Opioid Analgesics

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Reference: Basic & Clinical Pharmacology: Bertrum G. Katzung and Anthony J. Treveror, 13th edition, 2015, chapter 30: p.510-530; chapter 29: p.503-507

Learning Objectives:

At the end of session, the student should be able to:

1. Define analgesic.
2. Classify analgesics.
3. Define the term of opioids.
4. Specify opioid receptors.
5. Classify opioids based on their actions on opioid receptors.
6. List opioids in each class.
7. State the differences between pure and mixed agonist-antagonist opioids.
8. Explain the mechanism of analgesic action of opioids at spinal and supraspinal sites.
9. Explain the pharmacological effects of opioids.
10. Describe the clinical uses of opioids.
11. Explain side effects of opioids.
12. Define tolerance, physical dependence, psychological dependence and abuse in use of opioids.
13. Describe the clinical use of opioid antagonists.
14. Explain contraindications and cautions in use of opioids.

Opioid Analgesics

Source

Morphine, the prototypic opioid agonist, has long been known to relieve severe pain with remarkable efficacy. Opium, the source of morphine, is obtained from the poppy, *Papaver somniferum* and *P album*. After incision, the poppy seed pod exudes a white substance that turns into a brown gum that is crude opium. Opium contains many alkaloids, the principal one being morphine, which is present in a concentration of about 10%.

Opioids include not only the natural and semisynthetic alkaloid derivatives from opium but also synthetic surrogates, other opioid-like drugs whose actions are blocked by the nonselective antagonist naloxone, plus several endogenous peptides that interact with the different subtypes of opioid receptors. The term **opioid** describes all compounds that work at opioid receptors.

Opioid Receptors

Opioid receptors include μ, κ, and δ. Each receptor has different subtypes with different CNS distribution and actions. However all opioid receptors and their subtypes mediate analgesia. Three major classes of opioid receptors (μ, κ, and δ) have been identified in various nervous system sites and in other tissues. All are members of the G protein-coupled family of receptors and show significant amino acid sequence homologies. Multiple receptor subtypes have been proposed based on pharmacologic criteria, including μ1, μ2; δ1, δ2; and κ1, κ2, and κ3.

opioid receptors form a family of proteins that physically couple to G proteins and through this interaction affect ion channel gating, modulate intracellular Ca^{2+}disposition, and alter protein phosphorylation. The opioids have two well-established direct Gi/0 protein-coupled actions on neurons: (1) they close voltage-gated Ca^{2+}channels on presynaptic nerve terminals

and thereby reduce transmitter release, and (2) they open K^+ channels and hyperpolarize and thus inhibit postsynaptic neurons.

Classification

Opioid drugs can be classified based on their action at the opioid receptors as follows:

1. **Pure agonists** bind three opioid receptors subtypes but have greater binding affinity at the μ receptors so are known as m agonists. Based on their efficacy, this group is classified to strong opioid agonists and mild to moderate opioid agonists. Strong opioids are full agonists at the μ receptors such as morphine, methadone, fentanyl and meperidine. Mild to moderate opioid agonists are partial agonist at the μ receptor such as codeine and propoxyphene.

2. **Mixed agonist-antagonists** are capable of producing an agonist (or partial agonist) effect at one opioid receptor subtype and an antagonist effect at another. Care should be taken not to administer any partial agonist or drug with mixed opioid receptor actions to patients receiving pure agonist drugs because of the unpredictability of both drugs' effects; reduction of analgesia or precipitation of an explosive abstinence syndrome may result.

Buprenorphine is a partial μ-receptor agonist (low intrinsic activity) and an antagonist at the κ and δ receptors

Pentazocine is a κ agonist with weak μ-antagonist or partial agonist properties.

Nalbuphine is a strong κ-receptor agonist and a partial μ-receptor antagonist.

Butorphanol is considered to be predominantly a κ agonist. However, it may also act as a partial agonist or antagonist at the μ receptor.

3. **Pure antagonists**

The pure opioid antagonist drugs **naloxone, naltrexone,** and **nalmefene** have a relatively high affinity for μ-opioid binding sites. They have lower affinity for the other receptors but can also reverse agonists at κ and δ sites.

Naloxone is usually given by injection and has a short duration of action (1–2 hours) when given by this route. The major application of naloxone is in the treatment of acute opioid overdose. *It is very important that the relatively short duration of action of naloxone be borne in mind, because a severely depressed patient may recover after a single dose of naloxone and appear normal, only to relapse into coma after 1–2 hours*.

