally, patients with pseudocholinesterase deficiency have a normal response to remifentanil (as also appears true for esmolol).

D. Excretion

The end products of morphine and meperidine biotransformation are eliminated by the kidneys, with less than 10% undergoing biliary excretion. Because 5–10% of morphine is excreted unchanged in the urine, kidney failure prolongs morphine duration of action. The accumulation of morphine metabolites (morphine 3-glucuronide and morphine 6-glucuronide) in patients with kidney failure has been associated with prolonged narcosis and ventilatory depression. In fact, morphine 6-glucuronide is a more potent and longer-lasting opioid agonist than morphine. As previously noted, normeperidine at increased concentrations may produce seizures; these are not reversed by naloxone. Renal dysfunction increases the likelihood of toxic effects

from normeperidine accumulation. However, both morphine and meperidine have been used safely and successfully in patients with kidney failure. Metabolites of sufentanil are excreted in urine and bile. The main metabolite of remifentanil is eliminated in urine, is several thousand times less potent than its parent compound, and thus is unlikely to produce any clinical opioid effects.

Effects on Organ Systems

A. Cardiovascular

In general, opioids have few direct effects on the heart. Meperidine tends to increase heart rate (it is structurally similar to atropine and was originally synthesized as an atropine replacement), whereas larger doses of morphine, fentanyl, sufentanil, remifentanil, and alfentanil are associated with a vagus nerve–mediated bradycardia. With the exception of meperidine (and only then at very large doses), the opioids do not depress cardiac contractility provided they are administered alone (which is almost never the circumstance in surgical anesthetic settings). Nonetheless, arterial blood pressure often falls as a result of bradycardia, venodilation, and decreased sympathetic reflexes, sometimes requiring vasopressor support. These effects are more pronounced when opioids are administered in combination with benzodiazepines, in which case drugs such as sufentanil and fentanyl can be associated with reduced cardiac output. Bolus doses of meperidine, hydromorphone, and morphine evoke histamine release in some individuals that can lead to profound drops in systemic vascular resistance and arterial blood pressure. The potential hazards of histamine release can be minimized in susceptible patients by infusing opioids slowly or by pretreatment with H_1 and H_2 antagonists, or both. The end effects of histamine release can be reversed by infusion of intravenous fluid and vasopressors.

Intraoperative hypertension during large-dose opioid anesthesia or nitrous oxide–opioid anesthesia is common. Such hypertension is often attributed to inadequate anesthetic depth, thus it is conventionally treated by the addition of other anesthetic agents (benzodiazepines, propofol, or potent inhaled agents). If depth of anesthesia is adequate and hypertension persists, vasodilators or other antihypertensives may be used. The inherent cardiac stability provided by opioids is greatly diminished in actual practice when other anesthetic drugs, including nitrous oxide, benzodiazepines, propofol, or volatile agents, are typically added. The end result of polypharmacy can include myocardial depression.

B. Respiratory

Opioids depress ventilation, particularly respiratory rate. Thus, monitoring of respiratory rate provides a convenient, simple way of detecting early respiratory depression in patients receiving opioid analgesia. Opioids increase the partial pressure of carbon dioxide ($Paco_2$) and blunt the response to a CO_2 challenge, resulting in a shift of the CO_2 response curve downward and to the right (Figure 10–3). These effects result from opioid binding to neurons in the respiratory centers of the brainstem. **The apneic threshold—the greatest $Paco_2$ at which a patient remains apneic—rises, and hypoxic drive is decreased**. Morphine and meperidine can cause histamine-induced bronchospasm in susceptible patients. **Rapid administration of larger doses of opioids (particularly fentanyl, sufentanil, remifentanil, and alfentanil) can induce chest wall rigidity severe enough to prevent adequate bag-and-mask ventilation**. This centrally

