PHARMACOLOGY TEAM

Lecture : 5

Drugs In Management Of Pain

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OBJECTIVES

- Revise how pain is perceived and modulated, emphasizing
  on neurotransmitters, receptors, channels involved.

- Classify drugs used in management of pain

- Expand on pharmacology of opiates, patterns of
  classification, mechanism of action,indications, ADR,…etc.
  detailing on morphine as an example.

- Compare in brief actions and indications of other opiate
  agonists and antagonists.

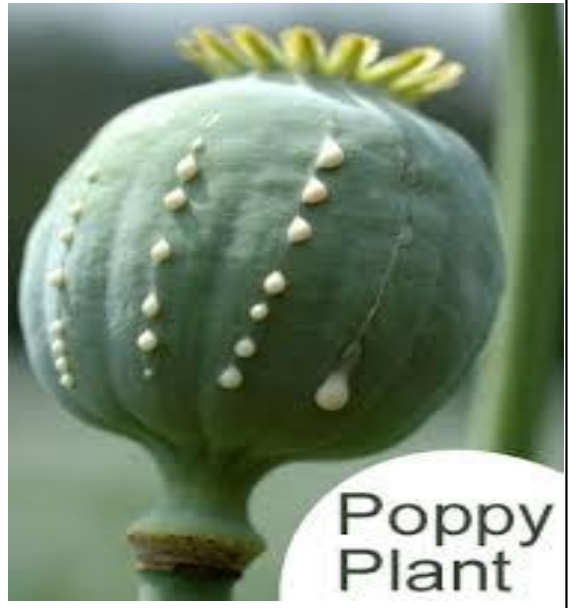
- **Nociceptive pain :** the organ is affected and it's firing through the nocicereceptors (also called sensory pain receptors)
- **Neuropathic :** nerve pathway it self is affected, pain produced by normally non-painful stimuli
- **NSAIDs :** For Mild To Moderate Dull Aching (somatic pain)
- **Opioids :** For Moderate To Severe(Visceral pain)

Analgesics(opioids) induce analgesia.
Analgesia is a state in which a painful stimuli is modulated (felt no more pain). NSAIDS+OPIOIDS are analgesics

Slides Important Doctor's Notes Explanation

OPIOIDS

- Derived from poppy plant , (papaver somniferum) (potent vasodilator) ..when it is yield it gives sticky material called narcotic opioid alkaloids which are the main component in morphine and codien(morphine derivative) that mimic the action of endogenous opioids such as (Endorphins, Dynorphins , Encephalins) and they act on endogenous opioid receptors (mu ,delta , kappa , sigma)
- Sigma is removed now cuz it's an element of hallucinations



Function of endogenous opioids receptores

Mu μ	**supraspinal analgesia, respiratory depression, euphoria, physical dependence (addicted)**
Delta δ	spinal analgesia, respiratory depression, ↓GIT motility (constipation)
Kappa k	spinal analgesia, sedation, pupil constriction, dysphoria **All of the above are typical G-protein coupled receptor
Sigma	dysphoria, hallucination , pupil dilation, anxiety bad dreams,… (the dr saied it is not important to know about sigma receptor)

Classification of opioid receptors

According to their source :

we need the analgesic effect so we use the agonis

- **Natural** (morphine)
- **Semisynthetic** (codine)
- **Synthetic** (mepiridine , methadone , fentanyle , tramadol)

According to agonistic/antagonistic actions at receptors:

- **Agonists** (Morphine, Codeine, Pethidine, Methadone, Fentanyl, Tramadol, Loperamide) Loperamide >[no BBB ➔ diarrhea] (doesn't cause addiction)
- **Mixed agonists /antagonists** (Pentazosine, Buprenorphine)
- **Pure antagonist** (Nalaxone, Naltraxone, Nalmefene)

According to their specificity of action on receptors:

Most of opioids are not specific which means that they can work on more the one receptor(there is overlapping in their action),but each one works more on one receptor

د.امنيه قالت هذا السلايد للتوضيح فقط ليس للحفظ

How do opioids induce analgesia?

