Non-Steroidal Anti-Inflammatory Drugs

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Clinical Pharmacology


It's Quiz Time!

1. What is the precursor of prostaglandins..?

2. What is the main enzyme involved in the synthesis of Prostaglandin..?

3. Mention two NSAIDs..?

4. Mention one indication for NSAIDs..?

5. Mention two adverse effects for NSAIDs..?


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History

- **Salicylate** from the bark of the willow tree and was used to treat fever and rheumatism for centuries

- In the late 19th century, salicylic acid and later acetylsalicylic acid was synthesized and called aspirin.

- **Aspirin** was widely used to treat fever and pain till the availability of other drugs with similar mechanisms of action. It continues to be used in many parts of the world

- There are diverse group of compounds which were later synthesized, with actions similar to that of aspirin and became known as NSAIDs.

- The mechanism of action of Aspirin / NSAIDs was discovered in the 1960's by Prof Vane, who was awarded a Nobel prize in Medicine in 1982.

Mechanism of Action-NSAIDs

- They act through inhibition of the two isoforms of the enzyme cyclooxygenase (COX) – i.e. **COX-1** and **COX-2**
- NSAIDs that act on both enzymes are known as **non-selective NSAIDs (ns-NSAIDs)**
- NSAIDs which act predominantly on the COX-2 enzyme are known as **specific COX-2 inhibitors** (also referred to as **Coxibs**)

The Two Isoforms of COX

- **COX-1** is a normal constituent in the body for homeostasis, such as in:
  - Gastric mucosa – gastric cytoprotection
  - Kidney – Sodium and water balance / renal perfusion
  - Platelets – for aggregation

- **COX-2** is induced in the presence of injury and inflammation

- **COX-2** is also a normal constituent in the many organs such as: Kidney, brain, endothelium, ovary and uterus

COX-1: Constitutive

- **Homeostatic**
  - Protection of gastric mucosa
  - Platelet activation
  - Renal functions
  - Macrophage differentiation

