Introduction to Opioids/Opiates

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Learning Objectives: After studying the material of this lecture, the student should:
1. Be able to list the precursors of the endogenous opioids and the opioid receptors with which the endogenous opioids interact.
2. Know the effects mediated by the interaction of opioids with each of the specific opioid receptors.
3. Learn the mechanism of the analgesic action of morphine.
4. Know the similarities and differences in the profile of clinically observed effects of the opioids.
5. Understand the clinical signs associated with opiate overdose and with opiate withdrawal and the therapies used for each condition.
6. Know the most common drugs used in the maintenance of opiate abstinence.
7. Understand therapeutic precautions when administering opiates.

NOTE: ALL TESTS WILL USE ONLY GENERIC NAMES OF DRUGS.
ANY TERM IN BOLD OR UNDERLINED IS ABSOLUTELY REQUIRED INFORMATION FOR TESTING.
ALL DIAGRAMS ARE REQUIRED INFORMATION FOR TESTING.
I. TERMINOLOGY
A. Narcotics
“Narcosis” = sleep
Legalistic term, proper pharmacological term is
“Opioid Analgesics”
B. Opium
extract of opium poppy
C. Opiates
drugs derived from opium. Examples are
morphine, codeine.
D. Opioids
any drug or peptide that has opiate-like effects
via binding to opiate receptors. Examples are the
endogenous opioids.

II. HISTORY
1806 - Serturner - isolated morphine
1832 - Robiquet - isolated codeine
1951 - Nalorphine- the first opiate antagonist
and treatment for overdose
1967 - William R. Martin first described opiate
receptor subtypes
Lots of things can modify pain sensitivity.

III. ENDOGENOUS OPIOIDS

I.e. those opioid peptides which occur naturally in the body

A. Beta-Endorphin
   Goldstein, 1975
   31 amino acids
   pituitary/hypothalamus/adrenal

B. Met-Enkephalin
   Hughes and Kosterlitz, 1975
   Leu-Enkephalin
   Hughes and Kosterlitz, 1975
   5 amino acids

C. Dynorphin important in modulation of analgesia

D. Orphanin FQ -- anti-analgesic

E. Endomorphins 1 and 2 -- mu receptor endogenous ligands - analgesic

Four genes are involved:
1. Pro-opiomelanocortin
2. Proenkephalin
3. Prodynorphin
4. Pronociceptin/orphanin FQ
Figure 1. Schematic representation of the structures of the protein precursors of the three families of opioid peptides.
Abbreviations: ENK = enkephalin; DYN = dynorphin; END = endorphin. The sequence of met-enkephalin is Tyr-Gly-Gly-Phe-Met, while that of leu-enkephalin is Tyr-Gly-Gly-Phe-Leu. (modified from Akil et al., 1984)

NEW "KIDS" ON THE BLOCK!

D. Orphanin FQ -- anti-analgesic

E. Endomorphins 1 and 2 - mu receptor endogenous ligands - analgesic
Table 1. Multiple Opiate Receptors (mu, delta, and kappa opioid receptors have been cloned)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonists</th>
<th>Antagonists</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MU</strong>&lt;sub&gt;1&lt;/sub&gt; endomorphins-endogenous ligands</td>
<td>morphine, codeine, meperidine, fentanyl, methadone, propoxyphene, oxycodone, tramadol</td>
<td>Naloxone, Naltrexone</td>
<td>Analgesia, Euphoria, Physical dependence</td>
</tr>
<tr>
<td><strong>MU</strong>&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Agonists: Same as MU&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Antagonists: Same as MU&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Effects: Respiratory depression (medulla), Bradycardia</td>
</tr>
<tr>
<td><strong>KAPPA 1, 2, 3</strong> Dynorphins - endogenous ligands</td>
<td>Pentazocine, Butorphanol</td>
<td>Naloxone*, Naltrexone*</td>
<td>Miosis, Sedation, Spinal Analgesia</td>
</tr>
<tr>
<td><strong>SIGMA</strong></td>
<td>NOT an opioid receptor</td>
<td></td>
<td>Dysphoria, Mydriasis, Hallucinations</td>
</tr>
<tr>
<td><strong>DELTA 1&amp;2</strong> Met and Leu Enkephalin - Endogenous ligands</td>
<td>ALL MU AGONISTS ALSO ACT AT DELTA RECEPTORS</td>
<td>Naloxone, Naltrexone</td>
<td>Spinal analgesia, Respiratory rate DECREASED</td>
</tr>
<tr>
<td><strong>EPSILON</strong> Beta-endorphin - Endogenous ligand</td>
<td>Effects similar to Mu&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. The molecular mechanism of action of morphine. Disruption of the opioid receptor (mu1) gene leads to amnesia, one of the most dramatic effects of the mu-receptors, demonstrating that the effects of morphine and other drugs are mediated by a single gene product. (From: Anand, B. L., 1995.)

