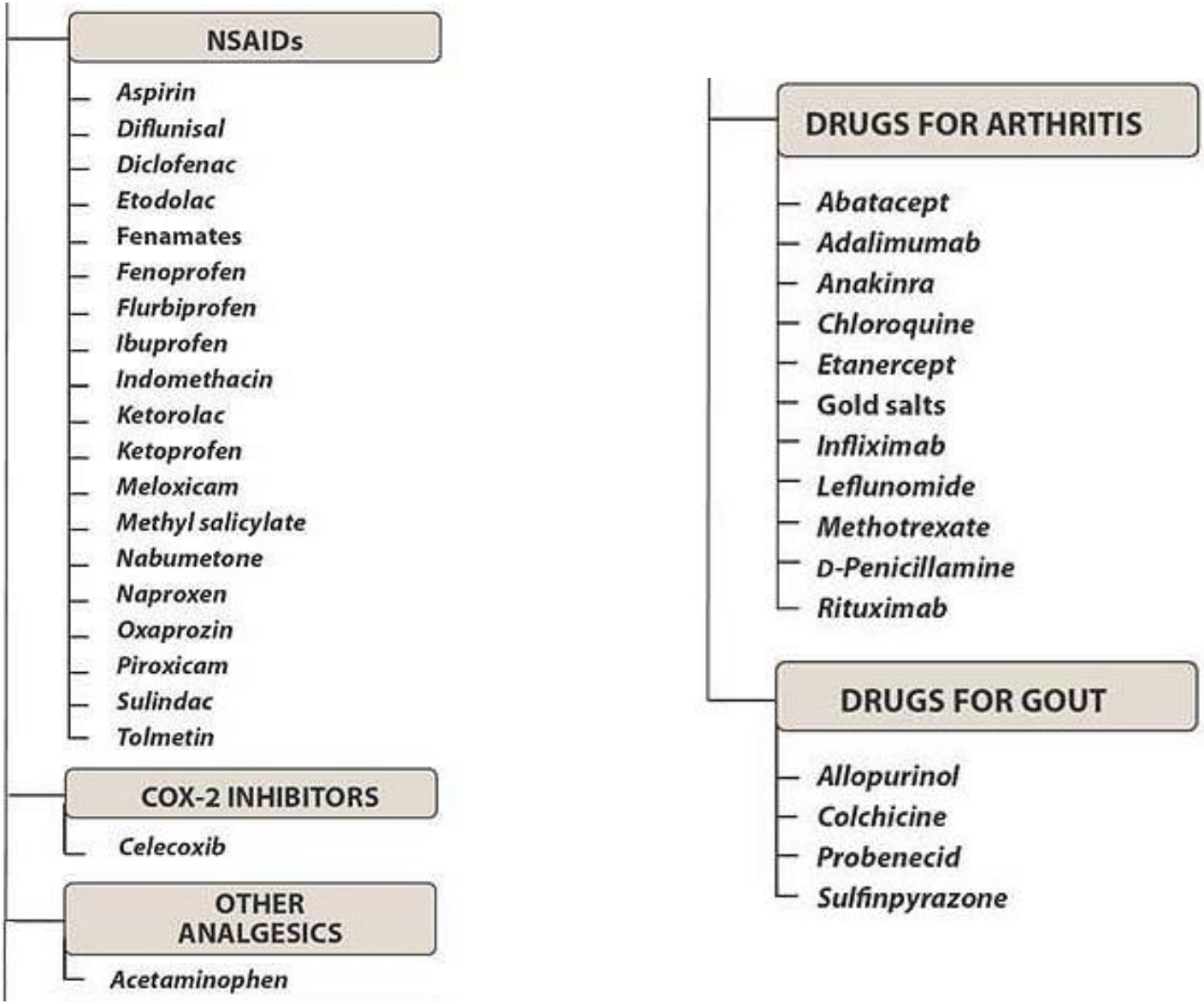
Anti-Inflammatory Drugs



Non Steroidal Anti-inflammatory Drugs

Dr Patrick Amoateng, *B.Pharm., MPSGh, PhD*

Dept of Pharmacology & Toxicology

University of Ghana

Non **S**teroidal **A**nti-Inflammatory **D**rug**s** **(NSAIDs)**

- The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities

- They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis
  - This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects

Introduction

- The NSAIDs, sometimes called the *aspirin-like drugs*, are among the most widely used of all drugs

- There are now more than 50 different NSAIDs on the global market

- They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures, sprains and other soft tissue injuries.