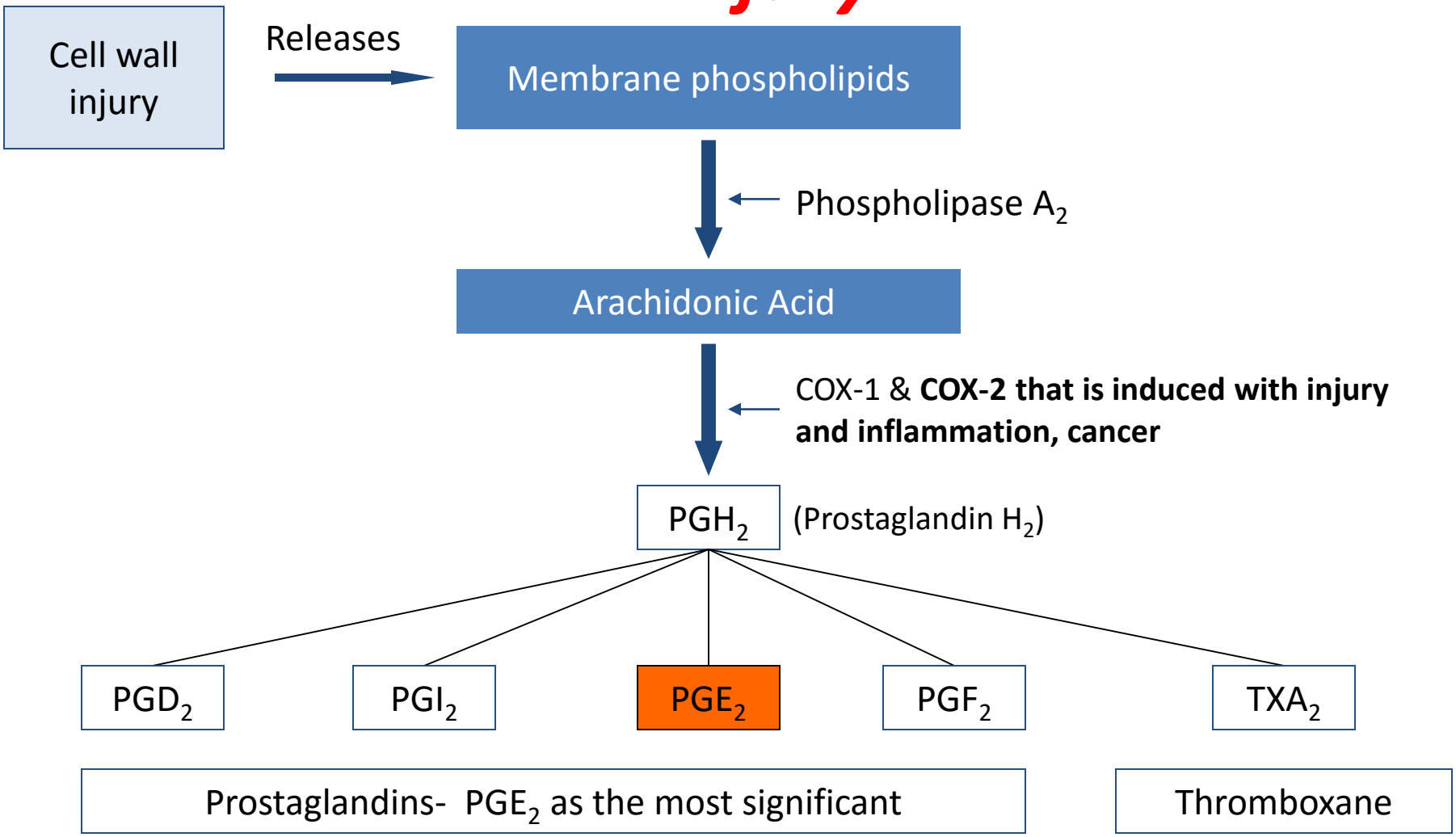
COX-2: Regulated

Pathologic

