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## Pain and Analgesia

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## Session Objectives

- Be able to describe how pain is perceived
  - Be able to describe how pain is assessed
  - Describe the active ingredients found in the S4 analgesics currently on the market and how they work (giving examples)
  - Understand and be able to apply clinical knowledge related to these analgesics
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## Relevant reading

- Therapeutic guidelines: Analgesics (4<sup>th</sup> ed).
  - Australian Medicines Handbook: Analgesics chapter.
  - MIMS.
  - Bryant, Knights and Salerno (2003). Pharmacology for the Health Professional. Chap 6.
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## Pain

- " An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".
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## Types of Pain

- N
    - burning, shooting, stabbing
    - ± ANS instability
    - allodynia (area not previously painful, e.g. clothing causes pain)
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## Types of Pain

- N
    - somatic: superficial, burning, dull ache  
± pain on movement
    - e.g. skin ulcer, bony metastases
    - visceral: deep, diffuse, nagging  
with nausea/vomiting, sweating  
may be referred  
e.g. bowel obstruction, colic
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## Types of Pain

- P
  - central syndrome
  - total suffering
  - (no obvious somatic source; anger/anxiety/depression)
  - requires a multi-modal approach

## Physiology of Pain

- Figure Bryant and Knights 16.3B

## Physiology of Pain

- Noxious stimuli in periphery detected by pain receptors (nociceptors)
- Signals transmitted to the spinal cord
- A-delta ( $\delta$ ) fibres: sharp, transient, fast pain
- C-fibres: burning, aching, slow, visceral pain
- A  $\delta$  fibres and C-fibres = primary afferents

## Physiology of Pain

- Primary afferents synapse in the dorsal horn of the spinal cord
- Secondary neurons cross the spinal cord and continue upwards in anterolateral spinothalamic tracts
- Synapse in the thalamus and cortex where pain perception occurs
- Efferent pathways from the cortex descend via periaqueductal grey matter to dorsal horn areas in the cord, may modify afferent impulses

## Gate-control theory of pain perception

## Gate-control theory of pain perception

- Proposes that pain perception is a balance between a number of inputs that synapse in the spinal cord.
- eg. Rubbing elbow after you've bumped it
- NB.  $A\alpha$  and  $A\beta$  fibres = mechanoreceptors = no pain  
 $A\delta$  and C fibres = nociceptors = pain

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## Mediators in the Pain Pathway

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## Kinins

- Bradykinin (BK) and kallidin
  - Formed from proteins, kininogens
  - Inactivated by kininases
  - Vasodilator and increased vascular permeability
  - Potent pain-producing agent
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## Mode of action of Bradykinin

- Produced under conditions of tissue injury
  - Acts via the B2 bradykinin receptor to phosphorylate and sensitise vanilloid 1 (VR1) receptors
  - Activation of VR1 excites nociceptive nerves
    - VR1 ligand gated ion channel
    - influx of  $\text{Na}^+/\text{Ca}^{2+}$  depolarising afferent fibres
    - also stimulated by capsaicin
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## Prostaglandins

- Figure 16.11 – Bryant and Knights
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## Prostaglandins

- Main source: arachidonic acid (in phospholipids)
  - Many types
  - Enzymes that convert arachidonic acid to prostaglandins are the fatty acid cyclooxygenases: COX1 and COX2
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## Prostaglandins

- Always released in the inflammatory process
  - Powerful vasodilators
  - Work together with (potentiate) BK and histamine
    - » redness and increased blood flow to areas of acute inflammation
  - Facilitate the opening of voltage gated  $\text{Na}^+$  channels
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## Prostaglandins

- Do not themselves produce pain
- Potentiate effect of BK by sensitising afferent C fibres

## Tachykinins

- Substance P, neurokinin A and B
- Distributed widely in the nervous system
- Especially in nociceptive primary afferent neurons and dorsal horn (produced and released in/by neurons)
- Receptors: NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>

## Tachykinin Receptors

|              | NK1 | NK2 | NK3 |
|--------------|-----|-----|-----|
| Substance P  | +++ | +   | +   |
| Neurokinin A | +   | +++ | +   |
| Neurokinin B | +   | +   | +++ |

N.B. NK1 receptor type most associated with pain sensation

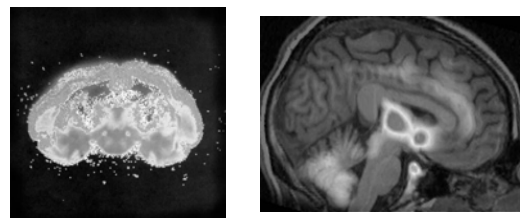
## Tachykinins

- Activation of these receptors = slow excitatory synaptic potentials (SESPs) in dorsal horn neurons
- Each SESP is not enough to make the neuron fire, so have to build up for this to occur

