

## ASPIRIN (ACETYLSALICYLATE)

### Use

Antiplatelet uses of **aspirin** are described in Chapters 29 and 30. As an antipyretic and mild analgesic it has similar efficacy to **paracetamol**. However, unlike **paracetamol** it also has anti-inflammatory properties when used in high doses. Various preparations are available, including regular as well as buffered, soluble and enteric-coated forms. Enteric coating is intended to reduce local gastric irritation, but much of the gastric toxicity is due to inhibition of gastric mucosal prostaglandin biosynthesis (see below), rather than to direct gastric irritation. Consequently, slow-release preparations do not eliminate the adverse effects of **aspirin** on the gastric mucosa.

### Mechanism of action

**Aspirin** inhibits prostaglandin biosynthesis, irreversibly acetylating a serine residue in the active site of cyclo-oxygenase (COX). There are two main isoforms, COX-1 and COX-2. COX-1 is a constitutive enzyme which is present in platelets and other cells under basal conditions. COX-2 is an inducible form, which is produced in response to cytokine stimulation in areas of inflammation and produces large amounts of prostaglandins. Acetylation of the serine in COX-1 active site prevents access of the endogenous substrate (arachidonic acid) to the active site, very effectively blocking thromboxane formation in platelets, as well as prostaglandin formation.

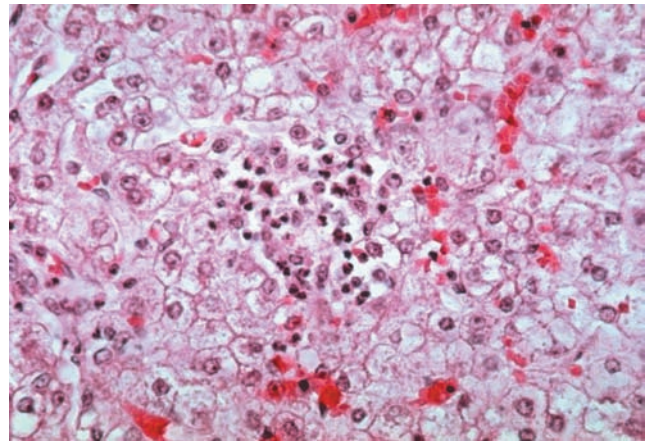
### Adverse effects and contraindications

These include:

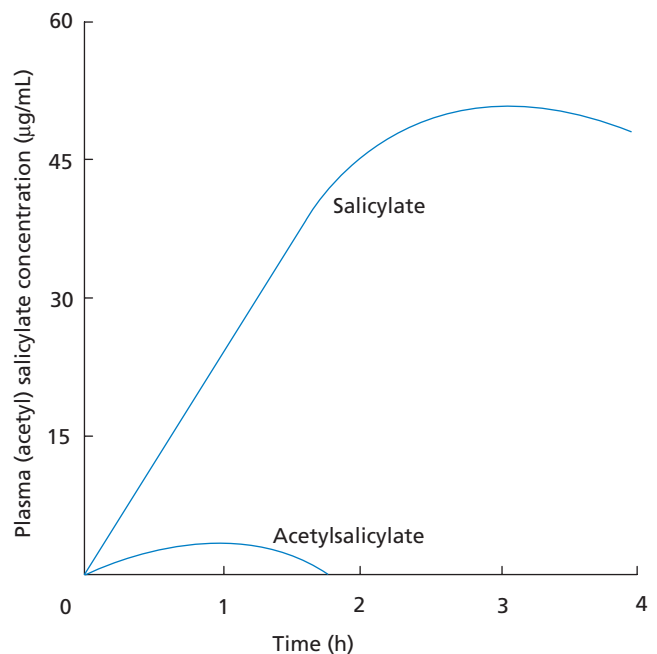
- *Salicylism* – toxic doses of salicylates, including **aspirin**, cause tinnitus, deafness, nausea, vomiting, abdominal pain and flushing and fever.
- *Dyspepsia* is common as is mild gastric blood loss. Severe blood loss from the stomach can be life-threatening. The mechanism is inhibition of gastric prostaglandin (PGE<sub>2</sub>) biosynthesis. PGE<sub>2</sub> is the main prostaglandin made by the human stomach, which it protects in several ways:
  - inhibition of acid secretion;
  - stimulation of mucus secretion;
  - increased clearance of acid from the submucosa via local vasodilatation.

Aspirin and other NSAIDs damage the stomach by impairing these protective mechanisms. **Aspirin** should not be given to patients with active peptic ulceration.

- *Aspirin-sensitive asthma* occurs in approximately 5% of asthmatics (Chapter 33). It is associated with nasal polyps. Reactions to other chemically unrelated NSAIDs commonly occur in such individuals. Abnormal leukotriene (Chapter 33) production and sensitivity are implicated. In addition, **aspirin** and similar drugs can directly activate eosinophils and mast cells in these patients through IgE-independent mechanisms.
- *Reye's syndrome*, a rare disease of children, with high mortality, is characterized by hepatic failure and encephalopathy, often occurring in the setting of a viral illness (Figure 25.3).



**Figure 25.3:** Histopathology of autopsy liver from child who died of Reye's syndrome as a result of taking aspirin. Hepatocytes are pale-staining due to intracellular fat droplets.



**Figure 25.4:** Plasma levels of salicylate and acetylsalicylate following 640 mg aspirin given orally, demonstrating rapid conversion of acetylsalicylate to salicylate.

### Pharmacokinetics

Gastro-intestinal absorption is rapid. **Aspirin** is subject to considerable presystemic metabolism (to salicylate), so the plasma concentration of **aspirin** (acetyl salicylic acid) is much lower than that of salicylate following an oral dose (Figure 25.4). Some of the selectivity of aspirin for platelet cyclo-oxygenase is probably due to exposure of platelets to high concentrations of aspirin in portal blood, whereas tissues are exposed to the lower concentrations present in the systemic circulation. Salicylate is metabolized in the liver by five main parallel pathways, two of which are saturable (Michaelis–Menten kinetics) and is also excreted unchanged in the urine by a first-order process. This is summarized in Figure 25.5. The formation of salicylurate (in mitochondria) is easily saturable. Consequently,