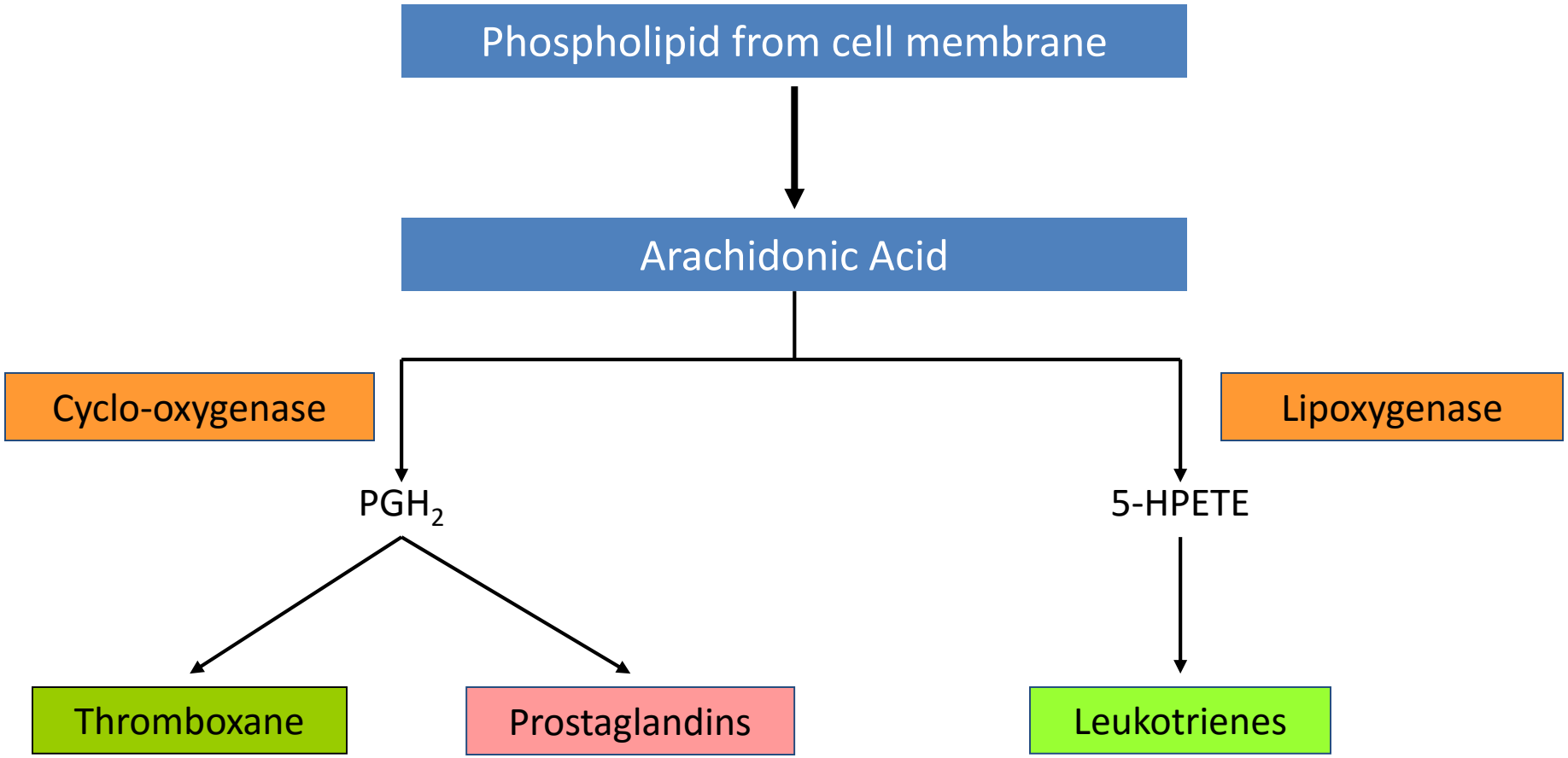
- Information
- Pain
- Fever
- Dysregulated proliferation