Naltrexone is well absorbed after oral administration. It has a half-life of 10 hours, and a single oral dose of 100 mg blocks the effects of injected heroin for up to 48 hours. Because of its long duration of action, naltrexone has been proposed as a maintenance drug for addicts in treatment programs.

Nalmefene, the newest of these agents, is a derivative of naltrexone but is available only for intravenous administration. Like naloxone, nalmefene is used for opioid overdose but has a longer half-life (8–10 hours).

Pharmacodynamics

Mechanism of Analgesic Action of Opioids

Opioid agonists produce analgesia by binding to specific G protein coupled receptors that are located in brain and spinal cord regions involved in the transmission and modulation of pain (Figure 31–1). Some effects may be mediated by opioid receptors on peripheral sensory nerve endings.

All three major receptors are present in high concentrations in the dorsal horn of the spinal cord. Receptors are present both on spinal cord pain transmission neurons and on the primary afferents that relay the pain message to them (Figure 2, sites A and B). Although opioid agonists directly inhibit dorsal horn pain transmission neurons, they also inhibit the release of excitatory transmitters from the primary afferents.

The fact that opioids exert a powerful analgesic effect directly on the spinal cord has been exploited clinically by direct application of opioid agonists to the spinal cord. This *spinal*

action provides a regional analgesic effect while reducing the unwanted respiratory depression, nausea and vomiting, and sedation that may occur from the *supraspinal actions* of systemically administered opioids. Under most circumstances, opioids are given systemically and thus act simultaneously at multiple sites. These include not only the ascending pathways of pain transmission beginning with specialized peripheral sensory terminals that transduce painful stimuli (Figure 2) but also descending (modulatory) pathways (Figure 3). At these sites as at others, opioids directly inhibit neurons; yet this action results in the *activation* of descending inhibitory neurons that send processes to the spinal cord and inhibit pain transmission neurons. This activation has been shown to result from the inhibition of inhibitory neurons in several locations (Figure 4). Taken together, interactions at these sites increase the overall analgesic effect of opioid agonists.

Animal and human clinical studies demonstrate that both endogenous and exogenous opioids can also produce analgesia at sites *outside* the CNS. Pain associated with inflammation seems especially sensitive to these peripheral opioid actions. The presence of functional μ receptors on the peripheral terminals of sensory neurons supports this hypothesis. Furthermore, activation of peripheral μ receptors results in a decrease in sensory neuron activity and transmitter release. The endogenous release of β-endorphin produced by immune cells within injured or inflamed tissue represents one source of physiologic peripheral μ-receptor activation. Intra-articular administration of opioids, eg, following arthroscopic knee surgery, has shown clinical benefit for up to 24 hours. For this reason opioids selective for a peripheral site of action may be useful adjuncts in the treatment of inflammatory pain.

