Analgesics opioids (anodynes)

Pain - types

A) According to length of experience

1) acute: sign of and disease, danger or damage to organism...

2) chronic: more than 3 months/ unusually long for and given disease

Breakthrough pain: sudden pain in chronic background drug-controlled pain (typically in progression of cancer)

Pain - types

B) According to pathophysiology

1) Nociceptive – irritation of nociceptors

Therapy: „analgesic ladder“

2) Neurologic:

Therapy: psychopharmacs (antidepressants) and anticonvulsants

3) Psychogennic:

Therapy: psychopharmacs (antidepressants – TCA, SSRI)

Pharmacologic modulation of pain

Analgesics – antipyretics

Analgesics – anodynes (opioids)

Local anaesthetics

General anaesthetics

Adjuvant therapy (antidepressants, antiepileptics - anticonvulsants, antimigrenics, corticoids, caffeine…)

Pharmacologic modulation of pain

Adjuvant therapy:

Bone pain: biphosphonates, corticoids

Neuropathic pain: antidepressants, antiepileptics, anticonvulsants

Visceral pain: spasmolytics, corticoids

Analgesics

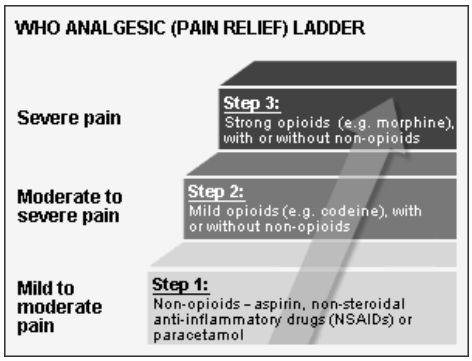
Analgesics – suppress perception of pain (increase the pain threshold) selectively without influencing perception of other stimuli

Analgesics – anodynes (opioids)

On spinal and supraspinal level
Effects on somatic and visceral pain
Strong effects on consciousness

Non-opioid analgesics

Mostly peripheral effects
Effects on inflammation
Weaker effects in general
No effects on visceral pain
No addiction



Analgetics - anodynes

Block transmission of pain signal among CNS (cells brain, spinal cord) by binding to opioid receptors (agonists)

Similarly to endogenous opioids :
endorphins, enkephalins, dynorphins

Opiates
natural compounds with effects similar to morphine

Opioids
+ synthetic and semi-synthetic substances

Opioid receptors - μ κ δ (σ)

G-protein coupled, i. adenylylcyklase, facilitate opening of K^+ channels postsynaptically, inhibit opening of Ca^{2+} channels presynaptically

μ - supraspinal analgesia, euphoria, sedation, miosis, breath depression, addiction, GIT effects
κ – spinal + peripheral analgesia, sedation, dysphoria, miosis, GIT
δ – spinal analgesia, breath depression, GIT

[**σ** – dysphoric effects (anxiety, hallucinations)]

Opioid receptors - μ κ δ (σ)

FOR ANALGETIC EFFECTS IS CRUCIAL ACTIVATION OF RECEPTORS:

μ - supraspinal analgesia

κ – spinal + peripheral analgesia

Pharmacological influention on opioid receptors

agonists
(mostly μ and κ)

antagonists
(affinity to μ and κ without IA – naloxon, metyl-naltrexon)

parcial agonists – dualists
(high affinity to μ with low IA - buprenorphin)

mixed agonists – antagonists
(agonist on κ, antagonist on μ - pentazocin)

+ atypical opioid tramadol – effect on μ + 5HT + NOR

Central effects of opioids

- analgetic
- supression of center of breathing
- sedation
- supression of anxiety
- euphoria/dysphoria
- antitussic effect
- nausea and vomiting
- increased tendency to convulsions/cramps
- miosis
- ↑secretion of ADH, ↓ GnRH, corticotropine, FSH, LH, ACTH

Peripheral effects of opioids

GIT

↑tonus, ↓motility
pro-spasmogennic effects

Urinary sys.

↑tonus of sphincter, ↓detrusor
urine retention (especially after surgery)

Kidneys

decreased perfusion and GF

KVS

vasodilatation - orthostatic hypotension
tachycardia

Uterus

↓ tonus, motility, elongation of labor

Mast cells

histaminoliberation

Bronchi, oviduct

inhibited function of cilliar epithelium

Side effects in clinical management:

- Depression of breath centre – the most feared
- Nausea and vomiting – 30 – 80% of patients on the beginning of the therapy
- Sedation, depression of cognitive functions
- Constipation – about 50 % of patients (or more)
- Itching

Rapid toleration evolves for most of these effects with exception of constipation

Comparison with non-opioid analgetics

Advantages	**Disadvantages**
No:	individual tolerability and efficacy
parenchym toxicity	typical AE
gastropathy	addictiv potential
hematotoxicity	imunosupression
Effect on coagulation	↓ endocrine functions
Useful in polymorbidity	

PHARMACOKINETICS

ABSORPTION – parenteral
p.o. – first pass effect
perrectal
transdermal

DISTRIBUTION – parenchymatous organs
muscles
fat tissue (lipophilic, e.g. fentanyl)
brain (fentanyl, heroin...)

Can cross placental barrier!!!

