Opi Oids

➲Classification of opioids according to nature:

- Natural (morphine)
- Semi-synthetic (codeine → derived from morphine)
- Synthetic (pethidine, methadone, fentanyl, tramadol, loperamide)
- Loperamide can't cross BBB, lacking analgesic effect & used to control diarrhea
- Opioids produce analgesia without loss of consciousness

➲Classification of opioids according to action:

- Pure agonist
- Mixed agonist/antagonist (buprenorphine, pentazocine)
- Pure antagonist (naloxone, naltrexome, nalmefene**)**

☛Mixed = partial= agonist & antagonist action

🛠 Mechanism of action:

1. Agonist at opioid receptors (Mu, delta, kappa, sigma)
2. Inhibit release of excitatory transmitters (e.g. substance p which carry pain stimuli)
3. Hyper-polarization of cell membrane by opening K^+ channels (efflux)
4. Change pain perception (psychological) e.g. in cancer pain, patient is aware of pain but without unpleasant feeling

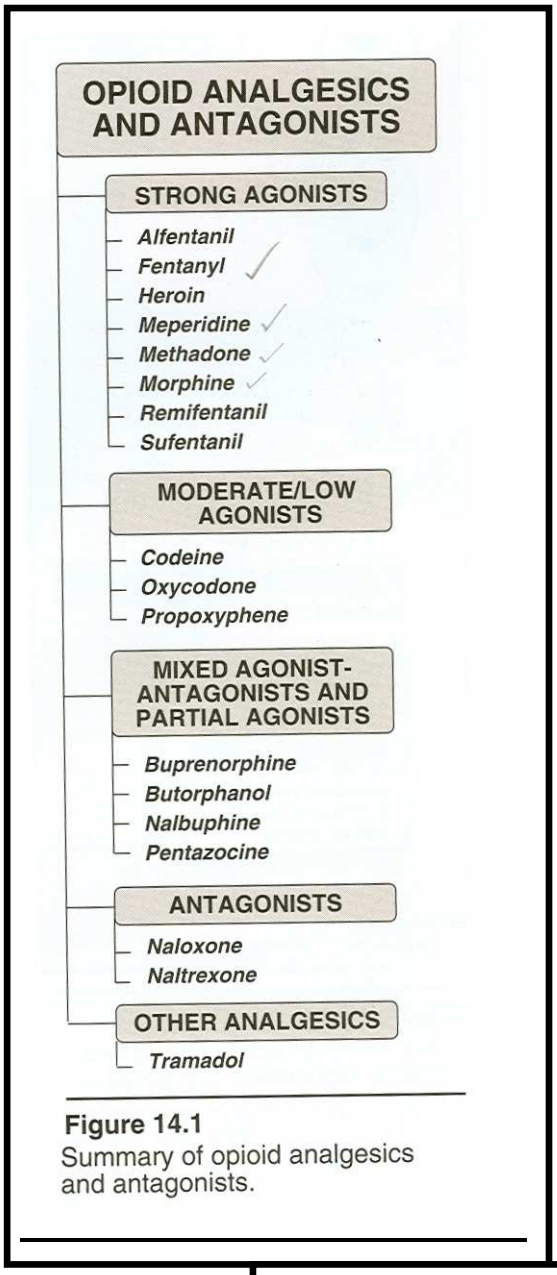

Figure 14.1
Summary of opioid analgesics and antagonists.