## Opioid peptides

- Peptides that have opiate like pharmacological effects
- $\beta$ -endorphin, met/leu-enkephalin, dynorphin
- Widely distributed throughout the brain
- Spinal cord:
  - dynorphin (interneurons)
  - enkephalins (desc. pathway from midbrain to dorsal horn)

## Opioid receptors



## Opioid receptors

- Three main types:  $\mu$ ,  $\delta$ , and  $\kappa$
- $\mu$ : central,  $\delta$ : periphery and  $\kappa$ : spinal
- All GPCRs: inhibit adenylate cyclase, ↓ cAMP production
- Also exert effects on ion channels via direct G-protein coupling
- Promote opening of  $K^+$  channels
- Inhibit opening of voltage gated  $Ca^{2+}$  channels

## Opioid receptor function

|                  | $\mu$ | $\delta$ | $\kappa$ |
|------------------|-------|----------|----------|
| <b>Analgesia</b> |       |          |          |
| Supraspinal      | +++   | -        | -        |
| Spinal           | ++    | ++       | +        |
| Peripheral       | ++    | -        | ++       |
| Resp. Depression | +++   | ++       | -        |
| Pupil constrict. | ++    | -        | +        |
| ↓ GI motility    | ++    | ++       | +        |
| Euphoria         | +++   | -        | -        |
| Dysphoria        | -     | -        | +++      |
| Sedation         | ++    | -        | ++       |
| Physical Depend. | +++   | -        | +        |

## Other Central Mediators

| Inhibitory  | Excitatory  |
|-------------|-------------|
| - GABA      | - Glutamate |
| - 5-HT      | - Adenosine |
| - NA        |             |
| - Adenosine |             |

## Pain Assessment

## Pain Assessment

- Is there pain?
- Acute pain – quite obvious
- Chronic Pain – not so obvious
- Need to accept patients account and at the same time be objective in your assessment.

## Pain Assessment

- "Pain is what the patient says hurts"
- Describe the pain
- "Tell me about your pain"
- "Where is it?"
- If more than one site, may need to take each site separately

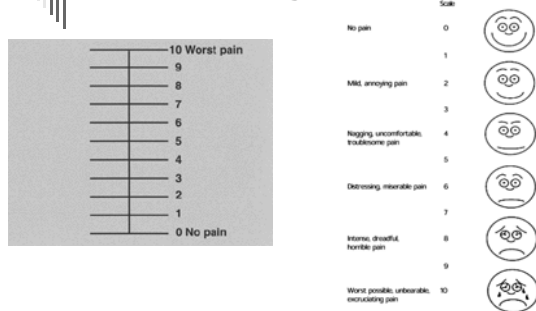
## PQRST

- P
  - What makes the pain better?
  - What makes the pain worse?
- Q
  - What is the pain like?
- R
  - Does it go anywhere?

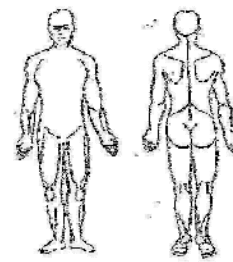
## PQRST

- S
  - how severe is it?
- T
  - Is it there all the time?
  - Does it come and go?
  - What brings it on?

## Visual Analogue Scales



## Locate the Pain



Equivalent for feet?

## Assessing the Type of Pain

- Mechanical pain - gets worse on use – opioid usually works better.
- Inflammatory pain – gets better when used –NSAIDs usually works better.
  - Only a general rule – rarely does one type of pain happen without the other.

## Reassessment

- Efficacy of analgesic treatment should be regularly reviewed.
- Common to change analgesics because of side effects and lack of effect or to add adjuvant medication
- Analgesics failing to control pain should lead to reassessment of:
  - the type of pain
  - drug selection and dose
  - psychological factors experienced by patients

## Pain Management using S4 analgesics

### Active ingredients in S4 analgesics

- P
- D
- C
- A
- T

### Paracetamol



- Analgesic and antipyretic properties
- Little anti-inflammatory action
- Can use alone for less severe pain or in combination with opioids and NSAIDs
- 4g/day with adults and children over 12 yoa b/c increased risk of hepatotoxicity
- Well absorbed after oral/rectal admin
- Almost entirely metabolised by liver
- Elimination half life is 4 hrs.
- Very safe drug (aka acetaminophen)

### Dextropropoxyphene HCl



- Structurally related to methadone:
  - less potent => less analgesic, less anti-tussive activity
- Mixed agonist antagonist
- More prominent dysphoric adverse effects
- Continuous use discouraged due to compromised renal function
- Rapid death with OD (particularly in association with alcohol)