- Tissue Repair
- Physiologic
  - Reproduction
  - Renal functions
  - Other (see text)
- Development
  - kidney

What happens when there is tissue injury?

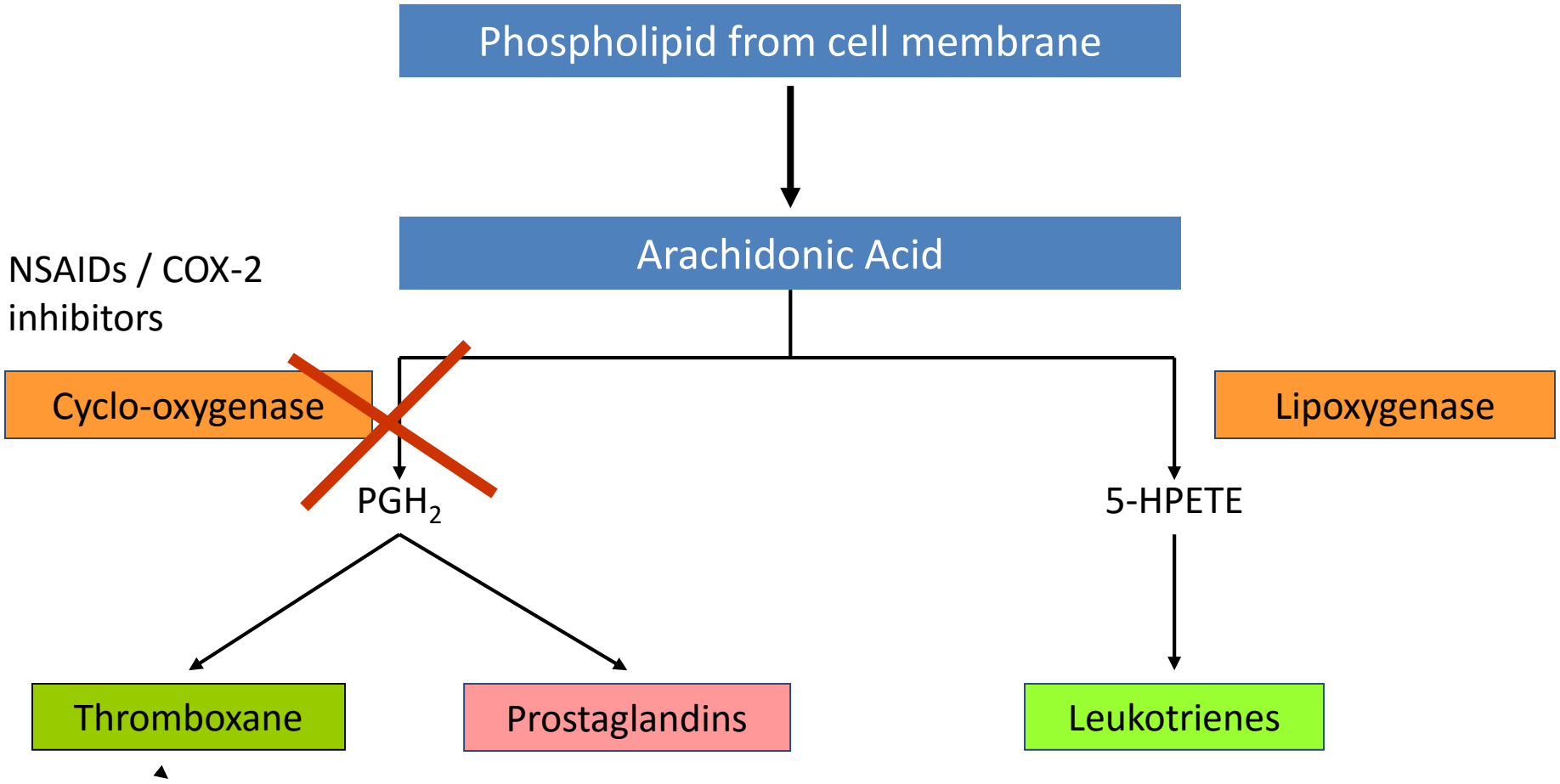


Arachidonic Acid Cascade



These inflammatory mediators activate the nociceptors on the Aδ and c fibres and result in pain and sensitization

Arachidonic Acid Cascade



Reduce Prostaglandins and Thromboxane, resulting in reduced pain

ROLE OF PROSTAGLANDINS

PATHOLOGIC

- Fever
- Asthma
- Ulcers
- Diarrhea
- Dysmenorrhea
- Inflammation
- Bone Erosion
- Pain

PHYSIOLOGIC

- Temperature Control
- Bronchial Tone
- Cytoprotection
- Intestinal Mobility
- Myometrial Tone
- Semen Viability

FUNCTION OF PROSTAGLANDINS IN INFLAMMATION

- PGE_2, PGI_2

  Vasodilation,

  Act Synergistically With Other Mediators

  Histamine, Complement, Ltb_4

  Bronchodilatation

  Inhibition Of Platelet Aggregation

- TXA_2

  Promotion Of Platlet Aggregation

ns-NSAIDs

Acetylsalicylic acid (aspirin)

- Tablet, suppository

Ibuprofen

- Tablet, suspension for children

Indomethacin

- Tablet

Diclofenac

- Oral tablet, suppositories, parenteral form available

Mefenamic acid

- Oral tablets

COX-2 specific inhibitors (Coxibs)

Celecoxib

- Oral capsules

Etoricoxib

- Oral tablets

Parecoxib

- parenteral

NSAIDS-THERAPEUTIC EFFECTS

- **Analgesia**
- **Anti-inflammatory**
- **Anti-pyretic**
- **Anti-neoplastic**

Absorption and Elimination

- When administered orally, aspirin, ns-NSAIDs and Coxibs are well absorbed and reach therapeutic levels within 30 to 60 minutes.

Indications

- Both the ns-NSAIDs and Coxibs have the same efficacy in postoperative analgesia
  - Sole analgesia for day surgery
  - Along with opioids for major surgery

- Musculo-skeletal pain – e.g. back pain, joints, muscle sprains etc.
  - Osteoarthritis
  - Rheumatoid arthritis

- **Not indicated for neuropathic pain**

Adverse effects

Gastrointestinal effects

•The risk of **erosions, ulcers and bleeding** is higher with ns-NSAIDs compared to Coxibs.

•This risk with ns-NSAIDs is also variable with some being less than others.

• Risk is greater

- In elderly patients
- Those who are also taking aspirin

•Risk can be reduced by adding a proton-pump inhibitor (e.g. omeprazole) to ns-NSAIDs.

- H2 receptor blockers are not very effective.