IV. MECHANISM OF ACTION

**ACUTE EFFECTS OF OPIOIDS**

<table>
<thead>
<tr>
<th>Mu1 receptor</th>
<th>Delta 1 receptor</th>
<th>Kappa 1 receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-endorphin</td>
<td>Met and leu enkephalin</td>
<td>Dynorphin A</td>
</tr>
</tbody>
</table>

**Endorphins**

**MORPHINE**

<table>
<thead>
<tr>
<th>AC</th>
<th>c-AMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>K+</td>
</tr>
</tbody>
</table>

**CALCIUM ENTR Y**

<table>
<thead>
<tr>
<th>Calcium entry</th>
<th>[Ca]</th>
</tr>
</thead>
</table>

**POTASSIUM CHANNELS**

Decreased release of neurotransmitters
A. Decrease cyclic AMP
1. mu and delta receptors are coupled to adenylate cyclase (AC) via a G protein (GTP-binding protein)
2. changes in phosphorylation of proteins resulting in decreases in calcium entry.
3. mu and delta receptor activation decreases c-AMP

B. Increase potassium efflux
1. results in decreased firing of neurons (hyperpolarization). This also decreases calcium entry.
2. All opioid receptor activation increases potassium efflux

C. Decreases calcium entry to neurons
1. mu, delta, and kappa receptor activation decreases calcium entry
2. blocks release of neurotransmitters since intracellular calcium levels ([Ca]i) levels fall.

Gate Control Theory of Pain

V. Pain pathways from Brody et al., 1995
VII. CLINICAL EFFECTS

A. Summary of clinical responses produced by opioid analgesics:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analgesia</th>
<th>Antitussive</th>
<th>Constipation</th>
<th>Respiratory</th>
<th>Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>heroin</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>codeine</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>meperidine</td>
<td>++</td>
<td>-</td>
<td>±</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>propoxyphene</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pentazocine</td>
<td>++</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>butorphanol</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

++++ (strongest effect); + (weak effect); ± (weak and variable effect); - (no effect)

B. Other effects of the opioid analgesics:

1. Miosis
2. Nausea
3. Constipation – may be particularly problematic in older people, concomitant use of a stimulant laxative is advised.
4. Histamine release
5. Tolerance and Physical dependence

VIII. CLINICAL SIGNS OF OPIATE OVERDOSE

A. Coma
B. Pin-point pupils (miosis)
C. Respiratory depression
D. Decreased blood pressure
E. Decreased body temperature
F. Convulsions with some opiates

IX. MAINTENANCE OF OPIOID ABSTINENCE

A. Methadone
   1. long acting mu agonist
   2. orally active
B. Clonidine - alpha-2 agonist which decreases the release of NE (norepinephrine) and thus, decreases some of the adrenergic effects of opiate withdrawal
C. Naltrexone - oral or long acting depo-injection (experimental)
D. Buprenorphine - “First-line drug” mixed agonist/antagonist, blocks self-administration in opiate addicts, low abuse potential, mild physical dependence.
X. WITHDRAWAL FROM OPIATES

A. GENERALLY not life threatening

B. "Flu-like", emesis, diarrhea, chills

C. Due to release of NE and ACh (acetylcholine)

XI. THERAPEUTIC USES OF SELECTED OPIATES

A. Opiate Agonists

1. Morphine

a. used for severe pain
b. duration of action 4-5 hrs
c. active i.v. and i.m., and epidurally, LOW activity if given orally (high "first pass" effect)
d. elevate head of patient to avoid rostral flow of CSF to medulla following epidural to prevent respiratory depression
e. drug of choice for pain associated with myocardial infarction

f. also administered by patient-controlled infusion pumps. 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.
g. Clearance of morphine depends upon adequate renal function to clear the glucuronidated form of the morphine. The active ANALGESIC metabolite of morphine, morphine-6-glucuronide, is also cleared mainly via the kidney. Inadequate renal function will result in a build-up of both the parent drug and the metabolite. The elderly are particularly susceptible to such a build-up of the drugs resulting in respiratory depression and sedation. However, an adequate dose for pain control must be used.

