Analgesics and Non-steroidal anti-inflammatory drugs (NSAIDs)

- BSR/BHPR AHP in Rheumatology
- Core Course in Rheumatoid Arthritis
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Learning Objectives

- By the end of the session, regarding analgesics and NSAIDs, students will be able to:
  - Identify common examples
  - Categorise
  - Describe, in basic terms, their mechanism of action
  - Describe common side effects
  - Explain the basis for the side effects
  - Discuss the appropriateness of the drugs for a given patient
  - Counsel a patient prescribed one of the drugs
Analgesics

- By definition, reduce pain
- Categorised into:
  - Simple and compound
  - Non-opioid and opioid
- May act
  - centrally (i.e., within the brain)
  - peripherally (i.e., on receptors at the site of injury, inflammation etc)
  - centrally and peripherally

Paracetemol

- A simple analgesic (Non-opioid) – good for mild-moderate pain
- Anti-pyretic
- Mechanism of action unclear:
  - Possibly central prostaglandin inhibition
- Usually well tolerated, little gastric irritation
- Potential hepatotoxicity
  - In overdose
  - In patients who already have liver impairment
Morphine (i)

- A narcotic analgesic (opiate). (As well as relieving pain, they cause narcosis –stupor)
- Acts to block receptors for enkephalins and endorphins (Neurotransmitters, mainly in the brain, some peripheral)
- Thus main action is central, (but also peripheral effects)
- Affects
  - pain threshold
  - pain tolerance (euphoric effect)

Morphine (ii): Side effects

- Direct central effects:
  - Respiratory depression – very important in overdose – can be fatal
  - Cough suppression
  - Emesis – nausea and vomiting
  - Pupillary constriction
- Peripheral effects:
  - Increased tone/decreased propulsion of GIT – hence constipation
Morphine (iii)

- Tolerance – ie decreasing response to a given dose
- Physical dependence
  - only occurs once tolerance has developed
  - Recognised by withdrawal symptoms on stopping the drug (diarrhoea, hyperventilation, sweating, cramps)

Ranking of the analgesic potency of opiates

1. Diamorphine
2. Morphine (+ methadone)
3. Pethidine
4. Dihydrocodeine
5. Codeine
6. Dextropropoxyphene
### Compound analgesics
- Aspirin or paracetemol + opioid (in low dose)
- Controversy about how much more effective than simple analgesics
- Widespread use
- Some opioid side effects in therapeutic doses eg constipation
- Risk of serious opioid side effects in overdose as well as risk of paracetemol hepatotoxicity

### Examples of compound analgesics
- Cocodamol
  - Codeine phosphate and paracetemol
  - (eg kapake, solpadol, tylex)
- Codydramol
  - Dihydrocodeine and paracetemol
  - (eg Remedeine)
- Coproxamol
  - Dextropropoxyphene and paracetemol
NSAIDs

• All act to decrease the cardinal features of inflammation by inhibiting prostaglandin synthesis
• Central (anti-pyretic, analgesic) and peripheral (anti-inflammatory) actions
• 14 million pts in USA take regularly
• > $2 billion spent on NSAIDs annually worldwide

Uses of NSAIDs

• To decrease pain and stiffness in
• Inflammatory arthitides – RA, AS etc
• Acute gout and pseudo-gout
• Osteoarthritis (NB not as routine)
• Some patients with:
  ◦ Back pain, soft tissue rheumatism problems
• Post-operative relief
• Renal colic etc
Adverse Effects of NSAIDs (i)

- Gastrointestinal
  - Indigestion, erosions, peptic ulceration
  - Symptomatic ulcers, perforations or bleeds in 2-4% of patients taking NSAIDs for 1 year

Adverse Effects of NSAIDs (ii)

- Renal - Hypertension, renal impairment
- Respiratory - Asthma
- Skin - Rashes
- Liver - Hepatitis, abnormal LFTs
- Haematological
- Cardiovascular
  - Myocardial infarctions
  - Strokes
Patients at higher risk of NSAID adverse effects

