Antipyretic-analgesic and antiinflammatory drugs

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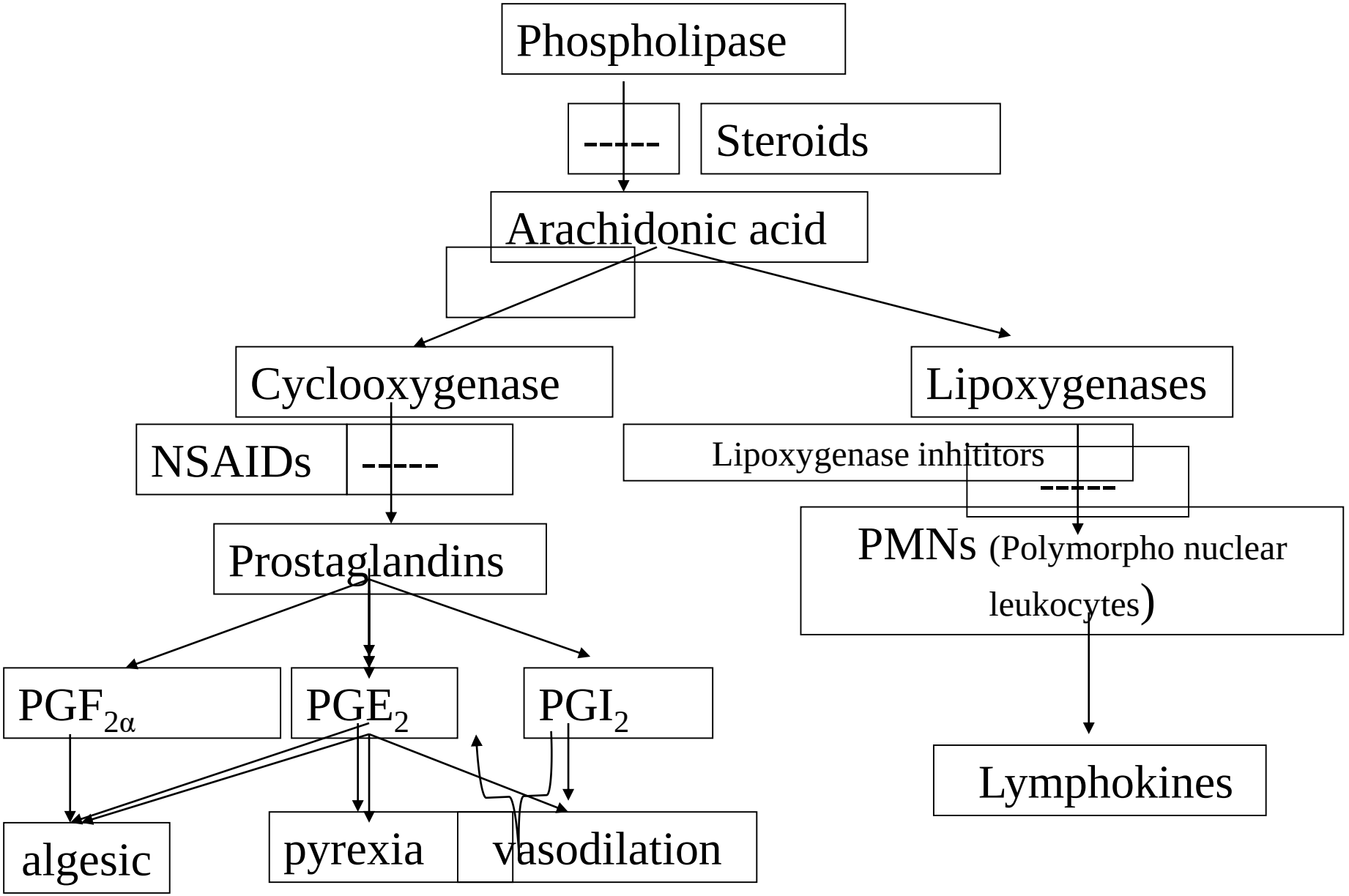

The events of the inflammtory response and mechanisms of anti-flammatory

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have three major actions, all of which are due mainly to the inhibition of arachidonic acid cyclo-oxygenase in inflammatory cells (the COX-2 isoenzyme), and the resultant decrease in prostanoid synthesis.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- An anti-inflammatory action:

(1) The decrease in vasodilator prostaglandins (PGE_2, PGI_2) means less vasodilatation and, indirectly, less oedema.

(2) The inhibition of activity of adhesion molecule.

(3) Accumulation of inflammatory cells is also reduced.

