Opioids

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Definition

- Opioids are natural, semisynthetic or synthetic compounds that produce morphine-like effects.
- The primary use is to relieve intense pain, have the potential to cause mood changes, physical dependence, tolerance and abuse.

All opioids act by binding to specific receptors in CNS (mu, kappa, and delta) to produce effects that mimic the action of endogenous neurotransmitters.
- In particular, inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord.
- All 3 receptors produce analgesia when an opioid binds to them (G-protein coupled receptors).
Mechanism of action

- Opioids have their action on 2 sites, the presynaptic nerve terminal and the postsynaptic neuron. The presynaptic effect of opioids to inhibit neurotransmitter release is the major effect on the CNS.

- The final effect of opioid in the brain is the result not only from its action on both inhibitory and excitatory neurons but also from postsynaptic effect. For example, presynaptic inhibition of neurotransmitter release may result excitatory effect on target neuron if the neurotransmitter normally produces inhibitory effect. So if the opioid also has a postsynaptic inhibitory effect on the target neuron, the excitatory effect may not occur. Thus the location and density of opioid receptors on a neuron determines the overall effect of opioid on the neuron.
• Opioids inhibit neurotransmitter release by:
  • 1/decrease ca++ entry
  • 2/increase outward movement of k+
  • 3/inhibition of adenylate cyclase
• **Decrease ca++ entry**
  - Neurotransmitter release from neurons is normally preceded by depolraisation of nerve terminal and ca++ entry through voltage sensitive channels
  - Activation of the opioid receptor decrease ca++ influx, this decreases release of excitatory neurotransmitters
- **Increased k+ efflux**
  - Opioids open voltage-sensitive k+ channels, thus shortening repolarization time and the duration of action potential
  - This occurs in brain, spinal cord, and myenteric plexus
• Inhibition of adenylate cyclase
  • Adenylate cyclase is an enzyme that breaks down ATP to form cAMP
  • Inhibition to this enzyme may result in inhibition of neurotransmitter release
Morphine

• Is the major analgesic drug contained in the opium in the seedpod poppy plant (natural opioid) and is a strong mu receptor agonist

• Morphine has higher affinity for Mu receptor than others, by the action on Mu receptors, it inhibits the release of several different neurotransmitters including noradrenaline, acetylcholine, and substance P

• Duration of action 6-8hrs
Dosage

• Oral ; 10 to 30 mg \(\text{4 hrly.}\)
• IM SC ; 5 to 20 mg \(\text{4hrly}\)
• IV ; initial dose is 4 to 10 mg slowly over 4 to 5 min \(\text{4 hrly}\)
• Pediatric IV 0.025-0.1 mg\(\text{kg}\)
• Epidurally 5mg – pain relief up to 24 hrs
• Intrathecally 0.2 to 1 mg
Actions

• 1\ analgesia
  • By raising the pain threshold at the spinal cord level and by altering the brain perception of pain

• 2\ euphoria
  • Caused by disinhibition of the dopamine-containing neurons
3. Respiration depression
   - By reduction of the sensitivity of respiratory center neurons to carbon dioxide, accentuated as the dose is increased.
   - It’s the most common cause of death in acute opioid overdoses.

4. Depression of cough reflex
   - Antitussive properties
• **5\miosis**
  By stimulation of M and K receptors “this is important diagnostically, because many other causes of coma and respiratory depression produce dilatation of the pupil.

• **6\emesis**
  Directly stimulates the chemoreceptors trigger zone in the area postrema that causes vomiting.
• GI tract
  • Relives diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscle
  • Also increases the tone of anal sphincter
  • Morphine and other opioids produce constipation with little tolerance developing
  • Laxative combination of stool softener docusate with the stimulant laxative senna is useful To treat opioid-induced constipation
  • Increase biliary tract pr. Due to contraction of gallbladder and constriction of biliary sphincter
• **8\ CVS**

• at lower doses no major effects on blood pressure or heart rate, with large doses HOTN and bradycardia may occur

• Because of respiratory depression and CO2 retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Therefore, morphine is usually contraindicated in patients with head trauma or severe brain injury
• **9\histamine release**
  • Histamine release from mast cells causing urticaria, sweating and vasodilation
  • Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma

• **10\urinary retention**
  • It increases antidiuretic hormone
  • ?

