

Opioid (“Narcotic”) Analgesics and Antagonists

(see posted self-study, objectives/study guide too)

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Some Terms and Concepts*

- Opioids
- Endogenous opioid peptides (endorphins, etc.)
- Narcotic(s)

*See your text.

Morphine and Other “Strong” Opioid Analgesics Act As Agonists on One or More Types of Opioid Receptors Called Mu and Kappa

| <u>Response</u> | <u>Mu</u> (μ) | <u>Kappa</u> (κ) |
|------------------------|---------------------|---------------------------|
| • Analgesia | ✓ | ✓ |
| • Resp. Depression | ✓ | |
| • Euphoria | ✓ | |
| • Sedation | ✓ | ✓ |
| • Reduced gut motility | ✓ | ✓ |

Take-home point: activation of mu receptors is the most important in terms of the beneficial and adverse effects of morphine, the prototype.

The Main Drug Groups

- “Pure” opioid agonists -- morphine, many others
- Mixed agonist-antagonists -- pentazocine
 - stimulate (agonist for) *kappa* receptors, but rather weakly
 - block *mu* receptors rather strongly
- “Pure” opioid antagonists -- naloxone
 - block opioid receptors

What Do We Mean By “Pure”?

- In pharmacology, when we say (for example) that morphine is a “pure” opioid agonist, we mean it does nothing to opioid receptors other than activate them, as an agonist.
- Likewise, naloxone, a pure opioid antagonist, does nothing to opioid receptors but block them.
- Contrast this with pentazocine, which stimulates some opioid receptors, blocks others.

Legal Classifications of “Controlled Substances”

- Schedule I....Schedule IV, with Schedule I agents having the most/tightest legal controls, Schedule IV agents the least
- Reflects potential for abuse (I > II > III > IV)
- Schedule I drugs (e.g., heroin): illegal to possess, use, distribute (etc.) for any purpose (other than approved research); have *no* valid/recognized medical use
- Controlled substances aren’t just opioids (“narcotics”) – many drugs, nearly all having CNS activity of some sort, are “controlled”

Morphine Pharmacokinetics

- Absorbed well from all injection sites
- Oral... poor bioavailability if morphine administration is *started* with this route (so don’t start with oral therapy)
 - Effective oral dose about 6-X the subQ dose because of extensive 1st pass metabolism.. give initial doses orally and little gets into the systemic circulation
 - Slow onset, unsuitable for initiating prompt pain control (but OK for maintenance once opioid therapy has been started with parenteral route, since the liver enzymes responsible for morphine metabolism will have been saturated by prior doses)

Main Effects of Morphine: Analgesia

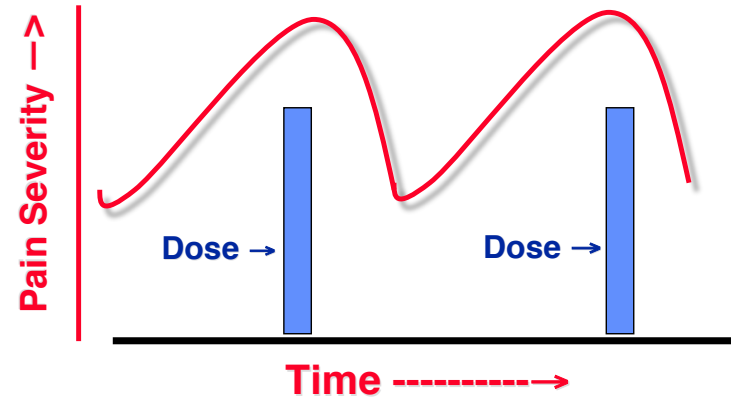
- An effect in the CNS (as opposed to peripheral action of analgesics such as acetaminophen, aspirin)
- Best for moderate - severe pain, considered “overkill” for mild pain, for which weaker analgesics are indicated
- Actual ↓ pain sensation, plus ↓ perception of pain as unpleasant (“it still hurts a bit, but it doesn’t bother me as much”)

Be Sure to See Your Text...

