Codeine and other Opiates

Codeine.
In contrast to morphine, **codeine** is approximately 60% as effective orally as parenterally, both as an analgesic and as a respiratory depressant. Very few opioids have so high an oral-parenteral potency ratio; levorphanol, oxycodone, and methadone also share this attribute. The greater oral efficacy of these drugs is due to less first-pass metabolism in the liver. Once absorbed, **codeine** is metabolized by the liver and excreted chiefly in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered **codeine** is demethylated to form morphine, and both free and conjugated morphine can be found in the urine after therapeutic doses of **codeine. Codeine** is methylmorphine. **Codeine** has an exceptionally low affinity for opioid receptors, and the analgesic effect of **codeine** is due to its conversion to morphine. However, its antitussive actions probably involve distinct receptors that bind **codeine** itself. The half-life of **codeine** in plasma is 2 to 4 hours.

CODEINE[a] (Chapter 23)

AVAILABILITY (ORAL) (%): 50 ± 7[b]
URINARY EXCRETION (%): Negligible
BOUND IN PLASMA (%): 7
CLEARANCE (ml ◊ min^{-1} ◊ kg^{-1}): 11 ± 2[c]
VOL. DIST. (liters/kg): 2.6 ± 0.3[c]
HALF-LIFE (hours): 2.9 ± 0.7
EFFECTIVE CONCENTRATIONS: 65 ng/ml
TOXIC CONCENTRATIONS: æ

Morphine is available orally in standard tablets and controlled-release preparations. Due to first-pass metabolism, morphine is two- to six-fold less potent orally than parenterally. This is important to remember when converting a patient from parenteral to oral medication. There is wide variability in the first-pass metabolism, and the dose should be titrated to the patient's needs. In children who weigh less than 50 kg, morphine can be given at 0.1 mg/kg every 3 to 4 hours parenterally or at 0.3 mg/kg orally.

Codeine is widely used orally due to its high oral/parenteral potency ratio. Orally, **codeine** at 30 mg is approximately equianalgesic to 325 to 600 mg of aspirin. Combinations of **codeine** with aspirin or acetaminophen usually provide additive actions, and at these doses analgesic efficacy can exceed that of 60 mg of **codeine** (*see* Beaver, 1988).

Dextromethorphan. *Dextromethorphan* (*d*-3-methoxy-N-methylmorphinan) is the *d* isomer of the **codeine** analog levorphanol; however, unlike the *l* isomer, it has no analgesic or addictive properties and does not act through opioid receptors. The drug acts centrally to elevate the threshold for coughing. Its effectiveness in patients with pathological cough has been demonstrated in controlled studies; its potency is nearly equal to that of **codeine**. Compared with **codeine**, dextromethorphan produces fewer subjective and gastrointestinal side effects (Matthys *et al.,* 1983). In therapeutic dosages, the drug does not inhibit ciliary activity, and its antitussive effects persist for 5 to 6 hours. Its toxicity is low, but extremely high doses may produce CNS depression.

Although slightly less selective than morphine, propoxyphene binds primarily to mu-opioid receptors and produces analgesia and other CNS effects that are similar to those seen with morphine-like opioids. It is likely that at equianalgesic doses the incidence of side effects such as nausea, anorexia, constipation, abdominal pain, and drowsiness would be similar to those of **codeine**.

As an analgesic, propoxyphene is about one-half to two-thirds as potent as **codeine** given orally. Ninety to 120 mg of propoxyphene hydrochloride administered orally would equal the analgesic effects of 60 mg of **codeine**, a dose that usually produces about as much analgesia as 600 mg of aspirin. Combinations of propoxyphene and aspirin, like combinations of **codeine** and aspirin, afford a higher level of analgesia than does either agent given alone (Beaver, 1988).

Chemistry of Morphine and Related Opioids. The structure of morphine is shown in Table 23-5.

Many semisynthetic derivatives are made by relatively simple modifications of morphine or thebaine. **Codeine** is methylmorphine, the methyl substitution being on the phenolic hydroxyl group. Thebaine differs from morphine only in that both hydroxyl groups are methylated and that the ring has two double bonds ($D^{6,7}$, $D^{8,14}$). Thebaine has little analgesic action, but is a precursor of several important 14-OH compounds, such as oxycodone and naloxone. Certain derivatives of thebaine are more than 1000 times as potent as morphine (*e.g.,* etorphine). Diacetylmorphine, or heroin, is made from morphine by acetylation at the 3 and 6 positions. Apomorphine, which also can be prepared from morphine, is a potent emetic and dopaminergic agonist. Hydromorphone, oxymorphone, hydrocodone, and oxycodone also are made by modifying the morphine molecule. The structural relationships between morphine and some of its surrogates and antagonists are shown in Table 23-5.