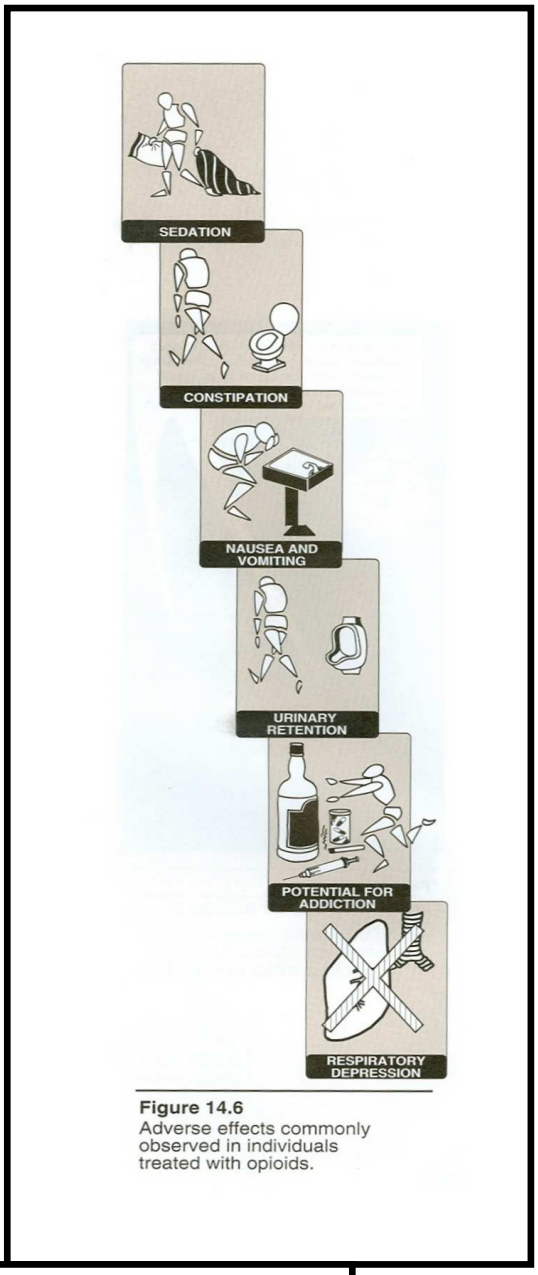

Figure 14.6
Adverse effects commonly observed in individuals treated with opioids.

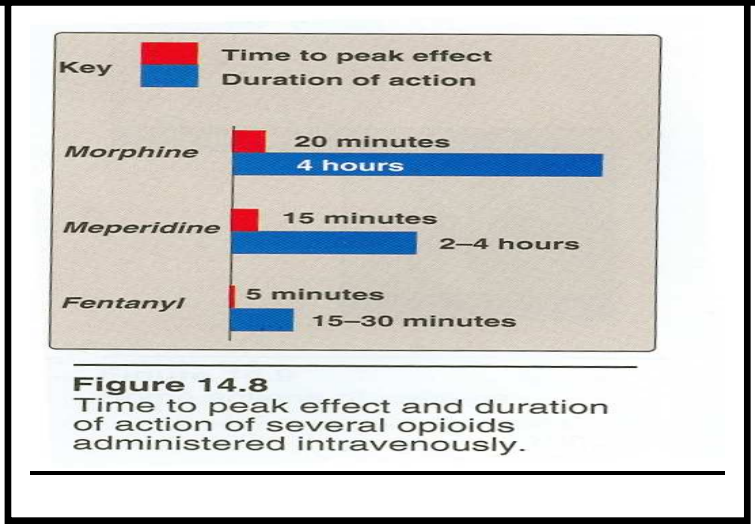

Figure 14.8
Time to peak effect and duration of action of several opioids administered intravenously.

✹ *Pure agonist*

❶Morphine

♦Pharmacokinetics:

- Can't be given orally due to low oral bioavailability (absorption is erratic, extensive 1st pass hepatic metabolism)
- *Given:* SC, IM ,IV, epidural (medical use)
- Inhalation (non-medical use)
- *Metabolized* in liver to active & inactive metabolite (active as morphine-6-glucuronide)
- *Excreted* through kidney as metabolite, some unchanged
- *Half-life* = 4-6 hrs
- *Distribution*: weak lipophilic in comparison with other opioids, cross BBB & placenta

♦ Pharmacological actions:

- Analgesic
- Euphoria (in patient with pain but in normal subjects it will cause dysphoria :)

(in normal person → initially euphoria + ↑sexual appetency→ then disphoria + ↓sexual appetency→after addiction)