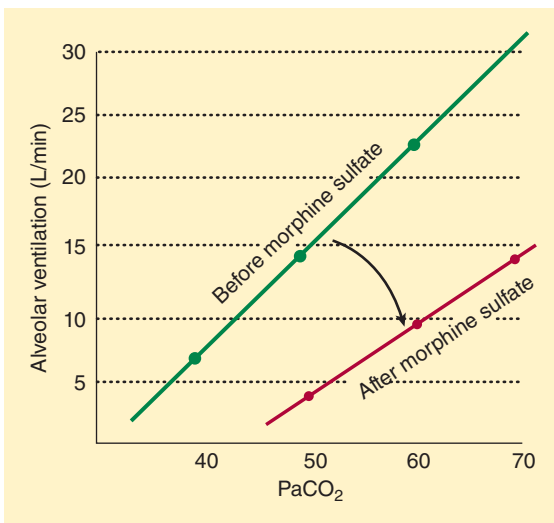

FIGURE 10–3 Opioids depress ventilation. This is graphically displayed by a shift of the CO_2 curve downward and to the right.

mediated muscle contraction is effectively treated with neuromuscular blocking agents. This problem is rarely seen now that large-dose opioid anesthesia is less often used in cardiovascular anesthesia practice. Opioids can effectively blunt the bronchoconstrictive response to airway stimulation such as occurs during tracheal intubation.

C. Cerebral

The effects of opioids on cerebral perfusion and intracranial pressure must be separated from any effects of opioids on $Paco_2$. In general, opioids reduce cerebral oxygen consumption, cerebral blood flow, cerebral blood volume, and intracranial pressure, but to a much lesser extent than barbiturates, propofol, or benzodiazepines. These effects will occur during maintenance of normocarbia by artificial ventilation; however, there are some reports of mild—but transient and almost certainly unimportant—increases in cerebral artery blood flow velocity and intracranial pressure following opioid boluses in patients with brain tumors or head trauma. If combined with hypotension, the resulting fall in cerebral perfusion pressure *could* be deleterious to patients with abnormal intracranial pressure–volume relationships. Nevertheless, the important clinical message is that any trivial opioid-induced increase in intracranial pressure would likely be much less important than the much more likely large increases in intracranial pressure associated with intubation that might be observed in an inadequately anesthetized patient (from whom opioids were withheld). Opioids usually have almost no effects on the electroencephalogram (EEG), although large doses are associated with slow δ-wave activity. There are curious sporadic case reports that large doses of fentanyl may rarely cause seizure activity; however, some of these apparent seizures have been retrospectively diagnosed as severe opioid-induced muscle rigidity. EEG activation and seizures have been associated with the meperidine metabolite normeperidine, as previously noted.

Stimulation of the medullary chemoreceptor trigger zone is responsible for opioid-induced nausea and vomiting. Curiously, nausea and vomiting are more common following smaller (analgesic) than very large (anesthetic) doses of opioids. Prolonged oral dosing of opioids or infusion of large doses of remifentanil during general anesthesia can produce the phenomenon of opioid-induced tolerance. Repeated dosing of opioids will reliably produce tolerance, a phenomenon in which larger doses are required to produce the same response. This is not the same as physical dependence or addiction, which may also be associated with repeated opioid administration.

3 Prolonged dosing of opioids can also produce "opioid-induced hyperalgesia," in which patients become more sensitive to painful stimuli. Infusion of large doses of (in particular) remifentanil during general anesthesia can produce acute tolerance, in which much larger than usual doses of opioids will be required for postoperative analgesia. Relatively large doses of opioids are required to render patients unconscious (Table 10–3). Regardless of the dose, however, opioids will not reliably produce amnesia. Parenteral opioids have been the mainstay of pain control for more than a century. The relatively recent use of opioids in epidural and intrathecal spaces has revolutionized acute and chronic pain management (see Chapters 47 and 48).

Unique among the commonly used opioids, meperidine has minor local anesthetic qualities, particularly when administered into the subarachnoid space. Meperidine's clinical use as a local anesthetic has been limited by its relatively low potency and propensity to cause typical opioid side effects (nausea, sedation, and pruritus) at the doses required to induce local anesthesia. **Intravenous meperidine (10–25 mg) is more effective than morphine or fentanyl for decreasing shivering in the postanesthetic care unit and meperidine appears to be the best agent for this indication**.