Presynaptic inhibition:

Binding to presynaptic opioid receptors coupled to G inhibitory protein → ↓ AC & cAMP → ↓ voltage-gated Ca^{2+} channels →↓ excitatory transmitter.

Postsynaptic inhibition:

Binding to postsynaptic opioid receptors → ↑ opening of K channels → ↓ neuronal excitability (makes the receptor refractory=not responding even if the signal is firing

It will lead to :

- ↓firing of nociceptive pathways converging PAG
- This will allow the inhibitory firing along the descending pathway returning dorsal horn cells by that decreasing the pain
- Also inhibit pain transmission by acting directly on the dorsal horn, and by ↓ excitation of peripheral nociceptive afferent neurones.

Morphine

Pharmacodynamic action of morphine

1- Analgesia [in acute & chronic pain]

2- Euphoria → powerful sense of contentment & well being

3- Respiratory depression→↑pCO_2 >> ↑ICP

4- Depression of cough reflexes >> so used in dry cough

5- Nausea & vomiting → ↑CRTZ

6- Pin point pupil(due to stimulation of occulomotor center.diagnostic in drug abuse when overdose is taken

7- Effects on GIT:-↑in tone ↓motility

→severe constipation

↑pressure in the biliary tract +

constriction of biliary sphincter →

contraction of gall bladder (contraindicated in renal+biliary colic)

8- Releases histamine from mast cells (itching)

9- ↓LH, FSH, ACTH , testosterone

↑Prolactin, GH, ADH → urine retention (alteration in the hormonal profile)

Clinical Indications of Morphine

- Control pain: cancer pain, severe burns, trauma
- 2)Severe visceral pain (not renal/biliary colics, acute pancreatitis)
- diarrhea
- cough
- Acute Pulmonary Oedema
- Myocardial ischemia
- non painful condition: (Any condition accompanied by severe pain or severe distress is given opioids such as HF)
- Preanesthetic medication (group of drugs that is given before the operation to decrease the secreations , causing sedative effect , also decrease the pain during the operation and postoperative)

Morphine

Adverse effect	Contraindications
• Sedation • Respiratory depression. • Constipation. • Nausea & vomiting.(affect sutures cuz it increases peronieal pressure) • Itching → histamine release (contraindicated in bronchial asthma) • Tolerance; *not to meiosis, convulsion or constipation* • Dependence. • Euphoria. Even in depressed pationats it's considered as adverse effects	• Head injury (administration of morphine lead to pinpoint pupil. Pupillary action is an important sign for the level of consciousness. In addition it causes Respiratory depression and the head injury itself might cause resp depression) • Pregnency (It is prohibited to give the morphine in PREANAESTHETIC medication during delivery because it will lead to fetal death from respiratory depression.) • Elderly are more sensitive;↓metabolism, lean body mass & renal function (you decrease the dose) • Not given infants, neonates (cytochrome system is not well developed it may lead to toxicity) • Not given during child birth→(↓conjugating capacity → accumulate → Respiratory depression). • Bronchial asthma or impaired pulmonary function (due to histamine release) • Liver & Kidney diseases (contraindicated renal& biliary colics) • Endocrine diseases (myxedema & adrenal insufficiency) • With MAOIs

Tolerance & dependence of morphine

- Develop rapidly, withdrawal manifestations develops upon stoppage.
- Dependence comprises both:

Physical dependence:

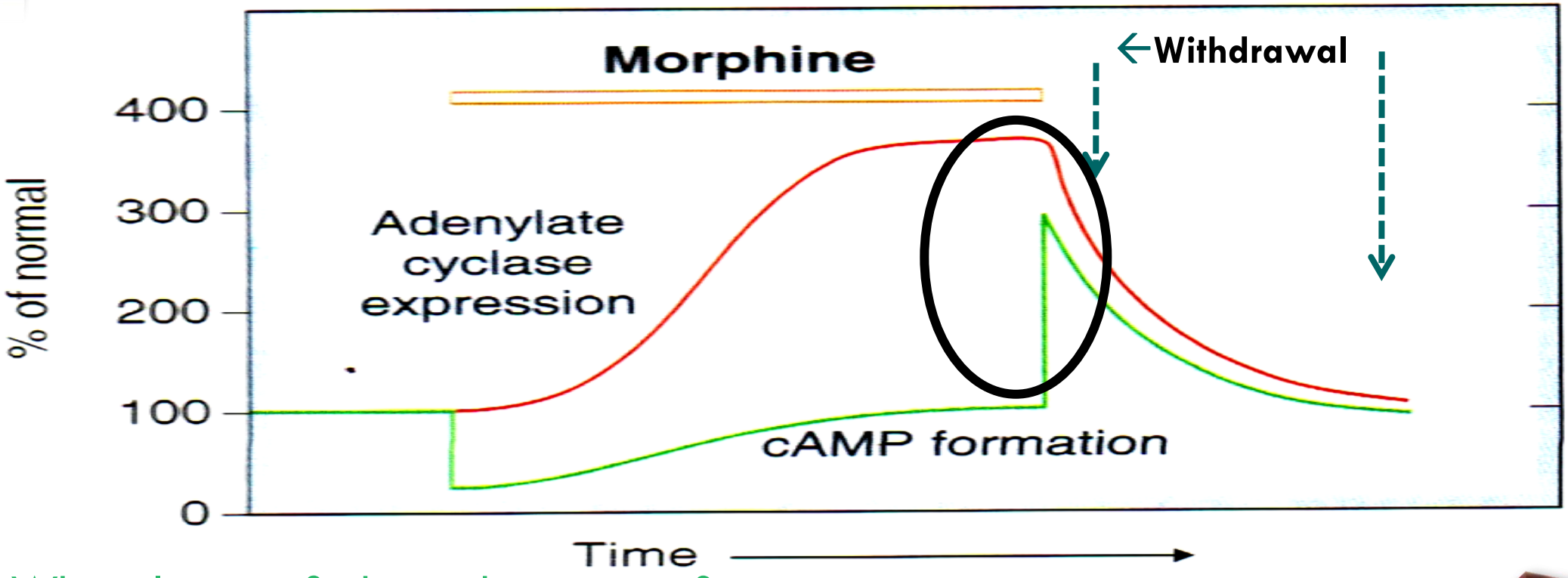
lasting for a few days in form of ↑ body ache, insomnia, diarrhea(morphine indicates constipation), goose flesh, lacrimation. (very important)

(physical dependence means manifestations that force him to take the drug „his body cells are dependent in their function on the presence morphine & the stoppage of morphine develop withdrawal manifestation.)

Psychological dependence:

lasting for months / years → craving

Continue…



- Why tolerance & dependence occur ?

The morphine activate the Gi protein which decrease the level of cAMP .

When the body feels the low levels of cAMP , to adapt it will increase the level of opioid receptors.

- Withdrawal manifestation is due to high levels of cAMP.tell the body adapt and decrease the receptors

Morphine

Pharmacokinetics of Morphine:

- t ½ is 2-3h (short duration of action)
- It is slowly & erratically absorbed orally. (not given orally)
- **Medically** given by IM or IV injection.

It should be repeated if sustained effect is needed.

- Undergoes enterohepatic recycling
- crosses BBB
- crosses placenta.

Heroin & Codeine

Heroin

- μ agonist
- Crosses BBB
- Converted to morphine
- No medical use
- Strong addicting drug

Codeine

- μ Agonist
- Dependence less than morphine (less effect than morphine)
- Used in mild& moderate pain, cough, diarrhea

Very effective in cough

Meperidine /Pethidine

Actions Synthetic>effective K agonism	indication	Adverse effect (Atrooine Like)
• ↓analgesic • ↓ constipating • ↓ depressant on faetal respiration than morphine • Has atropine –like action (Smooth muscle relaxant) • No cough suppressant effect **(less effective κ agonism)**	• as in morphine but not in cough & diarrhea (because it has a muscle relaxant action)(oppose morphine that induces constipation) • Used in severe visceral pain, (renal & biliary colics smooth muscle relaxant). (classical drug used in renal & billary colic) • Used in obstetric analgesia (No ↓ resp.) • Preanaesthetic medication (better than morphine)	• Tremors, Convulsions, Hyperthermia, Hypotension • Burred vision, Dry mouth, Urine retention • Tolerance & Addiction(don't give it for more than 3 days)