- Sedation (NOT HYPNOSIS) →due to action on opioid receptors, in old patient it may cause light sleep MCQ
- Respiratory system: depression, decrease sensitivity to Co2 → Co2 retention → cerebral VD →↑ ICP, broncho-constriction due to histamine release
- Cough center: depression (anti-tussive)
- Eye: most of opioids produce meiosis due to central action on 3rd nerve nuclei → enhance parasympathetic supply to eye,

- Morphine produce strong meiosis (pin point pupil PPP)***
- GIT: Nause & vomiting due to stimulation of chemo-trigger zone, constipation due to:
    1) decrease in peristalsis.
    2) increase in tone.
    3) inhibition of defecation reflex.
    4) constriction of anal sphincter
- Gall bladder: contraction of the wall & sphincter →increase in bile pressure → reflux of bile & pancreatic secretion into plasma (increase in serum lipase & amylase)
- Urinary system:
    1) urine retention due to ADH release & inhibition of micturition reflex
    2) Spasm of ureter wall
- Endocrine:
    ↑(testosterone, LH, FSH, ACTH)
    ↓ (prolactine, ADH)
- histamine release:
    1) hypotension,
    2) broncho-constriction
    3) itching
- CVS:
    1) Bradycardia
    2) hypotension →due to 1- central inhibition of VMC &2- histamine release
- Uterus:
    1) decrease uterine contraction
    2) Teratogenic effect (depress fetal respiration) coz it crosses placental barrier, also the fetus will be addict & when he is born will show withdrawal symptoms :'(

♦Clinical uses:

- Cancer pain
- Severe burns
- Severe diarrhea
- Severe visceral pain except: MCQ
    1. Renal & biliary colic →it contracts the wall worsening the condition, but if morphine is given add atropine
    2. Acute pancreatitis →it will increase serum lipase & amylase more & more)
- Cough
- Acute pulmonary edema (these suffer from dyspnea & pain) morphine is analgesic & decrease congestion by VD
- Pre-anesthetic medication

👽 Adverse effects:

- Respiratory depression
- Nausea, vomiting
- Constipation
- Urine retention
- Hypotension
- Allergy
- Tolerance (with chronic use)→ to respiratory depression, analgesics, sedation, euphoria. No tolerance to *constipation or meiosis*
- Addiction (abstince syndrome, withdrawal symptoms)

☒ Contraindication:

→ Head injury (↑ ICP)

→ Pregnancy (due to uterine side effects + post-partum hemorrhage due to VD)

→ Bronchial asthma

→ Liver & kidney disease (including renal & biliary colic)

→ Endocrine disease as myxodema, adrenal insufficiency

→ Pancreatitis**

❖ Drug interaction:

- Sedative-hypnotics → CNS depression → respiratory depression
- Anti-psychotic (respiratory depression + their anti-muscarinic & alfa-blocking action will be exaggerated by morphine)
- MAOI → hyperthermia, HTN, coma, death

For ur knowledge :

➲ Dose = 8-20 mg

No more than 20 mg

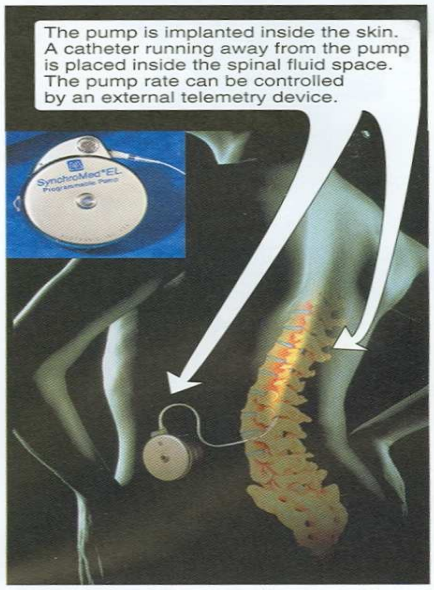

Figure 14.5
Implanted pump for delivery of morphine.