Introduction

- Some important examples are aspirin, ibuprofen, naproxen, indometacin, piroxicam and paracetamol

- Newer agents with more selective inhibition of COX-2 (and thus fewer adverse effects on the gastrointestinal tract) include celecoxib and etoricoxib

Examples of NSAIDs

Drug	Type	*RD*	*Gout*	*MS*	*PO*	*Dys*	*H&M*	Comments
Aceclofenac	Phenylacetate	•						-
Acemetacin	Indole ester	•		•	•			Ester of indometacin
Aspirin℞	Salicylate	•		•	•	•	•	Mainly cardiovascular usage
Celecoxib℞	Coxib	•						Fewer gastrointestinal effects
Dexketoprofen	Propionate				•	•		-
Diclofenac℞	Phenylacetate	•	•	•	•			Moderate potency
Diflunisal℞	Salicylate	•		•	•	•		-
Etodolac℞	Pyranocarboxylate	•						Possibly fewer gastrointestinal effects
Etoricoxib	Coxib	•	•					-
Fenbufen	Propionate	•		•				-
Fenoprofen	Propionate	•		•				Prodrug activated in liver
Flurbiprofen℞	Propionate	•		•	•	•	•	-
Ibuprofen℞	Propionate	•		•	•	•	•	Suitable for children
Indometacin	Indole	•	•	•		•		Suitable for moderate to severe disease
Ketoprofen℞	Propionate	•	•	•	•	•		Suitable for mild disease

Examples of NSAIDs

Ketorolac	Pyrrolizine				•			-
Mefenamic acid℞	Fenamate	•		•	•	•		Moderate activity
Meloxicam℞	Oxicam	•						Possibly fewer gastrointestinal effects
Nabumetone℞	Napthylalkenone	•						Prodrug activated in liver
Naproxen℞	Propionate	•	•	•		•		-
Parecoxib	Coxib				•			Prodrug activated in liver
Piroxicam℞	Oxicam	•	•	•				-
Sulindac℞	Indene	•	•	•				Prodrug
Tenoxicam	Oxicam	•		•				-
Tiaprofenic acid	Propionate	•		•				-
Tolfenamic acid	Fenamate						•	-

Dys, dysmenorrhoea; H&M, headache and migraine; MS, musculoskeletal disorders; PO, postoperative pain; RD, rheumatic diseases (e.g. rheumatoid arthritis and osteoarthritis).
(From British Medical Association and Royal Pharmaceutical Society of Great Britain 2005 British National Formulary. BMA and RPSGB, London.)

Classification of NSAIDs

- **Aspirin and other salicylic acid derivatives**
  - Aspirin (acetylsalicylic acid); sodium salicylate, methylsalicylate (topically used), diflunisal
- **Propionic acid derivatives**
  - Ibuprofen ;naproxen, fenoprofen , ketoprofen , flurbiprofen , and oxaprozin
- **Acetic acid derivatives**
  - indomethacin, sulindac, and etodolac
- **Oxicam derivatives**
  - Piroxicam and meloxicam
- **Fenamates**
  - Mefenamic acid and meclofenamate
- **Heteroaryl acetic acids**
  - Diclofenac and tolmetin
- **Nabumetone**
- **The Coxibs**
  - celecoxib; rofecoxib and valdecoxib; etoricoxib

COX-selectivity of NSAIDs

Group	Description	Selectivity ratio	Examples
I	Highly COX-1-selective	100-1000	Ketorolac
II	Very COX-1-selective	10-100	Flurbiprofen℞
III	Weakly COX-1-selective	1-10	Indometacin, aspirin℞, naproxen℞, ibuprofen℞
IVa	Non-selective; full inhibition of both enzymes	1	Fenoprofen
IVb	Non-selective; incomplete inhibition of both enzymes	1	Salicylate
V	Weakly COX-2-selective	1-10	Diflunisal℞, piroxicam℞, meclofenamate, sulindac℞, diclofenac℞, celecoxib℞
VI	Very COX-2-selective	10-100	Valdecoxib, etoricoxib
VII	Highly COX-2-selective	100-1000	Rofecoxib[a]

[a]Rofecoxib has been withdrawn from use and is shown here as an illustration only. (Based on data from Warner T D, Mitchell J A 2004 FASEB J 18: 790-804.)