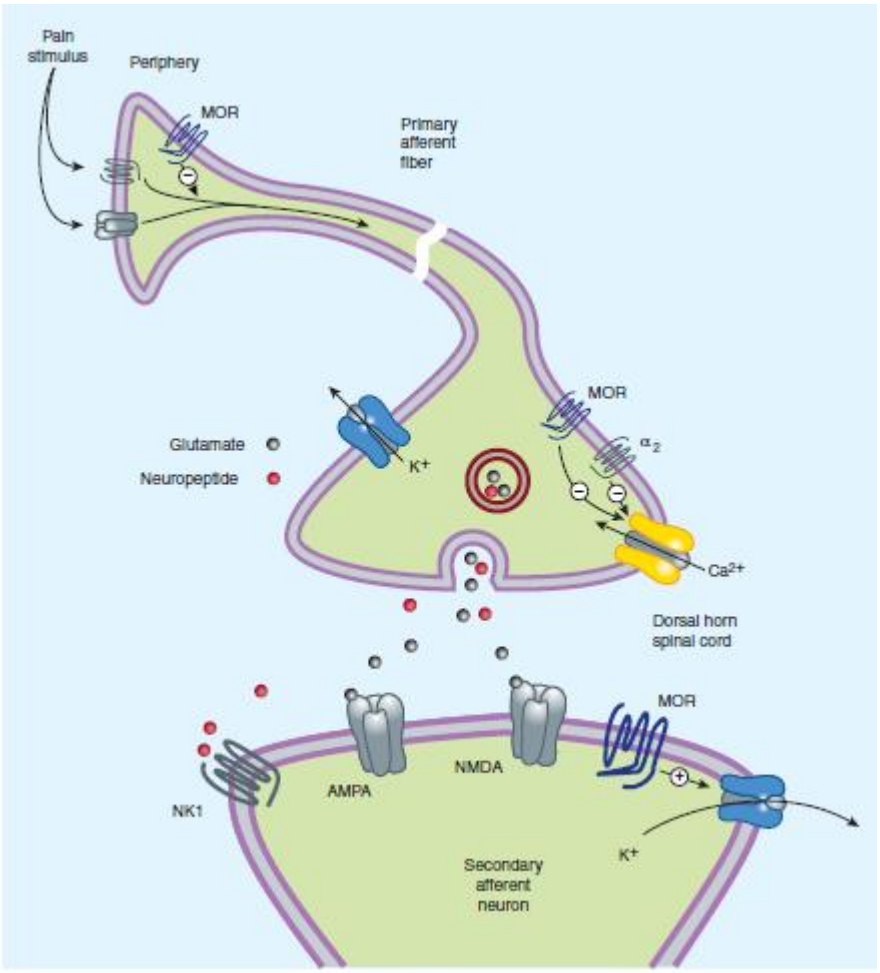

FIGURE 1 Potential receptor mechanisms of analgesic drugs. The primary afferent neuron (cell body not shown) originates in the periphery and carries pain signals to the dorsal horn of the spinal cord, where it synapses via glutamate and neuropeptide transmitters with the secondary neuron. Pain stimuli can be attenuated in the periphery (under inflammatory conditions) by opioids acting at μ-opioid receptors (MOR) or blocked in the afferent axon by local anesthetics (not shown). Action potentials reaching the dorsal horn can be attenuated at the presynaptic ending by opioids and by calcium blockers (ziconotide), α_2 agonists, and possibly, by drugs that increase synaptic concentrations of norepinephrine by blocking reuptake (tapentadol). Opioids also inhibit the postsynaptic neuron, as do certain neuropeptide antagonists acting at tachykinin (NK1) and other neuropeptide receptors.

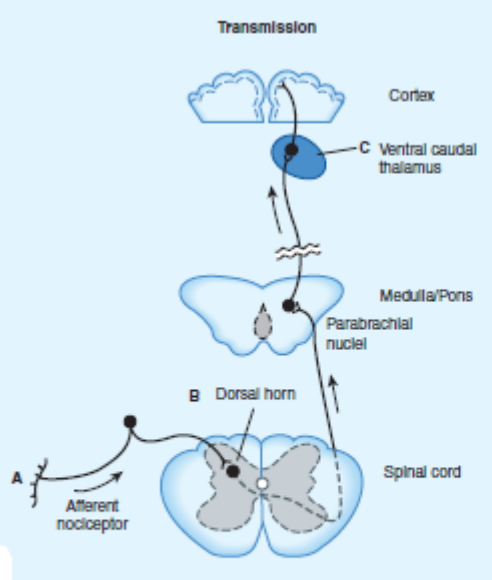

FIGURE 2 Putative sites of action of opioid analgesics. Sites of action on the afferent pain transmission pathway from the periphery to the higher centers are shown. **A:** Direct action of opioids on inflamed or damaged peripheral tissues (see Figure 31–1 for detail). **B:** Inhibition also occurs in the spinal cord (see Figure 31–1). **C:** Possible sites of action in the thalamus

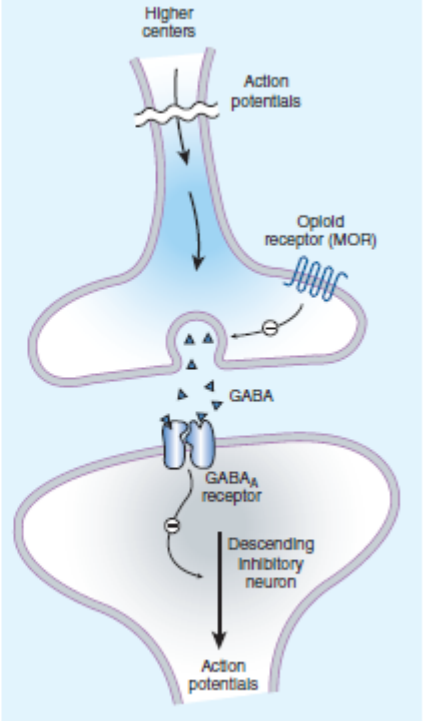

FIGURE 3 Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)–mediated analgesia on descending pathways. The pain-inhibitory neuron is indirectly activated by opioids (exogenous or endogenous), which inhibit an inhibitory (GABAergic) interneuron. This results in *enhanced* inhibition of nociceptive processing in the dorsal horn of the spinal cord (see Figure 31–4).