D. Gastrointestinal

Opioids slow gastrointestinal motility by binding to opioid receptors in the gut and reducing peristalsis. Biliary colic may result from opioid-induced contraction of the sphincter of Oddi. Biliary spasm, which can mimic a common bile duct stone on cholangiography, is reversed with the opioid antagonist naloxone or glucagon. Patients receiving long-term opioid therapy (eg, for cancer pain) usually become tolerant to many of the side effects but rarely to constipation. This is the basis for

TABLE 10–3 Uses and doses of common opioids.

Agent	Use	Route[1]	Dose[2]
Morphine	Postoperative analgesia	IM IV	0.05–0.2 mg/kg 0.03–0.15 mg/kg
Hydromorphone	Postoperative analgesia	IM IV	0.02–0.04 mg/kg 0.01–0.02 mg/kg
Fentanyl	Intraoperative anesthesia Postoperative analgesia	IV IV	2–50 mcg/kg 0.5–1.5 mcg/kg
Sufentanil	Intraoperative anesthesia	IV	0.25–20 mcg/kg
Alfentanil	Intraoperative anesthesia Loading dose Maintenance infusion	 IV IV	 8–100 mcg/kg 0.5–3 mcg/kg/min
Remifentanil	Intraoperative anesthesia Loading dose Maintenance infusion Postoperative analgesia/sedation	 IV IV IV	 1.0 mcg/kg 0.5–20 mcg/kg/min 0.05–0.3 mcg/kg/min

[1]IM, intramuscular; IV, intravenous.

[2]Note: The wide range of opioid doses reflects a large therapeutic index and depends upon which other anesthetics are simultaneously administered. For obese patients, dose should be based on ideal body weight or lean body mass, not total body weight. Tolerance can develop rapidly (ie, within 2 h) during IV infusion of opioids, necessitating higher infusion rates. Dose correlates with other variables besides body weight that need to be considered (eg, age). The relative potencies of fentanyl, sufentanil, and alfentanil are estimated to be 1:9:1/7.

the recent development of the peripheral opioid antagonists methylnaltrexone and alvimopan, and for their salutary effects in promoting motility in patients with opioid bowel syndrome, those receiving chronic opioid treatment of cancer pain, and those receiving intravenous opioids after abdominal surgery.

E. Endocrine

4 The neuroendocrine stress response to surgical stimulation is measured in terms of the secretion of specific hormones, including catecholamines, antidiuretic hormone, and cortisol. Large doses of opioids (typically fentanyl or sufentanil) block the release of these hormones in response to surgery more completely than volatile anesthetics. Although much discussed, the actual clinical outcome benefit produced by attenuating the stress response, even in high-risk cardiac patients, remains speculative (and possibly nonexistent).

Drug Interactions

The combination of meperidine and monoamine oxidase inhibitors should be avoided as it may result in hypertension, hypotension, hyperpyrexia, coma, or respiratory arrest. The cause of this catastrophic interaction is incompletely understood. (The results of failure to appreciate this drug interaction in the celebrated Libby Zion case led to changes in work rules for house officers in the United States.)

Propofol, barbiturates, benzodiazepines, and other central nervous system depressants can have synergistic cardiovascular, respiratory, and sedative effects with opioids.

The biotransformation of alfentanil may be impaired following treatment with erythromycin, leading to prolonged sedation and respiratory depression.

CYCLOOXYGENASE INHIBITORS

Mechanisms of Action

Many over-the-counter nonsteroidal antiinflammatory agents (NSAIDs) work through inhibition of cyclooxygenase (COX), the key step in prostaglandin synthesis. COX catalyzes the production of prostaglandin H_1 from arachidonic acid. The two forms

of the enzyme, COX-1 and COX-2, have differing distribution in tissue. COX-1 receptors are widely distributed throughout the body, including the gut and platelets. COX-2 is produced in response to inflammation.