BIOTRANSFORMATION
- liver – CYP 450 → polar metabolites, conjugates

- inactive metabolites
- active metabolites (codein, tramadol)

EXCRETION
- urine
- bile

Weak opioids

- Weak agonists on μ (codein, dihydrocodein)
- Atypical opioid tramadol
- Mixed agonist – antagonist - agonist on κ, antagonist on μ (pentazocin)

Ceiling effect – further increase of dosing does not lead to increased analgetic effects

Intermediate and weak opioid agonists

Codein, dihydrocodein

10 % mtb. to morphin

weak analg., better in combinations (e.g. with paracetamol – Ultracod, Talvosilen)

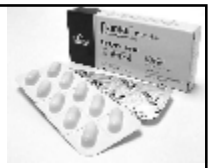
↓ risk of addiction

KI - CHOPN

Codeine - antitussic in subanagetic doses

Dihydrocodeine – often constipation

Atypical opioid



Tramadol

low affinity for μ receptors

+ blocked reuptake of noradrenaline and increased release of serotonin

about 1/6 of morphin analgesia – relatively weak,

usually combined with paracetamolem

AE – often dizziness and nausea

serotonine syndrom (in combination with SSRI)

Tramal, Tralgit, Noax UNO

Agonist - antagonist

Pentazocin

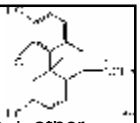
Not suitable for CHP

Lots of psychomimetic effects

Strong opioids

- full agonists for μ
- For strong resistant pain
- No ceiling effect, doses recommended in pharmacopoeia are often not enough, progressive dosing is necessary
- indications:
  cancer pain, dorzalgia, neuropatic pain, revmatic pain, osteoarthrosis

morphin



selective μ agonism

cca 10 % of opium, together with codeine + other phenantren alkaloids

- p.o. (with slow release - MST Cont) – for CHP
- parent. (i.v., i.m., s.c., epidural, intrathek.) – AP
- effervescent tablets – fastest onset – BP
- p.rect. administration

Disadvantages –

AE, cumulation of toxic metabolites – in renal insuff, elderly people, dehydration

Fentanyl

pure μ agonist for strong CHP

lipophilic – very well pass HEB and mucoses (100x higher potency than morphin)

TTS – 3-day release with very stable levels in plasma, less AE

Fentanyl-citrate – orally or nasally aplied on mucoses, rapis effect in 5 min – BP

disadvantage – it is necessary to titre the dose individually

Hydromorphon

relatively safe opioid

in p.o. retarded preparations (12 or 24h) for therapy of CHP

Oxycodon

Preparation with 2-phase release – at first bolus and than slow 12 hours release – for strong CHP, neuropatic pain

Metabolism via 2D6 to active metabolites – in fast metabolisers strong effect and vice versa

Combination with naloxone (antagonist) suppress constipation

Parc. agonists / agonists - antagonists

Buprenorphin

parc. agonist on μ, antagonist on κ rcp.

advantages – lower addiction potential and less AE

disadvantages - lower analgesic effects

- first pass effect → inj., sublingual, TTS
- ceiling effect

indications - analgesic
- therapy of opioid addiction

Pethidin / meperidin (Dolsin, Demerol)

• ↓ suppression of breathing centre and lower spasmogenic effect than morphin

• toxic metabolite norpethidin causes myoclonal convulsions and cramps → *p.o.* and parenterally in AP
• interaction with IMAO
• today less advantageous parenteral opioid

Piritramid

Inj. in strong AP (eg. after surgery)

Metadon

Substitution in addiction treatment

Heroin - diacetylmorphin

Antagonists of opioid analgesics

naloxon, naltrexon

Indications: treatment of intoxication, respiration depression, diff. dg. of addiction

! New preparation in combination with opioids

methylnaltrexon – peripheral antagonist

Intoxication by opioids

nausea, flush, hučení in uších, tinnitus

apathy, sedation, sleep, miosis

superficial breathing

cyanotic, cold skin, rapid heart rate

asfphyxia

TRIAS: coma, breath supression, miosis

Therapy
- naloxon i.v.
- ventilation, vital functions
- in unconsciousness parenteral liquids

Rotation of opioids

- Switch in case of AE
- Sometimes even in equianalgesic dose increase of effect
- Lately methadon is started to be used (cheap, long half-life, no active metabolites)

Other indications

- Antitussic effect
  - In dry not-productive cough - u codeine
- Constipative effect
- Premedication in general anesthesia
  - Calms down the patient and by means of synergism decreases the total dose of narcotics used (what increases safety of general anaesthesia)
  - Most often fentanyl and its derivates
  - Combination of analgesic anodyne with neuroleptic (eg. fentanyl + droperidol) in case of neuroleptanalgesia THALAMONAL inj.
- Substitution therapy in heroin or other opiates/opioid addiction– methadon, buprenorphin

Rules of pain therapy management

- Choice and course of analgetic therapy depends on intensity and character of pain described by the patient – individual dosing – titration may take weeks in CHP
- Acute pain – course - from up going down – start with strong medication (opioid), parenteral administration, fast onset (eg. pain in AIM, renal or biliar colic)
- In chronic pain – course – from down going up – non-invasive preparations (p.o., TTS), slower release according to a time plan
- In some types of fluctuating chronic pain it may be necessary to give patient rescue medication in case of breakthrough pain

- Combination of non-opioid and opioid analgesics has additive effect
- Benefits of analgesic therapy should exceed its side effects.
- AE must be prevented rather than treated when they appear – eg. antiemetics, diet, laxatives
- There is not a maximal dose of opioid – (in case of full agonists and cancer pain)
- Rotation of opioids

Morphini hydrochloridum trihydricum

- **i.v., i.m., s.c. DTS: 0,005-0,02**
- **p.o. DTS: 0,01-0,02 (! I více)**
- **p. rect. DTS: 0,015-0,03**