Pharmacology Team 431

(CNS BLOCK)

Drugs used in management of pain

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Introducation (and it is not important by the way :))

According the physiopathology pain divided to :

1- Nociceptive : **by activation of nociceptors** cause tissue damage e.g:

- **Crush Injuries**
- **Ischemic**
- **Inflammation**
- **Distention**

2- Neuropathic : **by damage to or malfunction of the nervous system e.g:**

- **Low back pain**
- **Cancer pain**
- **Diabetic neuropathy**
- **Post herpetic neuralgia**
- **Post amputation**

OPIOIDS: can use as analgesics in moderate to severe pain (especially Visceral)

Derived from the dried milky juice ➔ exuded by incised seed capsules of a species of poppy, *Papaver somniferum (kind of plants)*

It contains a mixture of alkaloids, the principal components being

morphine, codeine (Mimic action of endogenous opioids;

Endorphins, Dynorphins,Enkephalins

)& papaverine used to relieve spasm muscle .

Act on endogenous opioid receptors

mu, delta, kappa, sigma (sigma not considered as opioid receptor)

Functions mediated by endogenous OPIOIDS RECEPTORS (important to know)

μ→ supraspinal analgesia, respiratory depression, euphoria, physical dependence

δ→spinal analgesia, respiratory depression, ↓GIT motility (cause constipation)

K→ spinal analgesia, sedation, pupil constriction, dysphoria

All of them typical G-protein coupled receptors.

σ→ dysphoria, hallucination , pupil dilation, anxiety bad dreams,… ***It is not a true opioid receptor, as it binds psychotomimetic drugs. Exceptionally of opioids only benzomorphans binds to it.(not important).***

Mode of action (in general):

Nerve ending (pre&postsynaptic):

Binding to presynaptic opioid receptors coupled to Gi (inhibitory G protein in G protein coupled receptor **)→↓ AC (**adenylyl cyclase)**& cAMP →↓ voltage-gated Ca^{2+} channels →↓ excitatory transmitter.**

Binding to postsynaptic→↑ opening of K channels→↓ neuronal excitability

Prequaductal gray matter:

↓firing of nociceptive pathways converging at Periaqueductal GM

→to allow for inhibitory firing along the descending pathway returning

to dorsal horn→↓ pain

Pain gate of dorsal horn:

Also inhibit pain transmission by acting directly on the dorsal horn, and by ↓ excitation of peripheral nociceptive afferent neurones

Morphine :

Pharmacodynamic	**Analgesia , Euphoria (high mood), Respiratory depression , Depression of cough reflexes(not any more), Nausea & vomiting, Pin point pupil:- due to stimulation of occulomotor center by m, k effects. Diagnostic, Effects on GIT:-↑ in tone ↓ motility →severe constipation, Releases histamine from mast cells, disturbance of hormones .**
Pharmacokinetics	**t ½ is 2-3h (It should be repeated if sustained effect is needed), It is slowly & erratically absorbed orally. Medically given by IM or IV injection, Undergoes enterohepatic recycling, crosses BBB, crosses placenta(cause respiratory depression for the baby)**
Clinical indications	**CONTROL PAIN; cancer pain, severe burns, trauma Severe visceral pain (not renal/biliary colics, acute pancreatitis) because it cause constriction of sphincter . DIARRHOEA,COUGH ,ACUTE PULMONARY OEDEMA, MYOCARDIAL ISCHEMIA, NON PAINFUL CONDITIONS; HF to relieve distress ,PREANAESTHETIC MEDICATION(because it is decrease secretions)**
Side effects	**Sedation, Respiratory depression,Constipation,Nausea & vomitin, Itching → histamine release, Tolerance; *not to meiosis, convulsion or constipation* Dependence, Euphoria**

Contrindications of Morphine :

- HEAD INJURY (because when want to know the degree of coma for pt in ER you have to look to his eyes pupil and if you give his morphine you will not able to grad the coma because his pupil already constricted by morphine you gave)
- PREGNANCY(cross placenta may cause respiratory depression).
- BRONCHIAL ASTHMA or impaired pulmonary function (because morphine cause release of histamine)
- Liver & Kidney diseases (including renal& biliary colics) cause sphincter constriction
- Endocrine diseases (myxedema & adrenal insufficiency)
- Elderly are more sensitive;↓metabolism, lean body mass & renal function
- Not given infants, neonates or during child birth→ ↓conjugating capacity → accumulate → ↓ respiratory
- With MAOIs

TOLERANCE & DEPENDENCE develop rapidly .

Withdrawal manifestations develops upon stoppage.