...For comparisons (pros, cons) of the three main ways to control pain in patients who require an opioid analgesic:

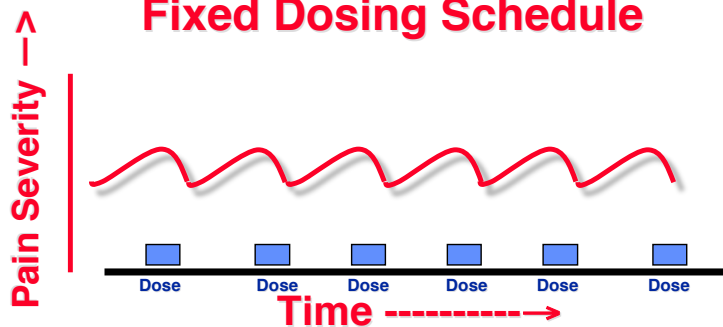
- PRN (as needed)... when the patient complains of worsening or recurring pain
- Fixed-dose schedules (give drug at specified times, not just when the patient “hurts”)
- Continuous IV infusion/patient-controlled analgesia

P.R.N. (as needed) Administration of Analgesic



“As needed” (prn) treatment waits until the patient is in significant pain to give next dose; results in higher daily doses than with regular (fixed-time) dosing, far less patient comfort.

Fixed Dosing Schedule



Giving an opioid on a fixed schedule, rather than waiting for the patient to redevelop severe pain before giving the next dose, lowers the total daily dose of the opioid and provides much better patient comfort. Giving the drug by continuous infusion, with dosing controlled by the patient (see Patient Controlled Analgesia in text) provides even better pain control, patient satisfaction

Euphoria, Dysphoria from Morphine, Other Opioids

- Usually euphoria, esp. when used for pain
- Contributes to abuse
- Tolerance develops to euphoria
- Some people report dysphoria (a bad or ill-at-ease/unpleasant response), but seldom with therapeutic use for pain control

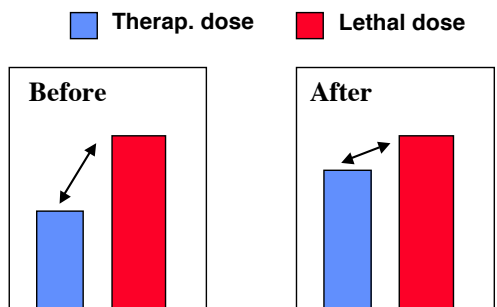
Sedation, Drowsiness, “Mental Clouding”

- Often clinically useful when pain present
- May be problematic for outpatients (interferes with many daily activities requiring unimpaired alertness, cognition)
- Potentiated by all CNS depressants

Ventilatory Depression

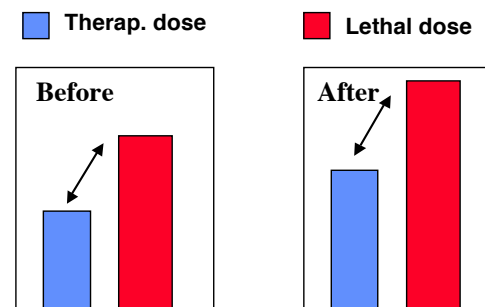
- Dose-dependent effect of opioids on the respiratory “control center” in the brain’s medulla
- ↓ ventilation → ↑ pCO₂
 - In presence of opioid, ↑ pCO₂ does *not* → ↑ ventilation as normally occurs
 - also → ↑ intracranial pressure (“brain swelling”) which → ↓ cerebral blood flow (see next slide)
- Ventilatory depression almost always the cause of death
- May also occur in newborns when mom receiving opioid, since many opioids cross “placental barrier”
- Tolerance to respiratory depressant effects develops (LD₅₀ rises) as tolerance to other effects develops... the therapeutic index does NOT change

Recall: Therapeutic Index (Margin of Safety) Before and After Barbiturate or Alcohol Tolerance Develops



Notice that as tolerance develops to a therapeutic effect (e.g., sedation), there’s little change in the lethal dose. The margin of safety gets smaller. You’ve seen this slide before!

Therapeutic Index (Margin of Safety) Before and After Opioid Tolerance Develops



Compare this with the previous slide. As opioid tolerance develops, the average therapeutic (e.g., analgesic) and lethal doses both rise, more or less in parallel, therapeutic index remains nearly constant.

Use Opioids with Extra Caution (or Avoid) in Patients with Closed-Head Injury (CHI)

- CHI → ↑ intracranial pressure (ICP) due to brain swelling, which in turn can ↓ cerebral blood flow, ↓ ventilation, cause other neurologic impairments, some of which are valuable in diagnosing the patient's head injury
- Morphine adds to problems by causing these same effects, causing further ↓ ventilation, ↑ of ICP, ↓ blood flow, and masking/obscuring some diagnostic indicators of CHI

GI and Urinary Tract Effects

- Constipation, urinary retention
- Morphine may → biliary tract spasm (“colic”)
 - Meperidine (DEMEROL) has fewer adverse effects on gall bladder/biliary tract, often considered preferred for short-term pain control in cases of bile duct spasm (gall bladder disease)