Pharmacological actions of NSAIDs

- The NSAIDs have three major pharmacologically desirable actions, stemming from the suppression of prostanoid synthesis in inflammatory cells through inhibition of the cyclo-oxygenase (COX)-2 isoform of the arachidonic acid COX

Pharmacological actions of NSAIDs:

- *an anti-inflammatory effect*: modification of the inflammatory reaction
- *an analgesic effect*: reduction of certain types of (especially inflammatory) pain
- *an antipyretic effect*: lowering of body temperature when this is raised in disease (i.e. fever)

Anti-inflammatory action of NSAIDs

- The NSAIDs reduce mainly those components of the inflammatory and immune response in which prostaglandins, mainly derived from COX-2, play a significant part
  - a decrease in prostaglandin E_2 and prostacyclin reduces vasodilatation and, indirectly, oedema

- The NSAIDs suppress the pain, swelling and increased blood flow associated with inflammation but have little or no action on the actual progress of the underlying chronic disease itself
  - Thus accumulation of inflammatory cells is not reduced.

Analgesic effect of NSAIDs

- Peripherally, NSAIDs decrease production of the prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin and 5-HT

- Relief of headache is probably a result of decreased prostaglandin-mediated vasodilatation

- A less well-characterised central action occurs possibly in the spinal cord
  - Inflammatory lesions increase prostaglandin release within the cord, causing facilitation of transmission from afferent pain fibres to relay neurons in the dorsal horn

Antipyretic effect of NSAIDs

- During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of a pyrogen-IL-1 - which stimulates the generation, in the hypothalamus, of E-type prostaglandins that elevate the temperature set point (causing fever)
  - COX-2 may have a role here, because it is induced by IL-1 in vascular endothelium in the hypothalamus
  - There is some evidence that prostaglandins are not the only mediators of fever, hence NSAIDs may have an additional antipyretic effect by mechanisms as yet unknown

- NSAIDs exert their antipyretic action largely through inhibition of prostaglandin production in the hypothalamus

Mechanism-based side-effects of NSAIDs

- Most of the common unwanted effects stem from inhibition of the constitutive housekeeping enzyme cyclo-oxygenase (COX)-1 isoform of COX (particularly in the elderly) and include the following:
  - Gastric irritation
  - Renal insufficiency
  - Inhibition of platelet function
  - Cardiovascular disturbances

Mechanism-based side-effects of NSAIDs

- Controversially, it is argued that they may also all-but especially COX-2 selective drugs- increase the likelihood of thrombotic events such as myocardial infarction by inhibiting prostaglandin (PG) I_2 synthesis

Unwanted effects of NSAIDs

- ***Dyspepsia, nausea and vomiting***
  - Gastric damage may occur in chronic users, with risk of haemorrhage
  - The cause is suppression of gastroprotective prostaglandins in the gastric mucosa

- ***Skin reactions***
  - Mechanism unknown

Unwanted effects of NSAIDs

- ***Reversible renal insufficiency***
  - Seen mainly in individuals with compromised renal function when the compensatory prostaglandin E_2-mediated vasodilatation is inhibited

- ***'Analgesic-associated nephropathy'***
  - This can occur following long-continued high doses of NSAIDs (e.g. paracetamol) and is often irreversible

Unwanted effects of NSAIDs

- ***Liver disorders, bone marrow depression***
  - Relatively uncommon

- ***Bronchospasm***
  - Seen in 'aspirin-sensitive' asthmatics

Clinical uses of NSAIDs

- For ***analgesia*** (e.g. headache, dysmenorrhoea, backache, bony metastases, postoperative pain):
  - short-term use: **aspirin**, **paracetamol** or **ibuprofen**
  - chronic pain: more potent, longer lasting drugs (e.g. **diflunisal**, **naproxen**, **piroxicam**)
  - to reduce the requirement for narcotic analgesics (e.g. **ketorolac** postoperatively)

Clinical uses of NSAIDs

- For ***anti-inflammatory effects*** (e.g. rheumatoid arthritis and related connective tissue disorders, gout and soft tissue disorders)
  - Note that there is substantial individual variation in clinical response to NSAIDs and considerable unpredictable patient preference for one drug rather than another