- COX:
- COX-1: constitutive enzyme: is involved in tissue homeostasis.
- COX-2: inducible enzyme: is responsible for the production of the prostanoid mediators of inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- An analgesic effect: decreased prostaglandin generation means less sensitisation of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-hydroxytryptamine.
- Relief of headache is probably due to decreased prostaglandin-mediated vasodilatation.

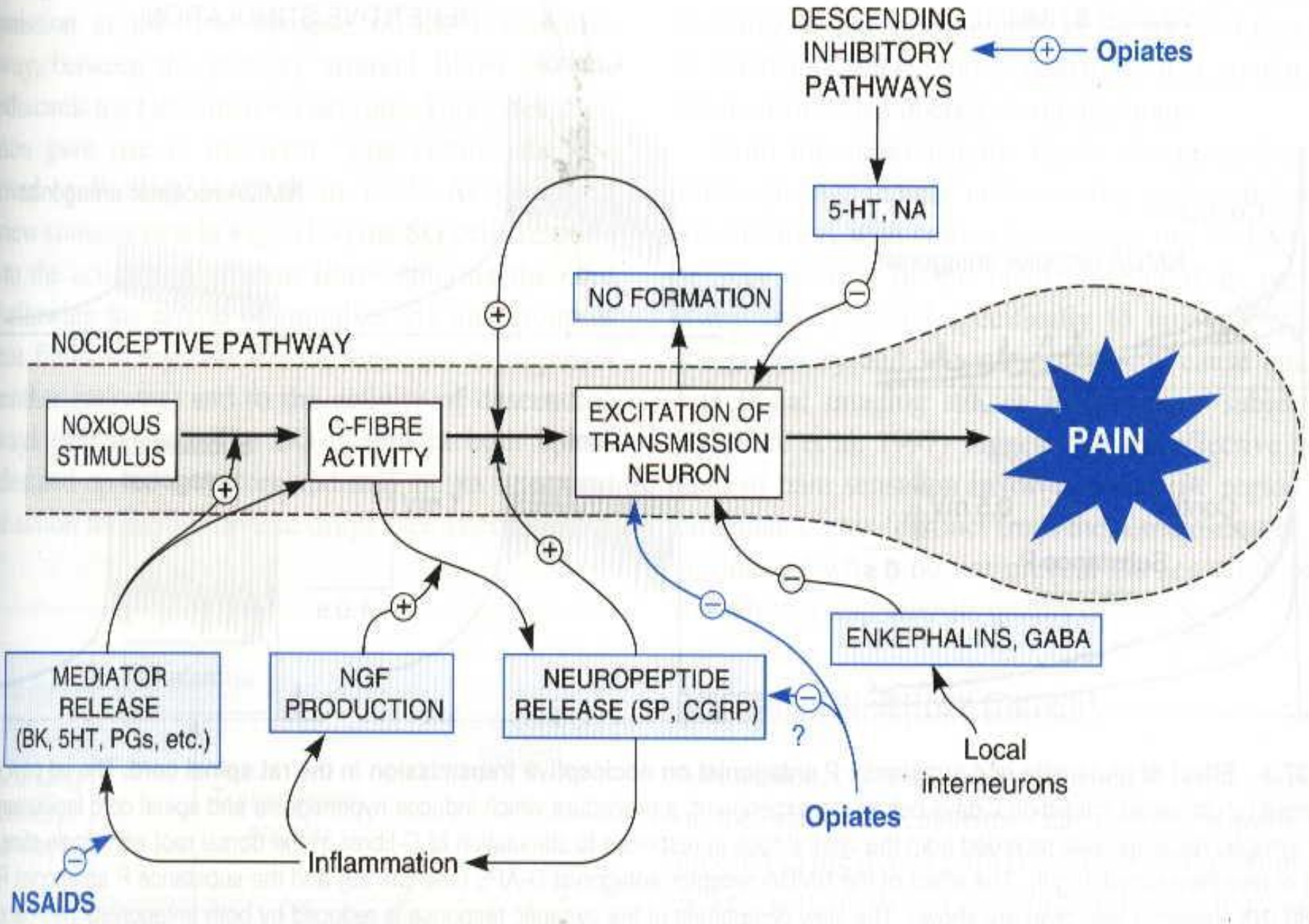

Fig 37.2 Summary of modulatory mechanisms in the nociceptive pathway.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- An antipyretic effect: this is partly due to a decrease in the mediator prostaglandin that is responsible for elevating the hypothalamic set-point for temperature control in fever.