Structure-Activity Relationship of the Morphine-Like Opioids. In addition to morphine, **codeine**, and the semisynthetic derivatives of the natural opium alkaloids, a number of other structurally distinct chemical classes of drugs have pharmacological actions similar to those of morphine. Clinically useful compounds include the morphinans, benzomorphans, methadones, phenylpiperidines, and propionanilides. Although the two-dimensional representations of these chemically diverse compounds appear to be quite different, molecular models show certain common characteristics; these are indicated by the heavy lines in the structure of morphine shown above. Among the important properties of the opioids that can be altered by structural modification are their affinity for various species of opioid receptors, their activity as agonists versus antagonists, their lipid solubility, and their resistance to metabolic breakdown. For example, blockade of the phenolic hydroxyl at position 3, as in **codeine** and heroin, drastically reduces binding to m receptors; these compounds are converted to the potent analgesics morphine and 6-acetyl morphine, respectively, *in vivo.*

History. Although the psychological effects of opium may have been known to the ancient Sumerians, the first undisputed reference to poppy juice is found in the writings of Theophrastus in the third century B.C. The word *opium* itself is derived from the Greek name for juice, the drug being obtained from the juice of the poppy, *Papaver somniferum.* Arabian physicians were well versed in the uses of opium; Arabian traders introduced the drug to the Orient, where it was employed mainly for the control of dysenteries. Paracelsus (1493-1541) is credited with repopularizing the use of opium in Europe after it had fallen into disfavor because of its toxicity. By the middle of the sixteenth century, many of the uses of opium were appreciated. In 1680, Sydenham wrote, "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."

Opium contains more than 20 distinct alkaloids. In 1806, Serturner reported the isolation of a pure substance in opium that he named *morphine,* after Morpheus, the Greek god of dreams. The discovery of other alkaloids in opium quickly followed that of morphine (**codeine** by Robiquet in 1832, papaverine by Merck in 1848). By the middle of the nineteenth century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

In the United States, opioid abuse was accentuated by the unrestricted availability of opium that prevailed until the early years of the twentieth century and by the influx of opium-smoking immigrants from the Orient. In addition, the invention of the hypodermic needle led to the parenteral use of morphine and to a more severe variety of compulsive drug abuse.

The problem of addiction to opioids stimulated a search for potent analgesics free of addictive potential. Just prior to and following World War II, synthetic compounds such as meperidine and methadone were introduced into clinical medicine, but proved to have typical morphine-like actions. Nalorphine, a derivative of morphine, was an exception. Nalorphine antagonized the effects of morphine and was used to reverse morphine poisoning in the early 1950s. Higher doses of nalorphine are analgesic in postoperative patients, but the drug is not used clinically as an analgesic because of side effects such as anxiety and dysphoria. However, its unusual pharmacological profile ushered in the development of new drugs, such as the relatively pure antagonist naloxone and compounds with mixed actions (*e.g.,* pentazocine, butorphanol, and buprenorphine). Such agents enlarged the range of available therapeutic entities and provided tools needed to explore the mechanisms of opioid actions.

The complex interactions of morphine and drugs with mixed agonist/antagonist properties, such as nalorphine, led Martin to propose the existence of multiple classes of opioid receptors (Martin and Sloan, 1977). This proposal has now been confirmed, first by receptor binding studies and more recently with the

cloning of four distinct but closely related opioid receptors. Soon after the demonstration of the existence of opioid binding sites, three classes of endogenous opioid peptides were isolated. They are encoded by different genes, are expressed in distinct neuronal pathways or cell types, and have differing selectivities for the various classes of opioid receptors (*see* Herz, 1993; Reisine and Bell, 1993).

Other Endogenous Opioids. In addition to peptides, it now appears that morphine, **codeine**, and related morphinans occur naturally in mammalian tissues; they usually are found in a conjugated form or bound to proteins. Hepatic metabolic pathways that might accomplish the synthesis of morphine have been described in the rat (Donnerer *et al.,* 1987; Weitz *et al.,* 1987).

