



Semester 4

Narcotic analgesics



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ILO

Correlate knowledge of narcotic analgesic drugs to clinical situations

Analgesics

- drugs that **relieve pain**
- **without** significantly *altering consciousness* and **without** affecting its *cause*.
- **Classified into:**
 - **Opioids (Narcotic analgesics)**
 - **Non-opioids:**
 - ✓ Non steroidal anti-inflammatory (**NSAIDs**) e.g Aspirin , ibuprofen
 - ✓ ii. Analgesic antipyretics: e.g. **paracetamol**

Narcotic analgesics



Classification

Strong μ agonists	Weak/moderate μ agonists	Partial μ agonists (Mixed agonist-antagonists)
<ul style="list-style-type: none">• Morphine• Meperidine• Methadone• Fentanyl	<ul style="list-style-type: none">• Codeine• Oxycodone• Hydrocodone	<ul style="list-style-type: none">• Pentazocine \rightarrow partial μ agonist & κ agonist• Buprenorphine \rightarrow partial μ agonist & κ antagonist

Pharmacological effects

CNS

- **Analgesia**
- **Euphoria**
- Sedation
- **Inhibition of cough reflex** (codeine)
- **Tolerance** and **dependence**
- **Respiratory depression**
- **Miosis** (pinpoint pupil)

GIT

- **Constipation**
- Increased biliary sphincter tone and pressure
- Nausea and vomiting

Others

- CVS: Vasodilation and hypotension
- Flushing & **pruritis**
- Prolongation of labor (*except meperidine*)
- Urine retention

Cases



Case 1

A 22-year-old man is brought to the emergency room following an **injury to his knee**. Although he is in **considerable pain**, it is relieved by a small dose of **morphine**. He reports that his pain is still present, but it is less bothersome. He says the morphine ‘feels good’.

- What is the **mechanism of action** for morphine and other opiate ligands to produce **analgesia**?
- What are the **adverse effects** that should be taken into account when treating chronic pain with opiates?

What is the mechanism of action for morphine and other opiate ligands to produce **analgesia**?

- Natural or synthetic opioid analgesics relieve moderate to severe visceral or somatic pain by activating (agonists) a specific family of receptors known as opioid receptors.
- There are three major opioid receptor subtypes: μ (MOP), δ (DOP) and κ (KOP).
 - μ receptors → responsible for most of the analgesic effects of opioids & for the major adverse effects e.g., respiratory depression
 - δ receptors
 - κ receptors → contribute to analgesia at the spinal level

MOA:

- Opioid analgesics are mainly μ receptor agonists → either full agonists or partial agonists/mixed agonist-antagonists (agonists on one opioid receptor but antagonists or partial agonists on another)
 1. Opioid receptors localized at presynaptic neurons ↓ release of pain neurotransmitters (substance P & glutamate) mainly through ↓ in Ca^{++} influx.
 2. Opioid receptors localized at postsynaptic neurons decrease firing through increase in K^+ efflux → hyperpolarization.

The net effect of μ receptor activation is to inhibit neuronal activity → so pain transmission is either blocked or diminished.