- >65 years old
- Serious co-morbidity
- Using other medications known to increase the risk of upper GI events
- Previous history of peptic ulcers
- Requiring prolonged usage of maximum dose NSAIDs

NSAIDs differ in terms of:

- Chemical structure
- Physicochemical properties – eg lipid solubility
- Plasma half-life (the time taken for the concentration in the blood to reduce by ½)
- Pro-drug or not
- Delayed release preparation or not
- Method of administration (oral, rectal, IM, topical)
- Side effect profile
**Prostaglandins**

- Lipid soluble molecules synthesised from arachidonic acid (at least 16 different ones)
- PGE2 present in high concentrations in acutely inflamed tissues
  - Causes many of the features of inflammation (vasodilation, sensitisation of nerve endings to histamine…hence warmth, redness, pain)
- Other PGs important in gastric and renal homeostasis

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**NSAID mechanism of action**

- Membrane phospholipid
  - Arachidonic acid
    - Cyclooxygenase
      - Endoperoxide
        - Prostaglandins
        - Thromboxane A2
        - Prostacyclin
- NSAIDs inhibit cyclo-oxygenase (COX) and thus PG synthesis
**Cyclo-oxygenase has 2 forms**

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<thead>
<tr>
<th></th>
<th>COX I</th>
<th>COX II</th>
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<tbody>
<tr>
<td>Role</td>
<td>Housekeeping</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Presence</td>
<td>Constitutive</td>
<td>Induced</td>
</tr>
<tr>
<td></td>
<td>(ie all the time)</td>
<td>(ie when inflammation)</td>
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<tr>
<td>Actions</td>
<td>Gastroprotection</td>
<td>Pro-Inflammatory</td>
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<td></td>
<td>Salt/water balance</td>
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<td>Renal blood flow</td>
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**COX-II Selectivity**

- Some NSAIDs block COX I and COX II equally
- Some NSAIDs block COX II much more than COX II (are “COX II-selective”)
- COX II selective NSAIDs should be effective anti-inflammatory agents but not cause the same toxicity eg to stomach and dudodenum
Examples of NSAIDs

- **Non COX-II selective**
  - Ibuprofen
  - Diclofenac
  - Naproxen
  - Indomethacin
  - Azapropazone

- **COX-II selective**
  - Rofecoxib (withdrawn)
  - Celecoxib
  - Etoricoxib
  - Etodolac*
  - Meloxicam*

  * Controversial

Relative safety of the older NSAIDs

- Lowest risk: Ibuprofen
- Intermediate risk: Diclofenac
  - Naproxen
  - possibly in Indomethacin
  - this Ketoprofen
  - order Piroxicam
  -

- Highest risk: Azapropazone
The COX-II selective inhibitors

- More expensive
- Seem to be safer in GI terms than the non-selective drugs
- Not safer in terms of kidney, hypertension
- Increased risk of thromboses – MI and CVA
- NICE guidelines regarding their use
- CSM advice since their thrombotic risk identified

NSAIDs and risk of thromboses

- First identified with COX-II selective inhibitors
  ◦ Highly robust evidence
- More recently, anxiety regarding non COX-II selective inhibitors and risk of thromboses
  ◦ Studies of patient databases
  ◦ Meta analyses of randomised controlled trials
NSAIDs in clinical practice: conclusions

- NSAIDs give symptom relief to many people
- A considerable amount is known about:
  - Mechanism of action
  - Side effects
  - Relative toxicity of older NSAIDs
- A major cause of morbidity and mortality - None are safe
- Selective COX II inhibitors may cause fewer serious GI side effects
- Rofecoxib causes increased thromboses
  - the other COX II inhibitors cause increased thromboses too
  - The older NSAIDs may also cause increased thromboses
- Use carefully!
- Interpret studies with care (and trepidation!)