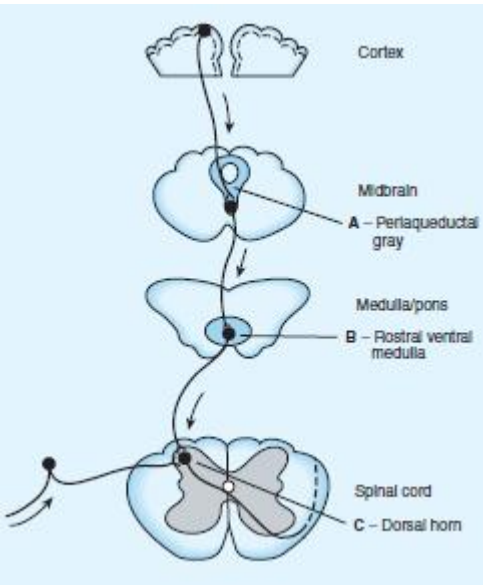

FIGURE 4 Opioid analgesic action on the descending inhibitory pathway. Sites of action of opioids on pain-modulating neurons in the midbrain and medulla including the midbrain periaqueductal gray area **(A),** rostral ventral medulla **(B),** and the locus caeruleus indirectly control pain transmission pathways by enhancing descending inhibition to the dorsal horn **(C).**

Pharmacologic Effects of Opioids

1. Central nervous system effects

The principal effects of opioid analgesics are on the CNS; the more important ones include analgesia, euphoria, sedation, and respiratory depression. With repeated use, a high degree of tolerance occurs to all of these effects

a. Analgesia: Pain consists of both sensory and affective (emotional) components. Opioid analgesics are unique in that they can reduce both aspects of the pain experience.

b. Euphoria: Opioids (especially m agonists) can cause a pleasant floating sensation with lessened anxiety and distress. However, dysphoria, an unpleasant state characterized by restlessness and malaise, may also occur (especially with κ agonists).

c. Sedation: Drowsiness and clouding of mentation are common effects of opioids. Marked sedation occurs more frequently with compounds closely related to the phenanthrene derivatives (e,g, morphine) and less frequently with the synthetic agents such as meperidine and fentanyl.

d. Respiratory depression: All of the opioid analgesics can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms. The respiratory depression is dose-related. Alveolar Pco2 may increase, and response to a carbon dioxide challenge depress. A small to moderate decrease in respiratory function, may be well tolerated in the patient without prior respiratory impairment. However, in individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, or cor pulmonale, this decrease in respiratory function may not be tolerated.

e. Cough suppression: Suppression of the cough reflex is a well-recognized action of opioids. Codeine in particular has been used to advantage in persons suffering from pathologic cough. However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

f. Miosis: Constriction of the pupils is seen with virtually all opioid agonists. Miosis is a pharmacologic action to which little or no tolerance develops, even in highly tolerant addicts; thus, it is valuable in the diagnosis of opioid overdose. This action, which can be blocked by opioid antagonists, is mediated by parasympathetic pathways, which, in turn, can be blocked by atropine.

g. Truncal rigidity: Several opioids can intensify tone in the large trunk muscles. Truncal rigidity reduces thoracic compliance and thus interferes with ventilation. The effect is most apparent when high doses of the highly lipid-soluble opioids (eg, fentanyl, sufentanil, alfentanil, remifentanil) are rapidly administered intravenously. The concomitant use of neuromuscular blocking agents can prevent truncal rigidity while preserving analgesia.

h. Nausea and vomiting*:* The opioid analgesics can activate the brainstem chemoreceptor trigger zone to produce nausea and vomiting. As ambulation seems to increase the incidence of nausea and vomiting there may also be a vestibular component in this effect.