Absorption, Distribution, Fate, and Excretion. ***Absorption.*** In general, the opioids are readily absorbed from the gastrointestinal tract; absorption through the rectal mucosa is adequate, and a few agents (*e.g.,* morphine, hydromorphone) are available in suppositories. The more lipophilic opioids are readily absorbed through the nasal or buccal mucosa (Weinberg *et al.,* 1988). Those with the greatest lipid solubility also can be absorbed transdermally (Portenoy *et al.,* 1993). Opioids are absorbed readily after subcutaneous or intramuscular injection and can adequately penetrate the spinal cord following epidural or intrathecal administration.

With most opioids, including morphine, the effect of a given dose is less after oral than after parenteral administration, due to variable but significant first-pass metabolism in the liver. For example, the bioavailability of oral preparations of morphine is only about 25%. The shape of the time-effect curve also varies with the route of administration, so that the duration of action is often somewhat longer with the oral route. If adjustment is made for variability of first-pass metabolism and clearance, it is possible to achieve adequate relief of pain by the oral administration of morphine. Satisfactory analgesia in cancer patients has been associated with a very broad range of steady-state concentrations of morphine in plasma (16 to 364 ng/ml; Neumann *et al.,* 1982).

When morphine and most opioids are given intravenously, they act promptly. However, the more lipid-soluble compounds act more rapidly than morphine after subcutaneous administration because of differences in the rates of absorption and entry into the CNS. When opioids such as morphine are given initially, their durations of analgesic action show relatively little variation (*see* Table 23-6). Other effects may persist longer than analgesia, and some drugs may accumulate with repeated administration.

Distribution and Fate. When therapeutic concentrations of morphine are present in plasma, about one-third of the drug is protein bound. Morphine itself does not persist in tissues, and 24 hours after the last dose tissue concentrations are low.

Although the primary site of action of morphine is in the CNS, in the adult only small quantities pass the blood-brain barrier. Compared with other more lipidsoluble opioids such as **codeine**, heroin, and methadone, morphine crosses the blood-brain barrier at a considerably lower rate.

Small amounts of morphine introduced epidurally or directly into the spinal canal can produce profound analgesia that may last 12 to 24 hours. However, there is rostral spread of the drug in spinal fluid, and prominent untoward effects, especially respiratory depression, can emerge later. With highly lipophilic agents such as hydromorphone or fentanyl, rapid absorption by neural tissues produces very localized effects and segmental analgesia. The duration of action is shorter because of distribution of the drug in the systemic circulation, and the severity of respiratory depression is largely proportional to its concentration in plasma (*see* Gustafsson and Wiesenfeld-Hallin, 1988).

The major pathway for the metabolism of morphine is conjugation with glucuronic acid to form both active and inactive products. *Morphine-6-glucuronide,* a major metabolite of morphine, has pharmacological actions indistinguishable from those of morphine. Morphine-6-glucuronide given systemically is approximately twice as potent as morphine in animal models (Paul *et al.,* 1989) and in human beings (Osborne *et al.,* 1988), but the difference between morphine and morphine-6-glucuronide becomes more impressive when the blood-brain barrier is bypassed. When administered intracerebroventricularly or intrathecally in either mice or rats, morphine-6-glucuronide is approximately 100-fold more potent than morphine (Paul *et al.,* 1989). The lower relative potency with systemic administration reflects the greater difficulty that morphine-6-glucuronide has crossing the blood-brain barrier compared to morphine.

Morphine-6-glucuronide plays a special role in morphine's actions. With chronic administration, it accounts for a significant portion of morphine's analgesic actions (Osborne *et al.,* 1988 and 1990; Portenoy *et al.,* 1991 and 1992). Indeed, with chronic oral dosing, the blood levels of morphine-6-glucuronide typically exceed those of morphine. Given its greater potency as well as its higher concentrations, morphine-6-glucuronide may be responsible for most of morphine's analgesic activity in patients receiving chronic oral morphine. Morphine-6-glucuronide is excreted by the kidney. In renal failure, the levels of morphine-6-glucuronide can accumulate, perhaps explaining morphine's potency and long duration in patients with compromised renal function. In young adults, the half-life of morphine is about 2 to 3 hours; the half-life of morphine-6-glucuronide is somewhat longer. Children achieve adult values by 6 months of age. In older patients, lower morphine doses are recommended. This is based on its smaller volume of distribution (Owen *et al.,* 1983) and the general decline in renal function in the elderly.

Excretion. Very little morphine is excreted unchanged. It is eliminated by glomerular filtration, primarily as morphine-3-glucuronide; 90% of the total excretion takes place during the first day. Enterohepatic circulation of morphine and its glucuronides occurs, which accounts for the presence of small amounts of morphine in the feces and in the urine for several days after the last dose.