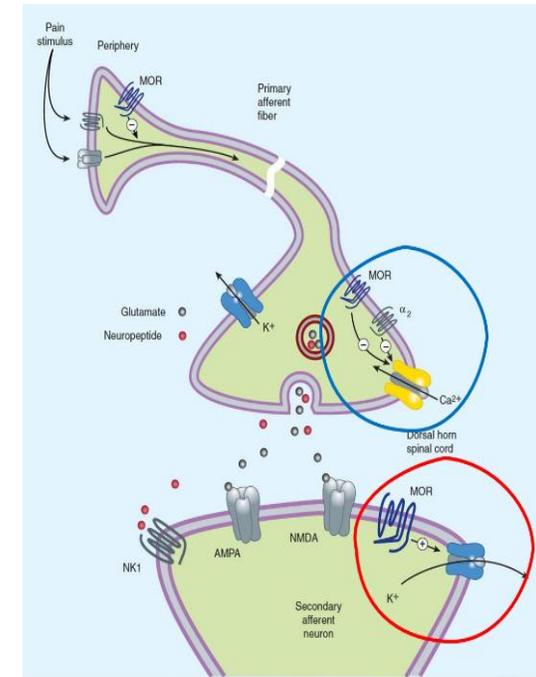
- Analgesia

- Supra spinal → Activation of the descending inhibitory tracts

- Spinal →

- Decrease substance P & glutamate release from presynaptic neuron.

- Hyperpolarization of the post synaptic neuron



What are the adverse effects that should be taken into account when treating chronic pain with opiates?

- **Respiratory depression**
- ↑ **intracranial tension** → CI in patients with *closed-head injury*
- **Nausea and vomiting** → direct stimulation of the *chemoreceptor trigger zone*.
- **Miosis** (pupil constriction) → direct stimulation of the *Edinger-Westphal nucleus of the oculomotor nerve*.
- **Constipation** → increases **smooth muscle tone** & decreases **peristalsis**.
- **Exacerbation of pain** in patients with **biliary dysfunction** or a **gallbladder attack**. Why??
- **Pruritis**, flushing & bronchospasm → due to histamine release from mast cells.
- **Tolerance** and **Dependence**

Case 2

A 19-year-old man is brought to the emergency room with a **suspected heroin overdose**. He is **unresponsive** and his **respiration is depressed**. He was discharged from 30 days in a **detoxification program**. **Naloxone** is administered **intravenously**.

- **What** is **naloxone** and **why is it effective** in this patient?
- What **precautions** must be taken with the administration of naloxone?

Naloxone is a **pure competitive antagonist** that quickly (in seconds to minutes) **displaces opioids** already bound to receptors and **reverses respiratory depression**.

Precautions:

- should be **used cautiously** because it also **can precipitate withdrawal** in **dependent** subjects.
- **The duration of action of naloxone is relatively short**, and it often must be **given repeatedly** or by **continuous infusion**.

Case 3

A 30-year-old man has been **abusing morphine** for some time. Gradually, He **started to increase the dose** to achieve the desired effect, until he was **found dead in the street**.

- What is your **comment**?
- What **regimen** do you recommend for the **treatment of opioid dependence**?

Tolerance:

- **decrease in the pharmacologic effect** of opioid analgesics observed **after chronic/long-term/repeated** drug administration.

- **Mechanism:**

pharmacodynamic tolerance to **all** opioid analgesics (cross-tolerance), primarily results from **down-regulation of opioid μ receptors** with repeated opioid administration.

- Tolerance develops **to most of the effects** of opioids but **Not to miosis** and **constipation**.

Treatment of opioid dependence:

Aim: **help** the patient experience **reduced symptoms of opioid withdrawal**, reduced cravings, and maintain abstinence from other illicit opioid use.

✓ **Phase 1** → **Medically supervised** opioid withdrawal (**detoxification**) Drugs used:

1. Longer acting opioid agonists: **methadone** and **buprenorphine**
2. Alpha-2 adrenergic agonists: **clonidine**.

✓ **Phase 2** → Opioid **replacement**, maintenance, or substitution therapy. Drugs used:

1. Agonists: **buprenorphine** and **methadone**.
2. Antagonists: **naltrexone** (N.B. as opioid antagonists precipitate withdrawal in patients actively using opioids, medically supervised withdrawal is necessary prior to initiation of naltrexone).

Adjunct drugs:

- Alpha-2 adrenergic agonists (**clonidine**) → to decrease anxiety associated with opioid withdrawal.
- **Benzodiazepines** or other **sedating** drugs → to treat anxiety and insomnia associated with opioid withdrawal
- **Anti diarrheal** and **antiemetic** drugs
- **NSAIDs** (naproxen) → to relieve pain

Case 4

Following **surgery for a hip replacement**, a 64-year-old woman is treated with a **parenteral opiate** for pain. Upon release from the hospital, she is given a prescription for oral **oxycodone** for pain. Three days after discharge she is complaining of **constipation**.