tramadol

action	indication	Adverse effect
▪ Synthetic ▪ MUE Agonist ▪ Less potent ▪ Decrease NE & 5HT serotonin ▪ given orally (↑ oral bioavailability) it's much weaker, can be given to the patient at home	▪ Mild – moderate pain (minor operation ex:tooth extraction) 2dry drug after surgery acute & chronic visceral pain during labor	▪ Seizures (so not in epileptics) ▪ Nausea ▪ Dry mouth ▪ Dizziness ▪ Sedation ▪ Less adverse effects on respiratory & C.V.S.

fentanyl

action	indication	Adverse effect
▪ synthetic, m agonism. ▪ Very strong as analgesic and more potent than morphine and meperdine..so it must be given in very low doses ..so it is save in operation compered to others . ▪ IV or intrathecal and transdermal patch.	▪ Commonest analgesic supplement during anesthesia. ▪ In cancer pain & severe postoperative pain, transdermal patches changed every 72 hours) ▪ May develop addiction but they're already in terminal stage so not prohibited (Major operation) ▪ To induce & maintain anesthesia in poor-risk patients [stabilizine heart.] ▪ In combination with droperidol as neuroleptanalgesics (Neuroleptanalgesia Produced by a combination of opioids (fentanyl) for and neuroleptics such as droperidol (also known as anti-psychotics) for psychiatry condition .),you want them to forget bad memory or severe trauma)	▪ Mimic opioid agonists respiratory depression most serious ▪ CV effects are less. Bradycardia may still occur

Methadone

Action	Synthetic, μ- Weaker Agonist , **t½ 55 h (very long acting**)and weaker than morphine
Inddication	• **treat opioid withdrawal manifestation & morphine and opioids abusers (addicted)(** individuals develop withdrawal manifestation… so we treat them by methadone it is weak (so doesn't develop withdrwal manifestation and doesn't cause euphoria) and it is long acting ..so it will occupy those receptors) • 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 Has fluctutating kinetics so has to be given under medical observation and day by day we decreae the dose
Adverse effects	• In non addicts, it causes tolerance & dependence but not as severe as that of morphine • If normal person take it >>>become addicted to methadone(ex: after surgery)

Antagonizing acute opioid toxicity

Naloxone	▪ **Pure opioid antagonist ,, used for acute opioid toxicity (NOT chronic opioid toxicity which develop intolerance and dependence)** ▪ **Used to treat respiratory depression caused by opioid overdose & to reverse the effect of analgesia on the respiration of the new born baby (in cyanosed babies)** ▪ **Effect lasts only for 2-4 hours. (short acting)** ▪ **Precipitates withdrawal syndrome in addicts (not given to addicts becaues it increase withdrawal manifestation)** **Given to addicted patients)**
naltrexone	Very similar to naloxone but with longer duration of action [t½=10h]

SUMMARY

- Morphine :control severe pain and used in preanasthetic medication .. Its main AE respiratory deppression and tolerance & dependence ..it is contraindicated in head injury and pregnancy & renal and biliary colic .
- **Meperidine /**Pethidine : it has atropine like action ..so it is aclassical drug in renal & biliary colic…it is used obstetric analgesia..
- Fentylen : it very strong drug more potent than morphine ..(low does) ..save in operation . Used in neuroleptanalgesics.
- Methadone : used to treat morphine and opioid abusers

QUESTIONS

Q1) 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

Q2) Pt suffered from morphine withdrawal manifestations which one of these drugs help to reduce the manifestations:

1-tramadol 2-meperidine 3-methadone

QUESTIONS

Q3) Which of the following drugs can be used in case of opioid overdose ?

1- naloxone 2-morphin 3-methadone

Q4)which of the following is used in case of renal colics ?

1- morphin 2- heroin 3- meperidine

QUESTIONS

Q5) which of the following has good oral bioavailability ?

1- methadone 2- morphin 3- tramadol

Answers : Q1) 1 – Q2) 3 – Q3) 1 – Q4) 3 – Q5) 3

THE END

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