2. Peripheral effects

a. Cardiovascular system: Blood pressure is usually well maintained in subjects receiving opioids unless the cardiovascular system is stressed, in which case hypotension may occur. This hypotensive effect is probably due to peripheral arterial and venous dilation, which has been attributed to a number of mechanisms including central depression of vasomotor-stabilizing mechanisms and release of histamine. Caution should be exercised in patients with decreased blood volume, because the above mechanisms make these patients susceptible to hypotension. Increased Pco2, as a consequence of respiratory depression, leads to cerebral vasodilation associated with a decrease in cerebral vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

b. Gastrointestinal tract: Constipation has long been recognized as an effect of opioids, an effect that does not diminish with continued use. The constipating effects of the opioids are

mediated through an action on the enteric nervous system as well as the CNS. In the large intestine, propulsive peristaltic waves are diminished and tone is increased; this delays passage of the fecal mass and allows increased absorption of water, which leads to constipation. The large bowel actions are the basis for the use of opioids in the management of diarrhea, and constipation is a major problem in the use of opioids for control of severe cancer pain.

c. Biliary tract*:* The opioids contract biliary smooth muscle, which can result in biliary colic.

d. Renal*:* Renal function is depressed by opioids. It is believed that in humans this is chiefly due to decreased renal plasma flow. In addition, μ opioids have an antidiuretic effect in humans. Ureteral and bladder tone are increased by therapeutic doses of the opioid analgesics. Increased sphincter tone may precipitate urinary retention, especially in postoperative patients. Occasionally, ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone.

e. Uterus*:* The opioid analgesics may prolong labor. Fentanyl and meperidine (pethidine) inhibit uterine contractility but only at supraclinical concentrations; morphine had no reported effects.

f. Endocrine*:* Opioids stimulate the release of ADH, prolactin, and somatotropin but inhibit the release of luteinizing hormone. Patients receiving chronic opioid therapy can have low testosterone resulting in decreased libido, energy, and mood. Women can experience dysmenorrhea or amenorrhea.

g. Pruritus*:* The opiates, such as morphine and codeine, produce flushing and warming of the skin accompanied sometimes by sweating, urticaria, and itching. Although peripheral histamine release is an important contributor, all opioids can cause pruritus via a central (spinal cord and medullary) action on pruritoceptive neural circuits.

3. Other Effects

A. Tolerance: With frequently repeated therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness; this loss of effectiveness is termed tolerance. To reproduce the original response, a larger dose must be administered. With repeated use, a high degree of tolerance occurs to analgesia, euphoria, sedation, respiratory depression, antidiuretic, emetic, and hypotensive effects but not to the miotic, convulsant, and constipating actions of opioids. Tolerance may not become clinically manifest until after 2–3 weeks of frequent exposure to ordinary therapeutic doses. Nevertheless, tolerance develops most readily when large doses are given at short intervals and is minimized by giving small amounts of drug with longer intervals between doses.

Cross-tolerance is an extremely important characteristic of the opioids, ie, patients tolerant to morphine often show a reduction in analgesic response to other agonist opioids. This is particularly true of those agents with primarily m-receptor agonist activity. Morphine and its congeners exhibit cross-tolerance not only with respect to their analgesic actions but also to their euphoriant, sedative, and respiratory effects. However, the cross-tolerance existing among the μ-receptor agonists can often be partial or incomplete. This clinical observation has led to the concept of "opioid rotation," which has been used for many years in the treatment of cancer pain. A patient who is experiencing decreasing effectiveness of one opioid analgesic regimen is "rotated" to a different opioid analgesic (eg, morphine to hydromorphone; hydromorphone to methadone) and typically experiences significantly improved analgesia at a reduced overall equivalent dosage.

B. Physical Dependence: Along with tolerance, physical dependence develops. Physical dependence is defined as a characteristic **withdrawal** or **abstinence syndrome** when a drug is stopped or an antagonist is administered. There are differences in the severity of withdrawal effects between opioids. For example, withdrawal from dependence on a strong agonist is associated with more severe withdrawal signs and symptoms than withdrawal from

a mild or moderate agonist. Administration of an opioid *antagonist* to an opioid-dependent person is followed by brief but severe withdrawal symptoms. The potential for physical and psychological dependence of the partial agonist-antagonist opioids appears to be less than that of the strong agonist drugs.

The signs and symptoms of withdrawal include rhinorrhea, lacrimation, yawning, chills, gooseflesh (piloerection), hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, and hostility.

C. Addiction: As defined by the American Society of Addiction Medicine, addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Addiction is characterized by inability to abstain consistently, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response.