- Endogenous pyogen(IL-1,TNF,IFN, IL-6)

  → BBB → CNS(PEG, Na+/Ca2+, cAMP,CRH)

  → fever

Classification

selection

Non-selective COX inhibitor

Selective COX inhibitor

chemcial constitution

Salicylates

Acetaminophen

Indomethacin

et al

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Some important examples are aspirin, ibuprofen, naproxen, indomethacin, paracetamol. (The last agent has analgesic and antipyretic effects but little anti-inflammatory action).

The Salicylates: Aspirin

- Aspirin (acetylsalicylic acid) was first isolated in 1829 by Leroux from willow bark.

- It can cause irreversible inactivation of cyclo-oxygenase, acting on both COX-1 and COX-2.

Aspirin

- Salicylates are given orally and are rapidly absorbed; 75% metabolized in the liver.

- Excretion: 85% in alkaline urine

  5% in acid urine

Pharmacologic effects

(1) Antipyretic action: is rapidly effective in febrile patients, yet has little effect on normal body temperature.

(2) Anti-inflammatory effects: the primary clinical application is in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

Pharmacologic effects

(3) Analgesic effects:

(a) is usually effective for low- to moderate-intensity pain. Integumental pain is relieved better than the pain from hollow visceral areas.

Pharmacologic effects

(b) relief of pain occurs through both peripheral and central mechanisms.

----Peripherally, it inhibits the synthesis of PGs in inflamed tissues, thus preventing the sensitization of pain receptors to both mechanical and chemical stimuli.

----Centrally, the analgesic site exists in close proximity to the antipyretic region in the hypothalamus. Its analgesia action is not associated with mental altertions, such as hypnosis or changes in sensation other than pain.

Pharmacologic effects

(4) Respiratory effects:

(a) High doses result in medullary stimulation, leading to hyperventilation and a respiratory alkalosis. Compensation rapidly occurs because the kidney is able to increase the excretion of bicarbonate, producing a compensated respiratory alkalosis.

(b) Toxic doses or very prolonged administration can depress the medullary resulting in an uncompensated respiratory acidosis.

Pharmacologic effects

(5) Cardiovascular effects:

(a)Therapeutic doses have no significant cardiovascular effect. However, the prophylactic use of aspirin to reduce thromboembolic events in coronary and cerebral circulation has increased. Studies have demonstrated that such use results in long-term survival and reduced frequency of second myocardial infarctions.

Pharmacologic effects

(5) Cardiovascular effects:

(b) High doses may cause peripheral vasodilation by exerting a direct effect on smooth muscle.

(c) Toxic doses depress circulation directly and by central vasomotor paralysis. Noncardiogenic pulmonary edema may occur in older patients on long-term salicylate therapy.

Pharmacologic effects

(5) Gastrointestinal effects:

(a) It can cause epigastric distress, nausea, and vomiting by irritating the gastric mucosal lining and stimulating the chemoreceptor trigger zone in the CNS.

(b) It may cause a dose-related gastric ulceration, bleeding, and erosive gastritis because of inhibiting the formation of PGE2, which inhibits gastric acid secretion and has a cytoprotective effect. Salicylate-induced gastric bleeding is painless and may lead to an iron deficiency anemia.

Pharmacologic effects

(6) Hepatic effects:

(a) dose-dependent hepatic damage. Usually, asymptomatic, elevated plasma transaminase levels are the key indication of hepatic insult.

(b) more severe and associated with encephalopathy seen in Reye's syndrome.

Use of salicylates in children with chickenpox or influenze is contraindicated.

Pharmacologic effects

(7) Hematologic effects:

(1) It inhibits the platelet aggregation by decreasing the production of TXA_2.

(2) In doses greater than 6g/d, aspirin may reduce plasma prothrombin levels.

Pharmacologic effects

(8)Renal effects: It can result in salt and water retention because of decreasing renal blood flow.

(9) Metabolic effects: It can produce hyperglycemia and glycosuria in large doses.

(10) Endocrine effects: In very large doses, it can stimulate steroid secretion by the adrenal cortex.

Therapeutic uses

(1) Aspirin is used in restricted situation for the symptomatic relief of fever. Because of an increased incidence of Reye's syndrome in children who previously were given aspirin for the relief of viral fevers, it is now recommended that a child with any fever be given paracetamol instead, if medication is required.

(2) It is useful as analgesics for certain categories of pain, such as headache, arthritis, dysmenorrhea.

Therapeutic uses

(3) It remains the standard, first-line drug in the therapy of rheumatoid arthritis, and can provide relief of symptoms in acute rheumatic fever.

(4) Some clinicians recommend small daily doses of aspirin for prophylaxis of thromboembolism, stroke, or myocardial infarction because of its antiplatelet activity.