- To lower temperature (***antipyretic***): **paracetamol**

Aspirin

- Aspirin (acetylsalicylic acid) is the oldest non-steroidal anti-inflammatory drug
- It acts by irreversibly inactivating both cyclo-oxygenase (COX)-1 and COX-2
- In addition to its anti-inflammatory actions, Aspirin inhibits platelet aggregation, and its main clinical importance now is in the therapy of myocardial infarction

Pharmacokinetic aspects of Aspirin

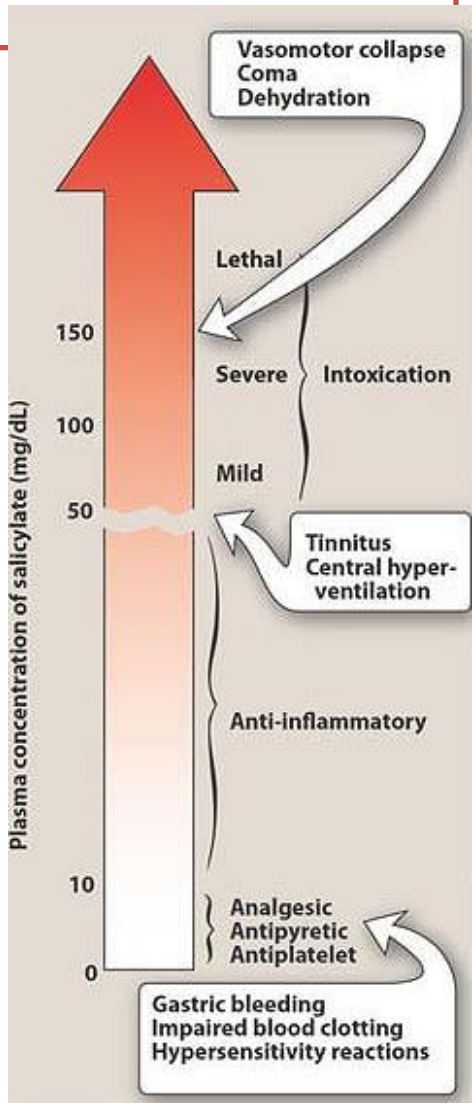
- It is given orally and is rapidly absorbed
  - 75% is metabolised in the liver

- Elimination follows first-order kinetics with low doses (half-life 4 hours), and saturation kinetics with high doses (half-life over 15 hours)

Unwanted effects of Aspirin

- At Therapeutic doses: some gastric bleeding (usually slight and asymptomatic) is common

- With large doses: dizziness, deafness and tinnitus ('salicylism'); compensated respiratory alkalosis may occur