Renal effects

- Both COX-1 & 2 are constituent enzymes in the kidney
  - Maintain renal perfusion and sodium/water balance

- Both ns-NSAIDs and Coxibs can cause
  - Hypertension, odema
  - Decrease in creatinine clearance that may be significant in patients with impaired renal function or transient hypotension / hypovolaemia in the postoperative period

Cardiovascular effects

- Some studies have shown that there was a higher risk of thrombotic cardiovascular events (stroke, heart attack) when on Coxibs when compared to ns-NSAIDs such as naproxen
- Other studies have shown that the cardiovascular events are similar
- Nevertheless, current recommendations are that Coxibs should not be used in patients with active cardiovascular disease and a known thrombotic condition

Effect on platelets

- ns-NSAIDs are able to prevent platelet aggregation as platelets do not have COX-2. There is therefore a potential for bleeding with ns-NSAIDs

- Coxibs do not prevent platelet aggregation

- ns-NSAIDs should be used with caution in patients who are already on aspirin

Others

- Some ns-NSAIDs can precipitate asthma in aspirin sensitive asthmatic patients.

- Coxibs are well tolerated by patients who have aspirin sensitive asthma

Summary

NS-NSAIDs / Coxibs

- Both drugs are effective in providing pain relief for moderate pain

- The mechanism of action of both groups of drugs is by inhibiting the COX-2 enzyme that is induced with injury, inflammation and cancer

- Gastrointestinal side effects are less with coxibs

NS-NSAIDs / Coxibs

- Coxibs have no effect on platelet aggregation
- Both drugs should be used with caution in patients with renal impairment and in the elderly
- Coxibs should not be used in patients with active cardiovascular disease or known thrombotic effects
- Coxibs can be given to patients with aspirin sensitive asthma
- Both drugs should be used for the shortest period of time at the lowest dosage

Cox-2 inhibiters

- **Similar to non-specific COX inhibitors**
  - **Anti-inflammatory**
  - **Analgesic**
  - **Some renal effects, e.g. sodium excretion, blood pressure**

- **Different from non-specific COX-inhibitors**
  - **No anti-platelet effects**
  - **Reduced endoscopic GI erosion and ulceration**
  - **Some renal effects, e.g. possibly less alteration of RBF and GFR**

Paracetamol

- Paracetamol has been in use for more than a century
- It has both analgesic and antipyretic action
- However, the exact mechanism of its action is unclear (There have been controversy over its action is central or peripheral and whether it targets another type of cyclooxygenase enzyme. COX3)

Absorption / Elimination from the body

- It is well tolerated when taken orally.
- On oral administration it is absorbed from the intestine (70%), stomach and colon (30%)
- Rate of absorption is rapid and depends on the dose

Absorption / Elimination

- The time taken to reach maximum plasma concentration (Tmax) is 15 - 30 minutes depends on the preparation
- It is available as tablets (adults), suspension or syrup for children and suppositories
- Tmax is 2 - 3 hours with suppositories
- Bioavailability ranges from 60-90%

Elimination

- Paracetamol is metabolized in the liver and only 2 - 5% is excreted unchanged

Indications and dosages

- It is used as an analgesic drug for mild to moderate pain
  - E.g. Tooth ache / teething pain in children, backpain, joint and muscle pain, headache, dysmenorrhoea
- Relief of fever in adults and children

Dosage

- Adults – Up to 1g oral / rectal, every 6 hours (4g should not be exceeded / day
- Children – Oral / rectal 20 mg / kg – every 6 hours

Side effects

- Paracetamol is well tolerated and has no side effects at therapeutic doses

- It has good haematological tolerability and does not alter haemostasis

Caution

- Since it is metabolized in the liver it must be used with caution / or omitted in the presence of liver impairment

- In patients with renal impairment, the dose of paracetamol should be reduced

- **Do not exceed 4g/day in adults and 125 mg/ kg in children**

Adverse effects

Hepatotoxicity with an overdose of paracetamol

- This can occur when a patient does not get adequate relief with paracetamol and decides to take more than the prescribed dose of a maximum of 4g/day (8 - 10 g / day)
- Intentional overdose (Paracetamol overdose / poisoning is the leading cause of acute liver failure in the US, UK and Australia)
- Overdose causes acute liver failure, as the elimination pathways are saturated resulting in elevated levels of toxic metabolites

Adverse Effects

- ***N-acetylcysteine*** (NAC) is the antidote for paracetamol poisoning and it is most effective when administered within 8 - 10 hours after ingestion

- **Renal toxicity** – Overdose can cause severe kidney necrosis

- Allergic reactions are rare

ANY QUESTIONS ????

Thanks