COX-1 and COX-2 enzymes differ further in the size of their binding sites: the COX-2 site can accommodate larger molecules that are restricted from binding at the COX-1 site. This distinction is in part responsible for selective COX-2 inhibition. Agents that inhibit COX nonselectively (eg, aspirin) will control fever, inflammation, pain, and thrombosis. COX-2 selective agents (eg, acetaminophen [paracetamol], celecoxib, etoricoxib) can be used perioperatively without concerns about platelet inhibition or gastrointestinal upset. Curiously, while COX-1 inhibition decreases thrombosis, selective COX-2 inhibition increases the risk of heart attack, thrombosis, and stroke.

Aspirin, the first of the so-called NSAIDs, formerly was used as an antipyretic and analgesic. Now it is used almost exclusively for prevention of thrombosis in susceptible individuals or for treatment of acute myocardial infarction. Aspirin is unique in that it irreversibly inhibits COX-1 by acetylating a serine residue in the enzyme. The irreversible nature of its inhibition underlies the nearly 1-week duration of its clinical effects (eg, return of platelet aggregation to normal) after drug discontinuation.

5

The first relatively selective COX-2 agent to be developed was acetaminophen (paracetamol). Curiously, this agent, while effective for analgesia, produces almost no effects on inflammation relative to other COX-2 selective agents. With few exceptions, the COX inhibitors are oral agents. Acetaminophen and ketorolac are available in an intravenous form for perioperative use.

Multimodal analgesia typically includes the use of COX inhibitors, regional or local anesthesia techniques, and other approaches aimed at reducing the requirement for opioids in postoperative patients. The hope is that reduced exposure to opioids will hasten and improve recovery from surgical procedures.

Structure–Activity Relationships

The COX enzyme is inhibited by an unusually diverse group of compounds that can be grouped into salicylic acids (eg, aspirin), acetic acid derivatives (eg, ketorolac), propionic acid derivatives (eg, ibuprofen), heterocyclics (eg, celecoxib), and others. Thus a conventional discussion of structure to potency (and other factors) is not useful for these chemicals, other than to note that the heterocyclics tend to be the compounds with the greatest selectivity for the COX-2 rather than COX-1 form of the enzyme.

Pharmacokinetics

A. Absorption

All COX inhibitors (save for ketorolac) are well absorbed after oral administration and all will typically achieve their peak blood concentrations in less than 3 hours. Some COX inhibitors are formulated for topical application (eg, as a gel to be applied over joints or as liquid drops to be instilled on the eye).

B. Distribution

After absorption, COX inhibitors are highly bound by plasma proteins, chiefly albumin. Their lipid solubility allows them to readily permeate the blood–brain barrier to produce a central analgesia and antipyresis, and to penetrate joint spaces to produce (with the exception of acetaminophen) an antiinflammatory effect.

C. Biotransformation

Most COX inhibitors undergo hepatic biotransformation. The agent with the most notable metabolite is acetaminophen which at toxic, increased doses yields sufficiently large concentrations of *N*-acetyl-*p*-benzoquinone imine to produce hepatic failure.

D. Excretion

Nearly all COX inhibitors are excreted in urine after biotransformation.

Effects on Organ Systems

A. Cardiovascular

COX inhibitors do not act directly on the cardiovascular system. Any cardiovascular effects result from the actions of these agents on coagulation. Prostaglandins maintain the patency of the ductus arteriosus, thus prostaglandin inhibitors have been administered to neonates to promote closure of a persistently patent ductus arteriosus.

B. Respiratory

At appropriate clinical doses, none of the COX inhibitors have effects on respiration or lung function. Aspirin overdosage has complex effects on acid–base balance and respiration.

C. Gastrointestinal

The classical complication of COX-1 inhibition is gastrointestinal upset. In its most extreme form this can cause upper gastrointestinal bleeding. Both complications result from direct actions of the drug, in the former case, on protective effects of prostaglandins in the mucosa, and in the latter case, on the combination of mucosal effects and inhibition of platelet aggregation.

Acetaminophen abuse or overdosage is a common cause of fulminant hepatic failure resulting in need for hepatic transplantation in western societies.

SUGGESTED READING

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