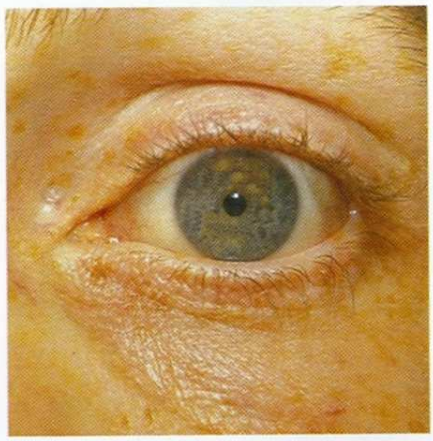

Figure 14.4
Morphine causes enhanced parasympathetic stimulation to the eye, resulting in pinpoint pupils.

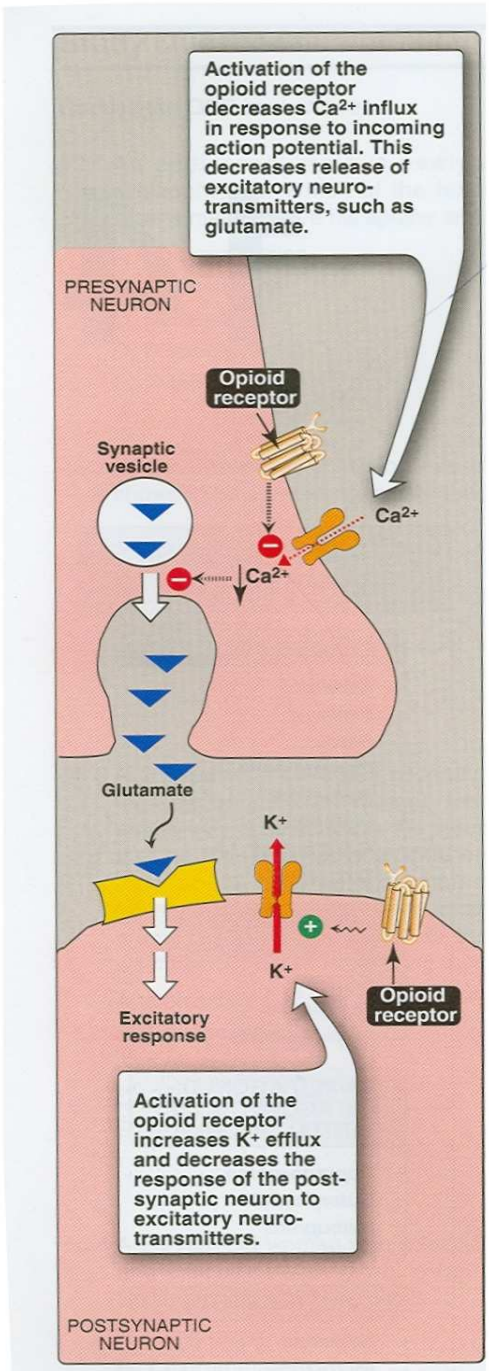

Figure 14.2
Mechanism of action of μ-opioid receptor agonists in the spinal cord.

❷Pethidine (meperidine)

✓ Acts as morphine but *more* on (kabba receptor).

♦Pharmacokinetics:

➲**4 v.imp points** :(in comparison with morphine)

1. More on kabba receptors
2. Taken orally → high bioavailability
3. Metabolized in liver →active metabolite
4. Shorter T½ =2-4

- Absorption: good oral absorption.
- Route of administration:
- Taken orally.
- Alternative route: IM,IV.
- Metabolism:
  - Metabolized in liver giving→ active metabolite (normeperidine)responsible of CNS AE of pethidine.
- Excretion:
  - It cross BBB & placenta barrier.
  - Excreted in kidney.
- Half-life (2-4 hrs).
- Short T1l2 in compared to morphine.

♦Pharmacological actions:

1) Less analgesic than morphine. Need high dose.
2) Less constipating
3) less depressant on foetal respiration
4) Atropine-like actions. (ie:mydriasis,tachycardia,spasmolytic effect &urinary retention).
5) Papaverine-like actions. (ie: direct spasmolytic effect)

6) No cough suppressant effect.