Dependence comprises both:

Physical dependence lasting for a few days in form of ↑ body ache, insomnia, diarrhea, goose flesh, lacrimation

Psychological dependence lasting for months / years → craving

HEROIN	Codeine
μ agonist **Crosses BBB** **Converted to morphine** **No medical use** **Strong addicting drug**	**μ agonist** **Dependence < morphine** **Used in mild& moderate pain, cough, diarrhea (not anymore because ppl become addicted to)**

Meperidine (Pethidine) (both of them important to know):

Actions	**Synthetic > effective k agonism** **↓analgesic, ↓ constipating , ↓ depressant on faetal respiration than morphine** **Has atropine –like action / Smooth muscle relaxant** **No cough suppressant effect (not like morphine)**
Indications	**As in morphine but not in cough & diarrhea** **Used in severe visceral pain; renal & biliary colics sm. relaxant)** **Used in obstetric analgesia (No ↓ resp.) =during labor** **Preanaesthetic medication (better)** **More than 3 days will cause addiction.**
Side effects	**Tremors, Convulsions, Hyperthermia, Hypotension** **Blurred vision, Dry mouth, Urine retention(atropine side effects)Tolerance & Addiction**

TRAMADOL:

Pharmacokinetics	**Synthetic, μ agonist , ↓ potent (weak), ↓ NE & 5HT also (not too much) Can be given orally; ↑ oral bioavailability (the only one can be given orally)**
Indications	**Mild - moderate acute & chronic visceral pain & during labor (I.V)**
Side effects	**Seizures (not in epileptics), Nausea , Dry mouth, Dizziness , Sedation** **Less adverse effects on respiratory & C.V.S(cardiovascular system)**

Fentanyl:(minor surgeries)

Pharmacokinetics	**Synthetic, μ agonism, ↑ potency > meperdine & morphine**
Indications	**Commonest analgesic supplement during anesthesia,(most common use with anesthesia)** **IV or intrathecal.** **To induce & maintain anesthesia in poor-risk patients [stabilizine heart.](with elderly pt who suffered from heart disease u can't give them morphine but fentanyl the best)** **In combination with droperidol as EUROLEPTANALGESIA(make anesthesia steady)** **In cancer pain & severe postoperative pain; transdermal patch changed every 72 hrs.**
Side effects	**Mimic opioid agonists / respiratory depression most serious (in over does but generally it isn't)/ CV effects are less. Bradycardia may still occur**

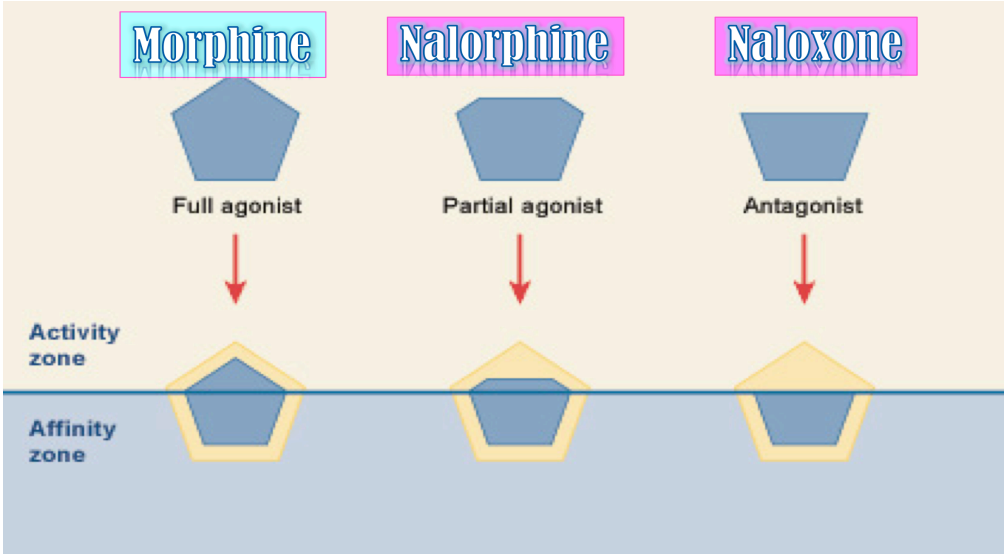
METHADONE

Pharmacokinetic	**Synthetic, μ- Weaker Agonist, t½ 55 h.(very long duration)** **Used to treat opioid withdrawal : Firm occupancy of opioid receptors by methadone ↓ desire for other opioid intake, because it is producing an ↓ effect that stop withdrawal manifestations. With time addicts improve → ↓ craving**
In non addicts, it causes tolerance & dependence but not as severe as that of morphine	

If the pt addicted to morphine don't give him antagonist he will suffered from withdrawal manifestation and may pt die.

Treatment: give him weak μ- agonist

Antagonizing Acute Opioid Toxicity :



Naloxone:

Pure opioid antagonist.

Used to treat respiratory depression caused by opioid overdose & to reverse the effect of analgesia on the respiration of the new born baby

Effect lasts only for 2-4 hours.

***Precipitates withdrawal syndrome in addicts**

Naltrexone:

Very similar to naloxone but with longer duration of action [t½=10h]

Questions:

Pt came to ER Unconscious, when doctor checked his eyes pupil you noticed sever pupil constriction which one of these drugs he may took in overdoes :

1-morphine

2-naloxone

3-tramadol

Pt suffered from morphine withdrawal manifestations which one of these drugs help to reduce the manifestations:

1-tramadol

2-meperidine

3-methadone

During Caesarean births doctor gave the mother morphine then the baby turn to be blue and Pco2 become high which one of these drug can used to treat respiratory depression:

1-naloxone

2- METHADONE

3-Pethidine

During extraction of teeth which one of these drugs the dentist will use as anesthesia drug :

1. **Heroin**
2. **Codeine**
3. **Tramadol**

Answers : 1,3,1,3