

operative site. COX-2 inhibitors, including celecoxib (Celebrex), are associated with increased cardiovascular risk. It appears that this is a class effect of NSAIDs, excluding aspirin. These drugs are contraindicated in patients in the immediate period after coronary artery bypass surgery and should be used with caution in elderly patients and those with a history of or significant risk factors for cardiovascular disease.

### OPIOID ANALGESICS

Opioids are the most potent pain-relieving drugs currently available. Of all analgesics, they have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief. Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone. Many physicians, nurses, and patients have a certain trepidation about using opioids that is based on an exaggerated fear of addiction. In fact, there is a vanishingly small chance of patients becoming addicted to narcotics as a result of their appropriate medical use. The physician should not hesitate to use opioid analgesics in patients with acute severe pain. Table 18-1 lists the most commonly used opioid analgesics.

Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor ( $\mu$ -receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. At higher doses of meperidine, typically greater than 1 g/d, accumulation of normeperidine can produce hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.

The most rapid pain relief is obtained by intravenous administration of opioids; relief with oral administration is significantly slower. Because of the potential for respiratory depression, patients with any form of respiratory compromise must be kept under close observation following opioid administration; an oxygen-saturation monitor may be useful, but only in a setting where the monitor is under constant surveillance. Opioid-induced respiratory depression is typically accompanied by sedation and a reduction in respiratory rate. A fall in oxygen saturation represents a critical level of respiratory depression and the need for immediate intervention to prevent life-threatening hypoxemia. Ventilatory assistance should be maintained until the opioid-induced respiratory depression has resolved. The opioid antagonist naloxone should be readily available whenever opioids are used at high doses or in patients with compromised pulmonary function. Opioid effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects. Synergistic respiratory depression is common when opioids are administered with other CNS depressants, most commonly the benzodiazepines. Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires determining whether the drug has adequately relieved the pain and frequent reassessment to determine the optimal interval for dosing. *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Because many patients are reluctant to complain, this practice leads to needless suffering.* In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

An innovative approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA uses a microprocessor-controlled infusion device that can deliver a baseline continuous dose of an opioid drug as well as preprogrammed

additional doses whenever the patient pushes a button. The patient can then titrate the dose to the optimal level. This approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for short-term home care of patients with intractable pain, such as that caused by metastatic cancer.

It is important to understand that the PCA device delivers small, repeated doses to maintain pain relief; in patients with severe pain, the pain must first be brought under control with a loading dose before transitioning to the PCA device. The bolus dose of the drug (typically 1 mg of morphine, 0.2 mg of hydromorphone, or 10  $\mu$ g of fentanyl) can then be delivered repeatedly as needed. To prevent overdosing, PCA devices are programmed with a lockout period after each demand dose is delivered (5–10 min) and a limit on the total dose delivered per hour. Although some have advocated the use of a simultaneous continuous or basal infusion of the PCA drug, this increases the risk of respiratory depression and has not been shown to increase the overall efficacy of the technique.

The availability of new routes of administration has extended the usefulness of opioid analgesics. Most important is the availability of spinal administration. Opioids can be infused through a spinal catheter placed either intrathecally or epidurally. By applying opioids directly to the spinal or epidural space adjacent to the spinal cord, regional analgesia can be obtained using relatively low total doses. Indeed, the dose required to produce effective localized analgesia when using morphine intrathecally (0.1–0.3 mg) is a fraction of that required to produce similar analgesia when administered intravenously (5–10 mg). In this way, side effects such as sedation, nausea, and respiratory depression can be minimized. This approach has been used extensively during labor and delivery and for postoperative pain relief following surgical procedures. Continuous intrathecal delivery via implanted spinal drug-delivery systems is now commonly used, particularly for the treatment of cancer-related pain that would require sedating doses for adequate pain control if given systemically. Opioids can also be given intranasally (butorphanol), rectally, and transdermally (fentanyl and buprenorphine), or through the oral mucosa (fentanyl), thus avoiding the discomfort of frequent injections in patients who cannot be given oral medication. The fentanyl and buprenorphine transdermal patches have the advantage of providing fairly steady plasma levels, which maximizes patient comfort.

Recent additions to the armamentarium for treating opioid-induced side effects are the peripherally acting opioid antagonists alvimopan (Entereg) and methylnaltrexone (Relistor). Alvimopan is available as an orally administered agent that is restricted to the intestinal lumen by limited absorption; methylnaltrexone is available in a subcutaneously administered form that has virtually no penetration into the CNS. Both agents act by binding to peripheral  $\mu$ -receptors, thereby inhibiting or reversing the effects of opioids at these peripheral sites. The action of both agents is restricted to receptor sites outside of the CNS; thus, these drugs can reverse the adverse effects of opioid analgesics that are mediated through their peripheral receptors without reversing their analgesic effects. Alvimopan has proven effective in lowering the duration of persistent ileus following abdominal surgery in patients receiving opioid analgesics for postoperative pain control. Methylnaltrexone has proven effective for relief of opioid-induced constipation in patients taking opioid analgesics on a chronic basis.

**Opioid and COX Inhibitor Combinations** When used in combination, opioids and COX inhibitors have additive effects. Because a lower dose of each can be used to achieve the same degree of pain relief and their side effects are nonadditive, such combinations are used to lower the severity of dose-related side effects. However, fixed-ratio combinations of an opioid with acetaminophen carry an important risk. Dose escalation as a result of increased severity of pain or decreased opioid effect as a result of tolerance may lead to ingestion of levels of acetaminophen that are toxic to the liver. Although