B. Heroin

1. metabolized to morphine and monoacetylmorphine (which crosses into brain rapidly)
2. no accepted medical use in the USA, is used in Europe
3. 3 times as potent as morphine
4. Heroin use in pregnant women can lead to low birth weight babies born addicted to heroin, immune suppression and increased incidence of infections in both the mother and newborn, and increased incidence of AIDS.

C. Codeine

1. antitussive
2. orally active. Codeine administered i.v. has a greater tendency to release histamine and produce vasodilation and hypotension than does morphine. Thus, the use of codeine via the i.v. route is rare
3. 10% of it is metabolized to morphine
4. useful for mild to moderate pain; approximately 12 times less potent than morphine
5. combined with aspirin or acetaminophen to increase pain relief and decrease amount of opiate used (Tylenol #3). 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.
Dextromethorphan (DXM):
– Synthetic morphine derivative
– Equally antitussive as codeine
– Does not act through opioid receptors
– No analgesic or GI effects

D. Meperidine

Meperidine is a derivative of morphine first developed in the late 1930’s by scientists attempting to produce an anti-cholinergic drug. The drug has some anticholinergic side effects leading to tachycardia, blurred vision and dry mouth.

1. 8-10 fold less potent than morphine
2. rapid onset and offset

D. Meperidine (CONT.)

3. toxicity = excitation, tremors, cardiac effects.

The use of meperidine in those patients with a history of seizures or taking medication to prevent seizures is contraindicated.

Hydantoins 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 in that it has anti-cholinergic effects and can increase both heart rate and ectopic beats.

E. Fentanyl, Sufentanil, Alfentanil, Remifentanyl

1. Used as adjuncts to anesthesia, transdermally as analgesics (fentanyl only), and in oral lozenge form (fentanyl only) for the induction of anesthesia especially in children who might become anxious if given i.v. anesthesia.

2. Fentanyl is 80-100 times more potent than morphine. Sufentanil is 5- to 7-fold more potent than fentanyl, while alfentanil is approximately 20 times more potent than morphine.

E. Fentanyl, Sufentanil, Alfentanil, Remifentanyl (CONT.)

3. Short duration of action. The onset of action of the drugs is rapid (<20 min). Dosage is determined by the lean body mass of the patient since the drugs are lipophilic and tend to get trapped in body fat. Body fat acts as a reservoir for the drugs thus prolonging their half-life. In addition, redistribution of the drugs from the brain to fat stores leads to a rapid offset of action inconsistent with the relatively long half-life of the drugs (6-8 hours).

4. Fentanyl transdermal patches are available for analgesia in chronic pain and postsurgical patients. The use of the patch is, however, contraindicated for patients immediately after surgery due to the resultant profound respiratory depression associated with such use. The patches need to be removed and replaced every 3 days. The onset of action of the transdermal fentanyl is slower than that of morphine (oral). Thus, patients may require the use of oral analgesics until the fentanyl levels from the patch have reached a therapeutic plateau.

5. The drugs produce stiffening of the chest wall musculature, an effect reversed by naloxone.
F. Methadone

1. equally potent to morphine, but orally active. Unlike morphine, it is generally not used epidurally due to the long duration of action. It is also rarely, if ever, used in PCA systems or in pregnant women during labor.

2. long onset and offset

3. The tricyclic antidepressants and certain benzodiazepines can inhibit the metabolism of methadone, thereby increasing accumulation of the drug, prolonging its half-life and intensifying its side effects.

4. In pregnant heroin-addicted women, substitution of methadone for heroin has been shown to be associated with less low birth weight newboms and less problems with learning and cognition later in the life of the child.

G. Propoxyphene

1. mild to moderate pain

2. often combined with aspirin or acetaminophen

3. very toxic when combined with alcohol. Toxicity from propoxyphene use, 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 min to 1 hour). The drug is not indicated for those with histories of attempted suicide or depressive illnesses.