Other

- Vasodilation, impaired activity of baroreceptor reflex, may → **hypotension, including orthostatic**
- **Miosis**
 - no tolerance -- pupils stay fixed (until patient is near death from overdose)
- **Emesis**, esp. in ambulatory patients (simplest and often most effective way to manage is to have patient lie down)
- **Antitussive** effects
- ↓ **Uterine tone, motility** (suppresses/slows labor; may also cause ventilatory depression in newborn)

Morphine and Acute Myocardial Infarction (AMI)

- Cautious use of morphine is “routine” in most cases of AMI, provides several benefits:
 - Reduces discomfort, anxiety
 - Lowers BP (modest) from vasodilation. reduces cardiac work-load, pulmonary congestion

Opioid Overdoses

- Death almost always from ventilatory depression
- Assisted ventilation by itself is usually sufficient to prevent death (if provided in time, done long enough)
- **Naloxone** (NARCAN) used for diagnosis, treatment
 - given IV
 - specifically blocks opioid receptors
 - duration of action usually << that of the agonist, so repeated doses almost always needed until the drug causing the ventilatory depression has been eliminated from the body
 - life-saving, but may → acute withdrawal in opioid-dependent person (better than being dead!)
- + Symptomatic, supportive tx.

Tolerance, Dependence

- **Definitions**
 - Physical (physiologic) dependence
 - Psychologic dependence
- Effective and resp. depressant doses usually ↑ in parallel
- Cross-tolerance
- Cross-dependence
- Be sure to read your text

Physical Dependence

- “Proof” of physical dependence is the development of a *withdrawal syndrome* that occurs when...
 - the drug is stopped abruptly, or...
 - its dose is ↓ to levels below what’s needed to maintain the drug-related “status quo” or...
 - a drug that blocks the drug’s receptors (if one exists) is administered in doses sufficient to block the agonist’s effects

Withdrawal Syndromes

- Have signs, symptoms, that are more or less unique to the drug class that caused the physical dependence
- Include, but *are not limited to*, signs, symptoms for which drug was originally given to relieve, and usually are more severe than signs, symptoms that existed before drug administration was started

Opioid Withdrawal Syndrome

- Signs, symptoms... see your text
- **Intensity** of s/sx roughly proportional to potency and dose of the opioid(s) that led to dependence: e.g., acute withdrawal from strong opioid agonist (e.g., heroin, morphine) much worse than with “milder” or weaker opioids (e.g., codeine)
- **Duration** parallels duration of action of opioid that caused the dependence: e.g., withdrawal from long-acting opioid (e.g., methadone) lasts longer than with shorter-acting opioids (e.g., morphine, heroin)
- **Rarely fatal**, often unpleasant

Which Opioid Analgesic to Choose?

- Strong opioids, such as morphine, are not indicated for short- or long-term control of mild pain, even though such drugs may alleviate pain
- Weak opioids such as codeine are not indicated or safe for severe pain: doses high enough to theoretically control such pain are more likely to cause serious toxicity, and even then won't control pain well... use strong opioids such as morphine, in proper dosages, instead.
- Be aware that some opioids (e.g., meperidine) are indicated and safe for only short-term use, no matter how severe the pain.

Other Pure Opioid Agonists (Selected)

- **Meperidine** (DEMEROL)
 - Lesser effects on gut, biliary tract, bladder, uterus, vs. most other opioids, and lack of biliary tract spasm, makes meperidine a reasonable choice for controlling pain with gall bladder disease, other selected indications
 - Overused — limit to short-term pain control in selected patients with moderate pain; excessive doses or long-term use leads to formation of highly toxic metabolite that can cause **seizures** at high/toxic doses
 - Possibly fatal reaction with MAO inhibitors... avoid it!
- **Codeine, Oxycodone**
 - Analgesic efficacy about same as aspirin, acetaminophen (not for severe pain... doses used to manage severe pain likely to cause toxicity)
 - Efficacy enhanced by aspirin, acetaminophen (many combinations with aspirin or acetaminophen)

Oxycodone

- Codeine-like analgesic activity
- Given orally or parenterally
- Schedule II (like morphine)
- Special comments about controlled-release (extended-acting; OXYCONTIN) tablets
 - Only indicated when moderate-severe pain must be controlled around the clock (slow onset of action, long duration), not indicated for prompt pain control or PRN administration schedules

Oxycodone Controlled-Release Tablets (OXYCONTIN)

- Illicit use and iatrogenic misuse have become a national problem, with many people using this formulation drug for a quick “high”
- Tablets are meant to be swallowed whole, which → gradual absorption, slowly developing (“controlled”) effects
- Abusers break/crush the tablet and “snort,” inject, or ingest the drug...
- This → rapid entry of high drug levels into bloodstream → not only quick euphoria, but sometimes → sudden, fatal overdose