Clinical Uses of Opioid Analgesics

A. Analgesia

Severe, *constant* pain is usually relieved with opioid analgesics having high intrinsic activity, whereas sharp, intermittent pain does not appear to be as effectively controlled. The pain associated with cancer and other terminal illnesses must be treated aggressively and often requires a multidisciplinary approach for effective management. Such conditions may require continuous use of potent opioid analgesics and are associated with some degree of tolerance and dependence. *However, this should not be used as a barrier to providing patients with the best possible care and quality of life.*

Opioid analgesics are often used during obstetric labor. Because opioids cross the placental barrier and reach the fetus, care must be taken to minimize neonatal depression. If it occurs, immediate injection of the antagonist naloxone will reverse the depression. The phenylpiperidine drugs (eg, meperidine) appear to produce less depression, particularly

respiratory depression, in newborn infants than does morphine; this may justify their use in obstetric practice.

The acute, severe pain of renal and biliary colic often requires a strong agonist opioid for adequate relief. However, the drug-induced increase in smooth muscle tone may cause a paradoxical *increase* in pain secondary to increased spasm. An increase in the dose of opioid is usually successful in providing adequate analgesia.

B. Acute Pulmonary Edema

The relief produced by intravenous morphine in patients with dyspnea from pulmonary edema associated with left ventricular heart failure is remarkable. Morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema.

C. Cough

Suppression of cough can be obtained at doses lower than those needed for analgesia. However, in recent years the use of opioid analgesics to allay cough has diminished largely because of the availability of a number of effective synthetic compounds that are neither analgesic nor addictive such as dextrometorphane.

D. Diarrhea

Diarrhea from almost any cause can be controlled with the opioid analgesics, but if diarrhea is associated with infection such use must not substitute for appropriate chemotherapy. Diphenoxylate or loperamide with more selective gastrointestinal effects and few or no CNS effects, are used to control diarrhea.

E. Shivering

Although all opioid agonists have some propensity to reduce shivering, meperidine is reported to have the most pronounced antishivering properties. Meperidine apparently blocks shivering mainly through an action on subtypes of the $\alpha 2$ adrenoceptor.

F. Applications in Anesthesia

The opioids are frequently used as premedicant drugs before anesthesia and surgery because of their sedative, anxiolytic, and analgesic properties. They are also used intraoperatively both as adjuncts to other anesthetic agents and, in high doses, as a primary component of the anesthetic regimen. Opioids are most commonly used in cardiovascular surgery and other types of high-risk surgery in which a primary goal is to minimize cardiovascular depression. In such situations, mechanical respiratory assistance must be provided.

Treatment of Opioid Overdose

Intravenous injection of naloxone dramatically reverses coma due to opioid overdose but not that due to other CNS depressants. Use of the antagonist should not, of course, delay the institution of other therapeutic measures, especially respiratory support.

Contraindications and Cautions in Therapy

1. Use of pure agonists with weak partial agonists: When a weak partial agonist such as pentazocine is given to a patient also receiving a full agonist (eg, morphine), there is a risk of diminishing analgesia or even inducing a state of withdrawal; thus combining a full agonist with partial agonist opioids should be avoided.

2. Use in patients with head injuries: Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation. In patients with elevated intracranial pressure, this may lead to lethal alterations in brain function.

3. Use during pregnancy: In pregnant women who are chronically using opioids, the fetus may become physically dependent in utero and manifest withdrawal symptoms in the early postpartum period including irritability, shrill crying, diarrhea, or even seizures. When withdrawal symptoms are judged to be relatively mild, treatment is aimed at control of these symptoms using such drugs as diazepam; with more severe withdrawal, camphorated tincture of opium (paregoric; 0.4 mg of morphine/mL) in an oral dose of 0.12–0.24 mL/kg is used. Oral doses of methadone (0.1–0.5 mg/kg) have also been used.

4. Use in patients with impaired pulmonary function: In patients with borderline respiratory reserve, the depressant properties of the opioid analgesics may lead to acute respiratory failure.

5. Use in patients with impaired hepatic or renal function: Because morphine and its congeners are metabolized primarily in the liver, their use in patients in prehepatic coma may be questioned. Half-life is prolonged in patients with impaired renal function, and morphine and its active glucuronide metabolite may accumulate; dosage can often be reduced in such patients.

6. Use in patients with endocrine disease: Patients with adrenal insufficiency (Addison's disease) and those with hypothyroidism (myxedema) may have prolonged and exaggerated responses to opioids.