4. 2 fold less potent than codeine

5. Like meperidine, propoxyphene has an active metabolite, norpropoxyphene, which is not analgesic, but has excitatory and local anesthetic effects on the heart similar to those of quinidine.

H. Oxycodone

1. Use Management of moderate to severe pain, normally used in combination with non-narcotic analgesics.

Oxycodone blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opioid receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers.

Mu and kappa are the two subtypes of the opioid receptor which oxycodone binds to to cause analgesia.

Acetaminophen and oxycodone [Percocet]
Aspirin and oxycodone [Percodan]

OxyContin® [timed-release oxycodone]

Use with caution in the elderly, debilitated, severe hepatic or renal function. Hemodynamic effects (hypotension, orthostasis) may be exaggerated in patients with hypovolemia, concurrent vasodilating drugs, or in patients with head injury.

Respiratory depressant effects and capacity to elevate CSF pressure may be exaggerated in presence of head injury, other intracranial lesion, or pre-existing intracranial pressure.

Tolerance or drug dependence may result from extended use. Healthcare provider should be alert to problems of abuse, misuse, and diversion.

Do not crush controlled-release tablets. Some preparations contain sulfites which may cause allergic reactions. OxyContin® 80 mg and 160 mg strengths are for use only in opioid-tolerant patients requiring high daily dosages (>160 mg (80 mg formulation) or >320 mg (160 mg formulation)).
J. Tramadol (Ultram)
- Used as analgesic in the United States.
- It exhibits a dual analgesic action:
  1. It is a partial agonist at mu receptors.
  2. It blocks the presynaptic reuptake of norepinephrine and serotonin.
- In the United States, it is only available for oral use.
- The drug will undergo a two step metabolism, and the first metabolite (mono-demethyl tramadol) is as active as the parent compound and is a potent ANALGESIC.
- Side effects include drowsiness, nausea, vomiting, constipation, and headache.
- The combination of tramadol and serotonin type anti-depressant drugs should be avoided. The combination of the two can increase toxicity of antidepressants.

XII. DRUGS WITH BOTH AGONIST AND ANTAGONIST PROPERTIES i.e. "mixed agonist/antagonist"

Definition:
The mixed opioid agonist/antagonists are potent analgesics in opioid-naive patients, but precipitate withdrawal in patients that are currently physically dependent on opioids. The drugs were developed to reduce the addiction potential of the opioids, while retaining the analgesic potency of the drugs. The analgesic effect of the drugs is generally attributed to interaction at the kappa, and to a lesser extent, the mu opioid receptor. Interaction at the kappa receptor increases the sedative effects of the drugs. The euphoric effect is due to interaction with the mu receptor. The dysphoric and psychotomimetic side effects of the drugs are attributed to interaction at the sigma receptor (non-opioid).

A. Pentazocine
  1. Pentazocine is contraindicated in patients with myocardial infarction because it increases heart rate and cardiac load.
  2. It is contraindicated in epileptic patients because it decreases seizure threshold.
  3. In head trauma patients, the drug can increase intracranial pressure and increase brain injury.
  4. Pentazocine use in patients with psychoses is contraindicated due to the psychotomimetic side effects of the drug.
  5. Pentazocine is not recommended in the elderly because of its propensity to cause delirium and agitation.

The combination of pentazocine with the antihistamine, tripelennamine, results in a combination known to drug abusers as "I"s and Blues". This combination produces heroin-like subjective effects and is used by heroin addicts in the absence of heroin.

B. Buprenorphine
  1. The drug is highly lipophilic and 25 to 50 times more potent than morphine as an analgesic.
  2. The side effects produced by the drug such as sedation and respiratory depression are more intense and of longer duration than those produced by morphine.
  3. The respiratory depressant effects of the drug are not readily reversed by naloxone.
  4. The abuse potential of the drug is low. High doses of the drug are perceived by addicts as being “morphine-like”. However, the drug has been shown to reduce the “craving” for morphine and also for the stimulant, cocaine. Thus, the drug represents a potential new recently approved therapy for the treatment of addiction to both classes of drugs.
Subutex (buprenorphine hydrochloride) and Suboxone tablets (buprenorphine hydrochloride and naloxone hydrochloride) is approved for the treatment of opiate dependence. Subutex and Suboxone treat opiate addiction by preventing symptoms of withdrawal from heroin and other opiates.