### Codeine Phosphate



- Oral analgesic for mild pain (headache, backache)
- 20% analgesic potency compared to morphine, doesn't really increase any further than this with increasing doses
- Little/no euphoria
- Rarely addictive » no prescription required up to certain amount (30mg)
- Often combined with paracetamol
- Antitussive
- Causes constipation and respiratory depression
- ~ 10% population resistant to analgesic effects of codeine because don't have the enzyme that converts it to morphine

### Aspirin



- Anti-inflammatory, anti-pyretic and analgesic effect
- For mild to moderate pain – particularly for superficial sites, mucosal linings and bone
- Mainly acts by inhibiting COX enzymes
- Predominant effects at the periphery

## Tramadol



- Weak opioid
- 2 modes of action:
  - weak agonist at opioid receptors
  - prevents the uptake of NA and 5HT
- May cause dizziness and sickness
- May be combined with NSAIDs/paracetamol

## S4 analgesics available on the market at the moment.....

| Brand Name     | Active ingredients              |
|----------------|---------------------------------|
| Capadex        | dextropropoxyphene HCl (32.5mg) |
|                | paracetamol (325mg)             |
| Codalgin Forte | codeine phosphate (30mg)        |
|                | paracetamol (500mg)             |
| Codapane Forte | codeine phosphate (30mg)        |
|                | paracetamol (500mg)             |
| Codral Forte   | aspirin (325mg)                 |
|                | codeine phosphate (30mg)        |
| Di-gesic       | dextropropoxyphene HCl (32.5mg) |
|                | paracetamol (325mg)             |

## S4 analgesics available on the market at the moment.....

| Brand Name      | Active ingredients              |
|-----------------|---------------------------------|
| Dolaforte       | codeine phosphate (30mg)        |
|                 | paracetamol (500mg)             |
| Doloxene        | dextropropoxyphene HCl (100mg)  |
| Dymadon Forte   | codeine phosphate (30mg)        |
|                 | paracetamol (500mg)             |
| GenRX Tramadol  | tramadol HCl (50mg)             |
| Mersyndol Forte | multiple active compounds       |
| Panadeine Forte | codeine phosphate (30mg)        |
|                 | paracetamol (500mg)             |
| Paradex         | dextropropoxyphene HCl (32.5mg) |
|                 | paracetamol (325mg)             |

## Clinical Aspects of S4 analgesics

### When would you prescribe these drugs?

- When pain relief is insufficient with conservative treatment and drugs available over the counter
- Examples of situations:
  - after a procedure that requires skin penetration
  - acute/chronic musc/skeletal pain
  - repetitive injury
- "By the clock"
  - regular analgesics to give pain relief
  - pre-emptively

### Which drug to chose?

- Level of analgesia governs the drug chosen => increase pain severity, increase strength of medication.
- Will become apparent with experience in clinic
- You can get drug information from:
  - MIMS, AMH, Pharmaceutical Reps
- The cheapest one

## Which drug to chose?

- Simple analgesics first
  - so start with paracetamol
  - if that doesn't work alone, add/change to NSAIDs
  - not working add/change to tramadol
  - not working – add/change to codeine
  
- Multi-modal therapy

## How much would you prescribe?

- Follow the dosing recommended in MIMS, AMH and in the product information sheet

## What are the problems associated with these drugs?

- Side effects:
    - drowsiness
    - dizziness
    - nausea/vomiting
    - constipation
    - respiratory depression
    - dependence/tolerance (dextropropoxyphene)
- } codeine

## Contraindications

- Tramadol:
  - can't be given to patients taking SSRIs and anti-depressants
  
  - may cause "serotonin syndrome"

## Contraindications

- Aspirin:
  - not for anyone with renal/suspected renal problems
  - not for the elderly (unless absolutely have to)
  - not for use over long periods of time
  - not for diabetics (more susceptible to renal problems)
  - not for ulcer patients
  - not for children (Reye's syndrome)

## Contraindications

- Paracetamol:
  - Possible to OD on this – causing hepatotoxicity
  
  - Need to be hospitalised and given antidote (Acetylcysteine )



## Contraindications

- Codeine Phosphate:
    - Only if absolutely necessary in children
    - Beware of potential misuse as a street drug
- 



## HELP!! I'm a little worried..

- Don't panic/worry
  - Prescribing will not be in isolation
  - Paper trail back to the GP or pharmacist
  - Don't feel confident – get some help/more information
  - Clinical experience – comes with time
  - Remember your information sources – MIMS, AMH etc.
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