A Few Important Others

- **Hydromorphone** (DILAUDID; DILAUDID-HP)
 - About 10x the potency of morphine
 - Important because accidental substitution of hydromorphone for morphine, without adjusting the dose, happens all too often
- **Methadone** (DOLOPHINE)
 - Injected, potency about same as morphine
 - Much better oral bioavailability than morphine
 - Long duration of action
 - Use in opioid detox or maintenance programs, or long-term pain control in, e.g., cancer patients

One More

- Fentanyl -- strong opioid about *100x* as potent as morphine
 - **SUBLIMAZE®**: anesthetic/preanesthetic drug, given IV in otherwise “lethal” doses; is usually the “other” drug, used in low doses along with midazolam (VERSED), for “conscious sedation.. sedation + analgesia” (see benzo slides)
 - **ORALET®**: “lollipop” for preanesthetic med, **DURAGESIC®**: topical (transdermal) analgesic for chronic pain management
 - not for initiating pain control
 - not for acute pain
 - not for managing “spikes” of acute pain

Food for Thought....

- How can we give “otherwise lethal doses” of injectable opioids such as fentanyl (or even morphine) to patients, such as those undergoing certain types of surgery, yet they survive with no problem?
- Hint: What’s the main cause of death of opioids?
- What can we do about that, even without giving another drug?

Heroin

- Highly lipid soluble precursor of morphine
 - Enters brain quickly
 - Metabolized to morphine once in the CNS
 - *It is the morphine formed from heroin that accounts for all the effects of heroin*
- Schedule I

Mixed Opioid Agonists-Antagonists Prototype: Pentazocine (TALWIN)

- Also called “partial opioid agonists”
 - Relatively “weak” agonist (analgesic) when given alone, is used mainly for moderate acute pain
 - Blocks μ receptors for more efficacious opioids (e.g., morphine), thereby counteracting/blocking effect of the more efficacious drug
- Can \downarrow cardiac output, so not for MI pts.
- Actions, mechanism of action

Pentazocine Blocks Mu Receptors, Stimulates (\checkmark) Kappas

| <u>Response</u> | <u>Mu</u> | <u>Kappa</u> |
|------------------------|-----------|-------------------|
| • Analgesia | blocked | stimulated (weak) |
| • Resp. Depression | blocked | |
| • Euphoria | blocked | |
| • Sedation | blocked | stimulated (weak) |
| • Altered gut motility | blocked | stimulated (weak) |

Compare the effects of morphine and pentazocine. What effects are more likely to be caused by morphine than pentazocine, according to the above?

Use of Mixed Opioid Agonists Antagonists

- OK to give as the only opioid for (up to moderate intensity) pain
- **Never give to patient already on morphine or other “pure” opioid agonist:**
 - will intensify pain by blocking μ receptors normally stimulated by stronger μ agonists
- Avoid giving to someone physically dependent on pure opioid agonist:
 - may induce withdrawal

Oral Pentazocine*

- **Contains**
 - pentazocine plus...
 - low dose of naloxone, an opioid agonist
- **Rationale**
 - pain relief occurs when taken orally because little/no naloxone is absorbed from GI tract
 - no effects when **injected** because sufficient naloxone gets into bloodstream to block them

*For info only; not testable

Pure Opioid Antagonists Prototype: Naloxone (NARCAN)

- **Blocks all opioid receptors, has no effects on other types of receptors or on drugs that don't work as opioid receptor agonists (e.g., benzodiazepines)**
- **No other significant effects in the absence of opioids**

Naloxone Uses

- **Dx., tx. of opioid ODs or drug ODs of unknown cause**
 - Always given for unknown drug OD
 - If patient gets better (e.g., starts breathing better), cause of OD was an opioid
 - Failure of ventilation recovery could mean either opioid was not involved, or other CNS/ventilatory-depressant drugs were also on-board (i.e., multiple drug overdose)
- **To speed recovery of spontaneous ventilation after therapeutic opioid use (e.g., postop)**
- **Managing vent. depression in newborns of women who were receiving/taking opioid at time of delivery**

Risks, Concerns, Problems with Using Opioid Antagonists

- **When used post-op: hard to restore ventilation (desired) without restoring pain (unwanted), since both effects occur simultaneously**
- **When used for opioid OD: Naloxone duration of action usually << cause of OD, so:**
 - Repeated naloxone doses usually required until effects of agonist “wear off” enough for patient to maintain adequate spontaneous ventilation
 - Ventilatory depression may return if repeated naloxone doses not given often enough
- **May → withdrawal in any opioid-dependent person**