**SUBOXONE** (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets)
**SUBUTEX** (buprenorphine HCl sublingual tablets)

Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. § 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

**DESCRIPTION**

SUBOXONE sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

SUBUTEX sublingual tablets contain buprenorphine HCl.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Who is qualified to prescribe SUBOXONE or SUBUTEX?

Physicians who:
- Meet one or more of the following training requirements
- Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
- Hold an addiction certification from the American Society of Addiction Medicine
- Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association
- Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, The American Academy of Addiction Psychiatry, the American Osteopathic Association, the American Osteopathic Association, and the American Psychiatric Association are authorized to provide this training.

Buprenorphine and naloxone replacement therapy: Buprenorphine competes with the full agonist opioids for the receptor. Since buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect, enough to stop withdrawal but not enough to cause intense euphoria.

Opioid receptors unsatisfied — Withdrawal: As someone becomes “tolerant” to opioids their opioid receptors become less sensitive. More opioids are then required to produce the same effect. Once “physically dependent” the body can no longer manufacture enough natural opioids to keep up with this increased demand. Whenever there is an insufficient amount of opioid receptors activated, the body feels pain. This is withdrawal.

Opioid receptors satisfied with a full-agonist opioid: The strong opioid effect of heroin and painkillers stops the withdrawal for a period of time (4-24 hours). Initially, euphoric effects can be felt. However, after prolonged use, tolerance and physical dependence can develop. Now, instead of producing a euphoric effect, the opioids are primarily just preventing withdrawal symptoms.

Who is qualified to prescribe SUBOXONE or SUBUTEX? (continued)

- Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, The American Academy of Addiction Psychiatry, the American Osteopathic Association, the American Osteopathic Association, and the American Psychiatric Association are authorized to provide this training.
XIII. OPIATE ANTAGONISTS
i.e. block the effects of opiates

A. Naloxone
1. I.V. for overdose of opioids
2. The drug is approved for use in neonates to reverse respiratory depression induced by maternal opioid use.

B. Nalmefene (Revex)
1. A long acting injectable pure opioid antagonist recently introduced in the United States.
2. The onset of action is 2 min after i.v. administration. Metabolism of the drug is slow in the liver. The metabolite is inactive.
3. The half-life of 11 hours is about 5 times that of naloxone.
4. Indications for the drug include use in postoperative settings to reverse respiratory depression, and use in opioid overdose. However, due to the long duration of action of nalmefene, naloxone may be preferred for treatment of overdose because it produces a shorter duration of withdrawal effects.

C. Naltrexone
1. 3-5-fold more potent than naloxone. The major metabolite, 6-beta-naltrexol, is also a pure opioid antagonist and contributes to the potency and duration of action of naltrexone.
2. Oral for opioid abstinence. It has been recently reported that naltrexone can reduce the “craving” for alcohol in alcoholic patients.
3. New preparations long-acting for implantation under skin.

C. Butorphanol
1. similar in action to pentazocine
2. 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.
3. Preparation of this is as a nasal spray is especially effective for migraine headaches, also used for postoperative pain.
4. Nasal administration of the drug decreases the onset of action to 15 min 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 4-5 hours. The convenience of such administration to those patients requiring repeat dosing with the opioids is a major advantage of the drug.
XIV. ADVERSE REACTIONS AND PRECAUTIONS FOR THE USE OF OPIATES:

A. Respiratory depression - by decrease in the response to CO₂, especially true in anesthesia and in the elderly, immobile patient.

B. Blockade of cough reflex - detrimental in patients with excessive respiratory secretions.

C. Patients in shock may exhibit severe hypotension if given opiates.

D. Head trauma patients should be given opiates with extreme caution since the hypercapnia and hypoventilation may dilate cerebral vessels and increase intracranial pressure. The miosis present following opiate administration may also mask pupillary dilation present with brain injury.

E. The opiates require functional hepatic metabolism for their excretion. These drugs also accumulate in patients with renal insufficiency, which is common in the elderly. Opiates increase the release of ADH and decrease urine output.

F. The opiates synergize with CNS depressants. 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, monoamine oxidase (MAO) inhibitors or the anxiolytics such as diazepam. The elderly are prone to experience side effects of opioids, including sedation and mental status alterations.