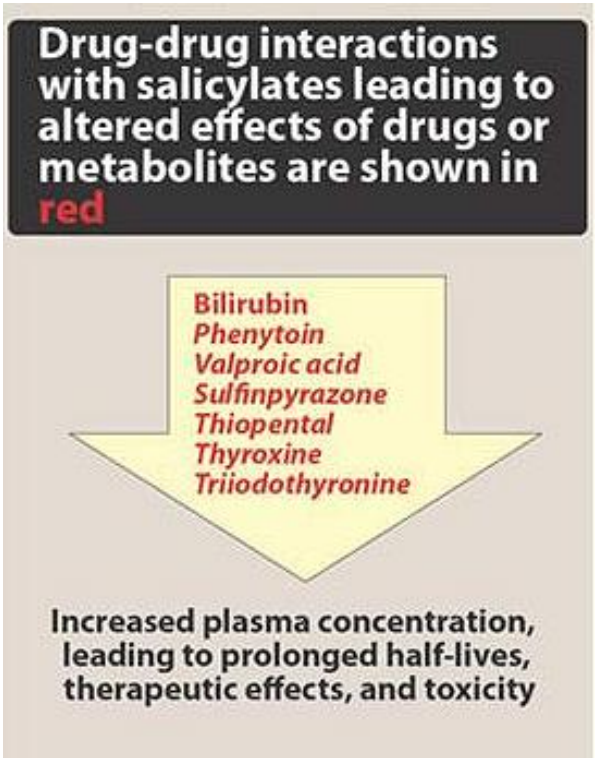
Unwanted effects of Aspirin

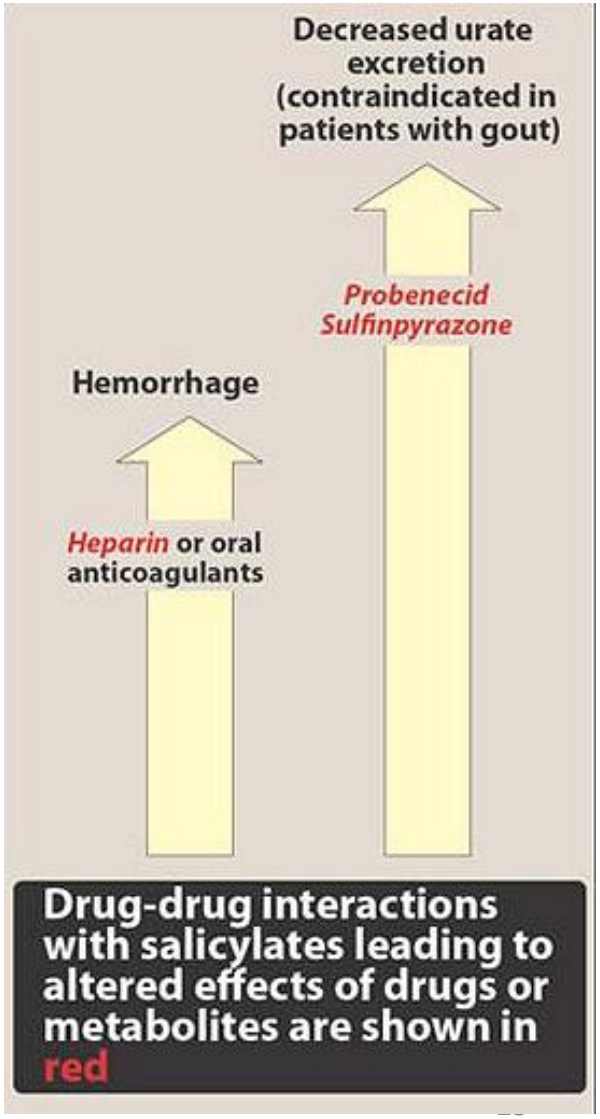
- At toxic doses (e.g. from self-poisoning): uncompensated respiratory acidosis with metabolic acidosis may occur, particularly in children

- Aspirin has been linked with a postviral encephalitis (Reye's syndrome) in children
  - which is an often fatal, fulminating hepatitis with cerebral edema

Aspirin: Interactions

- If given concomitantly with warfarin, aspirin can cause a potentially hazardous increase in the risk of bleeding





COX-2 Selective NSAIDs

- The “coxibs” agents selective for COX-2
- Current advice restricts the use of coxibs to patients:
  - for whom treatment with conventional NSAIDs would pose a high probability of serious gastrointestinal side effects
- Coxibs are prescribed only after an assessment of cardiovascular risk

Clinical Uses of Coxibs

- **Celecoxib** and **etoricoxib** are licensed for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis
  - Both are administered orally

- **Parecoxib** is a prodrug of valdecoxib
  - The latter drug has now been withdrawn, but parecoxib is licensed for the short-term treatment of postoperative pain
  - It is given by intravenous or intramuscular injection

Coxibs: Unwanted effects

- Common unwanted effects may include headache, dizziness, skin rashes, and peripheral oedema caused by fluid retention

- As with all COX-2 inhibitors, consideration should be given to the possibility of **serious adverse cardiovascular events**

Paracetamol

- Paracetamol has potent analgesic and antipyretic actions but rather weaker anti-inflammatory effects than other NSAIDs

- It may act through inhibition of a central nervous system-specific cyclo-oxygenase (COX) isoform such as COX-3, although this is not yet conclusive

Pharmacokinetic aspects of Paracetamol

- It is given orally and metabolised in the liver (half-life 2-4 hours)

- Toxic doses cause nausea and vomiting, then, after 24-48 hours, potentially fatal liver damage by saturating normal conjugating enzymes, causing the drug to be converted by mixed function oxidases to *N*-acetyl-*p*-benzoquinone imine
  - If not inactivated by conjugation with glutathione, this compound reacts with cell proteins and kills the cell

- Agents that increase glutathione (intravenous acetylcysteine or oral methionine) can prevent liver damage if given early

Summary of NSAIDs