Adverse effects

(1) Salicylism: usually occurs with repeated administration of large doses. Characteristic findings include:

----headache, mental confusion, lassitude, and drowsiness.

----tinnitus and difficulty in hearing.

----hyperthermia, sweating, thirst, hyperventilation, vomiting, and diarrhea.

(2) Bronchospasm in ‘aspirin-sensitive’ asthmatics.

Adverse effects

(3) Gastrointestinal disturbances.

(4) Prolongation of bleed time or reduce prothrombin level.

(5) Other: skin eruption, hepatic effects, Reye's syndrome.

Treatment of Aspirin poisoning

(1) Inducing emesis or administering gastric lavage.

(2) Appropriate infusion measures to correct abnormal electrolyte balance and dehydration.

(3) Alkalinization of the urine.

(4) Dialysis as required.

Paracetamol

Pharmacologic effects:

Paracetamol has analgesic and antipyretic actions but only weak anti-inflammatory effects.

- It appears to be an inhibitor of PG synthesis in the brain, thus accounting for its analgesic and antipyretic activity.
- It is much less effective than aspirin as an inhibitor of the peripherally located PG biosynthetic enzyme system that plays such an important role in inflammation.

Paracetamol

Pharmacologic effects:

- It exerts little or no pharmacologic effect on the cardiovascular, respiratory, or gastrointestinal systems, on acid-base regulation, or on platelet function.

Therapeutic uses

- Paracetamol provides an effective alternative when aspirin is contraindicated (e.g., in patients with peptic ulcer or hemophilia) and when the anti-inflammtory action of aspirin is not required.

Adverse effects

- At therapeutic doses, paracetamol is well tolerated; however, adverse effects include:

-----Skin rash and drug fever.

-----Rare instances of blood dyscrasias.

-----Renal tubular necrosis and renal failure.

-----Hypoglycemic coma

- At overdose, it can result in severe hepatotoxicity, resulting in centrilobular hepatic necrosis.

Indomethacin

- Pharmacologic effects :

(1) Inhibit COX nonselectively .

(2) Inhibit phospholipase A and C.

(3) Reduce PMN migration.

(4) Decrease T cell and B cell proliferation.

(10-40 time more potent anti-inflammatory than aspirin)

Indomethacin

- **Therapeutic uses:**

Because of its toxicity and side effect, it is not routinely used for analgesia or antipyresis.

The major uses of indomethacin are in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout.

Indomethacin

- **Adverse effect:**

(1) Gastrointestinal complaint:

(2) CNS effects: 25%-50%

(3) Hematologic reactions:

(4) Hypersensitivity reactions: asthma (aspirin-sensitive patients may exhibit cross-reactions to indomethacin).

Naproxen and Ibuprofen

- They have prominent anti-inflammatory action.
- Therapeutic uses: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute tendinitis, dysmenorrhea, et al.
- Adverse effect: gastrointestinal effects, dermatologic problems, thrombocytopenia.

☆ *apply to long-term treatment because they are better-tolerated.*

Selective COX-2 inhibitor

Celecoxib, Meloxicam and Rofenxib

- more selective for COX-2 than for COX-1.
- Adverse effects are slighter than other NSADs.
- Long-term studies of the incidence of clinically significant gastrointestinal ulcers and bleeding are not yet completed.

Clinical uses of the NSAIDs

- *For analgesia in painful conditions (e.g. headache, dysmenorrhoea, backache, bony metastases of cancers, postoperative pain):*
  - The drugs of choice for short-term analgesia are aspirin, paracetamol and ibuprofen; more potent, longer-acting drugs (diflunisal, naproxen, piroxicam) are useful for chronic pain.
  - The requirement for narcotic analgesics can be markedly reduced by NSAIDs in some patients with bony metastases or postoperative pain.

Clinical uses of the NSAIDs

For anti-inflammatory effects in chronic or acute inflammatory conditions (e.g. rheumatoid arthritis and related connective tissue disorders, gout and soft tissue diseases).

- With many NSAIDs, the dosage required for chronic inflammatory disorders is usually greater than for simple analgesia and treatment may need to be continued for long periods; Treatment could be initiated with an agent known to have a low incidence of side-effects. If this proves unsatisfactory, more potent agents should be used.

Clinical uses of the NSAIDs

- To lower temperature. Paracetamol is preferred because it lacks gastrointestinal side-effects and, unlike aspirin, has not been associated with Reye's syndrome in children.
- There is substantial individual variation in clinical response to NSAIDs and considerable unpredictable patient preference for one drug rather than another.