- What is the cause of her constipation?
- What are opioid agonists used as antidiarrheal drugs?

1- Opioid agonists **increase smooth muscle tone & decrease peristalsis.**

2- **Loperamide & Diphenoxylate**

Case 5

A 17-year-old boy is brought to the emergency room following an **injury to his arm while playing football**. He is administered **meperidine** by **intramuscular injection** for pain.

- What is meperidine and how does it act as an analgesic?

Pethidine (meperidine):

- **full** μ opioid receptor **agonist**
- produces a pattern of effects **similar** but **not identical** to morphine.
- The major use of meperidine is for **analgesia**.
 - Equianalgesic compared with morphine,
 - Does not cause constipation or increase biliary pressure → used in pancreatitis.
 - Does not prolong labor → used for analgesia in labor.
 - Has atropine like action → ↑ HR → used in inferior MI
 - Only short courses are allowed → accumulation of a toxic metabolite (normeperidine) might cause seizures in patients with renal failure.

Case 6

A 42-year-old man with **chronic pain** is brought to the emergency room because of **over-sedation** and **respiratory depression** while using **fentanyl patches**. He is given **intravenous naloxone**.

He is not given oral naloxone because naloxone:

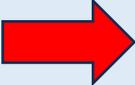
- A. is not absorbed from the GI tract.
- ➔ B. undergoes first-pass metabolism in the liver.
- C. is metabolized to an inactive metabolite in the GI lining.
- D. is excreted unchanged in the urine.
- E. is destroyed by the stomach



Case 7

A 47-year-old woman is recovering from a **hysterectomy**. Her physician prescribes an **opioid analgesic** as needed for **postoperative pain**. Opioids can cause many effects in addition to **analgesia** including **constipation**, **respiratory depression**, **euphoria**, **miosis**, and **drowsiness**. With prolonged use, **tolerance** develops to most of these effects.

Which of the following effects **persists despite tolerance**?

- A. Analgesia
-  B. Constipation
- C. Drowsiness
- D. Euphoria
- E. Nausea and vomiting

Case 8

A 48-year-old man is being treated with a **long-acting opiate** for **pain associated with terminal cancer**. He is also prescribed a **transmucosal fentanyl formulation (lollipop)** for **“breakthrough” pain**.

The transmucosal formulation is an effective analgesic because it:

- ➔ A. avoids first-pass metabolism of fentanyl.
B. delivers fentanyl directly to opiate receptors in the mouth.
C. avoids constipation.
D. avoids respiratory depression.
E. avoids nausea and vomiting that is associated with the systemic use of fentanyl.



Case 9

A 53-year-old man is requesting **meperidine** for his **chronic back pain**.

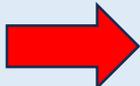
His physician is **hesitant** to use meperidine for the treatment for **chronic pain** because of

-  A. metabolite toxicity.
- B. poor oral absorption.
- C. increased addiction potential.
- D. patient non-compliance.
- E. likelihood that meperidine will be diverted for sale on the street

The **morphine metabolite** that may be responsible for **most of morphine's analgesic activity** is:

- A. desmethyldmorphine
-  B. morphine-6-glucuronide
- C. morphine sulfate
- D. N-acetylmorphine
- E. hydroxymorphine

Which drug **does not activate opioid receptors** and has been proposed as a **maintenance drug in treatment programs for opioid addicts**?

- A. Fentanyl
- B. Naloxone
- C. Buprenorphine
-  D. Naltrexone
- E. Codeine

References

- Workbook and Casebook for Goodman and Gilmans
- The Pharmacological Basis of Therapeutics
- Katzung & Trevor's Pharmacology Examination and Board Review.