🌡 Clinical uses:

1) Cancer pain.
2) Sever burn.
3) Sever visceral pain. (eg: biliary & renal colic coz it has atropine-like effect).
4) Obstetric analgesia. (has less fetal depressant effect with No release of histamine. No uterine side effect)
5) Preanesthetic medication.

👽 Adverse effects:

➲CNS:

- ✓ Tremors
- ✓ convulsion.

it's not in morphine & it's due to normeperidine metabolite.

➲CVS:

- ✓ hypotension.

due to :

1- vasomotor center depression.
2- papaverine like action, causing VD or muscle relaxation.

➲AEs due to atropine-like effect

- ✓ Blurred vision.
- ✓ Dry mouth.
- ✓ Urinary retention.

➲Tolerance.

➲Addiction.

☒Drug interaction:

1) With MAOI→convulsions&hyperthermia(more than morphine) →90% of patients will die because of it & it's absolute contraindication with pethidine.
2) Sedative&hypnotics.

3) Anti-psychotic drugs.

❸Methadone

✓ Synthetic opioid.

➲Potent analgesic as potent as morphine.

- Given : orally→ Higher oral bioavailability.(than morphine)

  IV,SC,rectally(suppositories).
- Acts on opioid receptors .
- Longer half-life (24 hrs)than morphine due to →↑ tissue binding.
- Less euphoric than morphine.
- Produces mild withdrawal syndrome.
- Tolerance&physical dependence develop more slowly than morphine.

Clinical uses:

→ Treatment of opioid abuse.

→ Detoxification &maintenance of (heroin addict .or morphine addict) through gradual withdrawal & gradual entrance of methadone.

→ Severe oral & facial pain (neuropathic, cancer pain).

➲Used in :

Opioid abuse

Heroin &morphine addict

Neuropathic

cancer pain

❹Codeine

- ✓ Asemisynthetic opioid.

  ➲Less potent as analgesic than morphine.

- × Effective orally.
- × Potent anti-tussive.
- × Less euphoric than morphine.
- × Given in combination with aspirin or acetaminophen → to ↑ analgesia
- × Relive musculoskeletal pain associated with cough.

➲Used in :

musculoskeletal pain associated with cough

given with aspirin or aceta.

Figure 14.9
Some actions of *codeine*.

❺Dextromethorphan:

- Free of analgesic & addictive effects.
- Less constipating than codeine.
- Potent as anti tussive.

➲Used as :
Anti -tussive

❻Fentanyl

- ✓ Synthetic opioid.

  ➲More potent as analgesic than morphine. (80-100 time)

- ❖ Rapis onset & very short duration of action (15-30 min). this's its disadvantage.
- ❖ Used as IV anesthesia.
- ❖ In cancer pain as transdermal patch.

➲Used in :
IV anesthesia
Cancer pain

❼Tramadol

- ✓ Synthetic opioid.
- ▪ Binds to μ receptor.(mu)
- ▪ Block reuptake *of serotonin & nor epinephrine.*
- ▪ Given by different routes of administration.(eg: oral,rectal ….etc).

Clinical uses:

1) acute visceral pain.
2) atypical pain(chronic neuropathic pain).

Adverse effects & contraindications:

- Seizures so → Contraindicated in patients with history of epilepsy.

♦Nausea ♦drymouth

♦Dizziness ♦sedation

- ✓ it causes vomiting through its action centrally so, it's given with antiemetic.
- ✓ Less adverse effects on respiratory & CVS→ In comparison with other opioid.