• **11\labor**
  • May prolong the second stage of labor by transiently decrease the strength, duration and frequency of uterine contractions (shouldn’t be used as analgesia during labor)
Administration

- IM, IV, SC injections are more reliable response
- Oral absorption is slow and erratic
- It has linear pharmacokinetic profile allows more predictable and more flexible doses
Distribution

- Morphine enters all body tissues including the fetus of pregnant women, infants born to addicted mothers show withdrawal symptoms.
- Only a small percentage of morphine crosses the BBB because it is a weak lipophilic, in contrast the more lipid-soluble opioids such as fentanyl readily penetrate into the CNS.
- The duration of action is 4 to 5 hours when administrated systemically to morphine-naïve individuals, longer when injected epidurally (low lipophilicity prevents redistribution).
Elimination

• Its conjugated with glucuronic acid in the liver to 2 main metabolites; morphine-6-glucuronide is a very potent analgesic + morphine-3-glucuronide doesn’t have analgesic activity
• Excreted primarily in urine, small amounts in bile
• With age

• Elderly patients consider low starting doses because they are more sensitive to the analgesic effect due to decreased metabolism, lean body mass, or renal function.

• Neonates shouldn't receive morphine because of their low conjugated capacity.
Adverse effect

- HOTN
- DYSPHORIA anxiety and depression
- SEDATION
- CONSTIPATION
- URINARY RETENSION
- NAUSEA
- POTENTIAL FOR ADDICTION
- RESPIRATORY DEPRESSION
CONTRAINICATIONS

- Elevated ICP
- Respiratory depression
- Paralytic ileus or delayed gastric emptying
- Pregnancy and lactation
- In children

- USED WITH CAUTION
- Asthma, liver dz., renal dysfunction
Drug interactions

• **MAO inhibitors**, absolute contraindication due to high incidence of hyperpyrexia coma

• **Sedatives** increased CNS depression, particularly respiratory depression

• **Tricyclic antidepressant and antipsychotic agents** increased sedation. Variable effect on respiratory depression
Fentanyl

• Synthetic opioid has 100 fold the analgesic potency of morphine, it binds to M receptor 50 to 100 times more strongly than morphine, can also bind to D and K receptors

• The drug is highly lipophilic, rapid onset of action and short duration of action
• Onset IV 1-2 min   IM  8min
• Peak IV 3-5 min
• Duration IV 30-60 min   IM 1-2 HRS
DOSAGE

1. Adjunct to general anesthesia \ slow IV
   Low dose 0.5-2mcg/kg/dose
   Moderate dose ;initial 2-20mcg/kg/dose
   maintenance 1-2mcg/kg
   High dose 20-50mcg/kg

2. Pain management \ IV
   Bolus; 1-2mcg/kg
   Infusion ; 1-2mcg/kg/hr
Medical use

• IV is often used for anesthesia and analgesia
  • Anesthesia along with hypnotic agent like propofol
  • Sedation along with benzodiazepines (endoscopy or cath)

• Epidurally combined with local anesthetics (labor)
• Intrathecally as part of spinal anesthesia
• Oral transmucosal preparation (lozenges) used in treatment of cancer pt. with breakthrough pain who are tolerant to opioids

• The transdermal patch delayed onset (12 hrs) and prolonged offset, duration (48 to 73 hrs), used in chronic pain management, absorption depends on skin TEMP

• In children intranasal fentanyl is useful for treatment of mild to moderate pain
Adverse effects

- 1. bradycardia
- 2. confusion, dizziness
- 3. dehydration
- 4. constipation, nausea and vomiting, xerostomia
- 5. pain at the injection site
- 6. muscle rigidity
- 7. miosis
- 8. respiratory depression
- 9. diaphoresis
• Rare adverse effects
  • Abdominal pain, headache and fatigue
  • Anorexia and weight loss
  • Hallucinations
  • Urinary retention
  • Aphasia

• Fentanyl induce less nausea and histamine mediated itching in relation to morphine
• Fentanyl is metabolized to inactive metabolites by the CYP450 3A4 system
• Drugs that inhibit this isoenzyme can potentiate the effect of fontanyl as amiodarone
• Eliminated in the urine
Naloxone

• Narcotic antagonist
• Used to reverse the coma and respiratory depression of opioid overdose (within 30 sec of IV injection)
• Rapidly displaces all receptor bound opioid molecules, competitive inhibition
• Dose 0.4 to 2 mg
Opioid induced neurotoxicity

• Agitation confusion hallucination and seizures

• Predisposing factors
  • 1. high and prolonged opioid doses
  • 2. recent rapid dose
  • 3. dehydration and renal failure and advanced age
  • 4. other psychoactive drugs
Management of OIN

- Rehydration
- Dose reduction
- Switch to different opioid