➲Used in :

Acute visceral pain

Atypical pain

✹Opioids with Mixed receptorsAction

❶Buprenorphine

💣partial μ(mu) receptor→ agonist &antagonist:

- ×in morphine users →act as antagonist (on other receptors)
- ×in non morphine users → act as agonist(on mu receptors)

- long duration of action
- poor oral bioavailability so→ <u>given</u>
  - <u>parentrally</u>
  - <u>sublingually or</u>
  - <u>as spray</u>
- excreted <u>in bile & urin</u>
- <u>Respiratory depression is difficult to be reversed by Naloxone</u>
- Is effective as Methadone in the detoxification & maintenance of Heroin addict
- <u>contraindicated with Morphine</u>

➲Used in :

detoxification & maintenance of Heroin addict

❷Pentazocine

➲Agonist at Kappa & antagonist at MU receptors

- ✓ Has high oral bioavailability
- ✓ Short duration of action
- ✓ Less potent than Morphine
- ✓ Not used for maintenance of morphine addict→it antagonize its receptors (mu)

Adverse effects & contraindications

➲CNS

1) Hallucination
2) Convulsion

So → #in epilepsy

➲CVS (centrally).

1) Hypertension
2) tachycardia

So→ # in heart diseases &hypertensive pnt .

contraindicated with Morphine

✹Opioid Antagonists

❶Naloxone

➲**pure** antagonism at MU receptors

- rapid onset(seconds) &short T1/2 =30-60 min
- <u>treat opioid overdose (acute toxicity) through I.V***</u>
- reverse the respiratory effect of Morphine within seconds**(reverse resp. depression of morphine within seconds

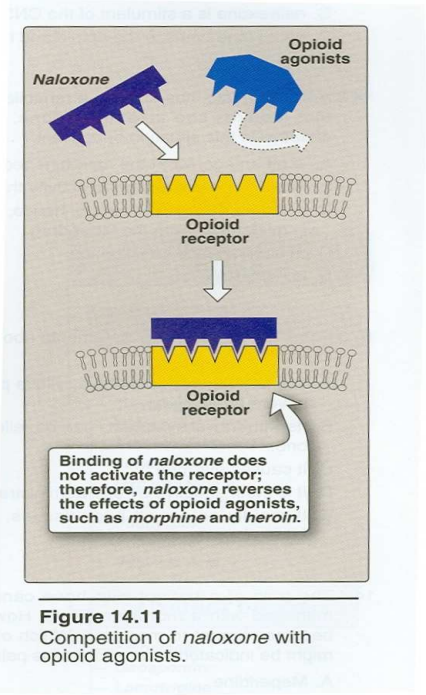

Figure 14.11
Competition of *naloxone* with opioid agonists.

❷Naltrexone

- long T1/2=10 hr
- delayed onset of action
- effective orally so
  - ✓ not used in acute toxicity
  - ✓ treat chronic alcoholism

☛Used as maintenance for opioid addicts

👽<u>Hepatotoxic (imp)(AE)</u>

❸Nalmefene

- ❖ derivative of Naltrexone
- ❖ only given by I.Vso → used to treat overdose (acute
- ❖ long T1/2=8-10 hr

opioid antagonist :

- when given in absence of an agonist→ *no* effect
- In dependent (addict) subject precipitate an ABSTINENCE syndrome
- *NO* tolerance to their antagonistic action
- *NO* ABSTINENCE syndrome when withdrawal after chronic use

We are afraid of losing what we have, whether it's our life or our possessions and property.
but this fear evaporates when we understand that our life stories and the history
of the world were written by the same hand
paulo coelho

Done by:

- دانة العيسى,حنان الشنقيطي
- أشجان الحجي, الدانة آل سعد

د/ عزة غلبتنا حبتين , السلايدات كانت فاضية تماماً
كتبنا اللي تقوله كله , وإن شا الله الملزمة كاملة مكملة

موفقين

424 final exam Qs :

MCQ

Naloxone :

a- Potentiates the respiratory depression caused by morphine.

b- Can be given orally.

c- has a long T1/2

d- It precipitates an abstinene syndrome in dependent subject (Addict).

T&F

Pentzocine :

a- Is used I.V
b- Used for the treatment of withdrawl symptoms of opoids (F)
c- Used to treat acute visceral pain (T)
d- Can be used as a transdermal patch (F)

Pethidine:

a- Has a T1/2 longer than morphine (F)
b- Causes less constipation than morphine(T)