**Mechanism of Action** of NSAIDs

NSAIDs are defined as "*agents which inhibit the formation of eicosanoids from arachidonic acid*". Prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs) are all eicosanoids which have an inflammatory-mediating action.

Chemical or physical injury to cells causes induction of the enzyme phospholipase-A2 (PLA2), which converts phospholipids to arachidonate. This newly-formed arachidonic acid is converted by the action of cyclo-oxgygenase (COX) enzymes to cyclic endoperoxidases, which can form inflammatory mediators including PGI2, PGD2, PGE2 and TXA2. Arachidonte may also be converted to 5-HPETE to eventually form leukotrienes, and some newer NSAIDs target this branch of the pathway.

NSAIDs interfere with the formation of inflammatory mediators by inhibiting the action of the enzyme cyclo-oxygenase. Two forms of the enzyme exist: COX-1, which is constitutively expressed, and COX-2, which is inducible and produced by inflammatory cells. To minimise the potential for side-effects of using NSAIDs for anti-inflammatory purposes it would be ideal to target COX-2 only, leaving the "housekeeping" functions of COX-1 intact. However, most NSAIDs are non-selective COX inhibitors.

**Actions**

Acting centrally, NSAIDs provide analgesia. The degree of analgesia provided is dependent on the type and cause of the pain in question.

NSAIDs also have anti-pyretic properties when acting centrally. Normally in pyrexia, IL-1 induced prostaglandin release causes the hypothalamus to raise the temperature "set-point". Because NSAIDs reduce prostaglandin production, this process is disrupted.

Non-steroidal anti-inflammatories also act peripherally. As well as the anti-inflammatory and analgesic actions you might expect, NSAIDs have anti-endotoxic and anti-thrombotic funtions. The anti-endotoxic action works by the drug preventing the release of vasoactive mediators from leucocytes and vascular endothelium following endotoxic insult. Finally, NSAIDs have effects on cartilage which may be both beneficial and adverse.

**Drug Interactions**

The concurrent use of two COX inhibitors will result in both additive efficacy and toxicity.

NSAIDs used with cimetidine or chloramphencicol may be subject to slower metabolism. This is because these drugs inhibit mixed function oxidases (MFOs) in the liver.

**Drugs in This Group**

**Aspirin**

Aspirin is the common name for acetyl salicylic acid. This is hydrolysed to an active form, salicylate, which irreversibly binds COX by an acetylation reaction and has a high affinity for COX in platelets. Because of this affinity, the drug has an anti-thrombotic effect which is more pronounced at low doses where platelet production of TXA2 (aggregatory) is inhibited but that of PGI2 (disaggregatory) is not. At higher doses, PGI2 formation is also affected, reducing the dis-aggregatory influence it provides and therefore the anti-thrombotic effects of aspirin.

Aspirin is not used very commonly in veterinary medicine, and huge dose variations exist between species. For example, the dose for a dog is 25mg/kg/8 hours, but in the cat is 25mg/kg/day. Half-life also differs between species, being only one hour in the pony but 37.6 hours in the cat.

Oxidisation is the main method of aspirin metabolisation, but some drug is also conjugated to glucuronide. Glucuronidation cannot be performed by the cat, accounting for the long half-life in this species.

[**Paracetamol**](http://en.wikivet.net/Paracetamol)

**Phenylbutazone**

Phenylbutazone (colloquially known as "bute") has a more potent anti-inflammatory than analgesic action. It is cheap and commonly used in veterinary practice.Administration of phenylbutazone with food reduces the rate of absorption. Although the drug's bioavailability remains the same, it is absorbed further down the gastro-intestinal tract than normal and plasma levels rise more slowly. Rate of metabolism varies vastly between species,.

Phenylbutazone has caused death by aplastic anaemia in man, and since safe milk and meat residue levels cannot be established, it is banned in food producing animals. Protein losing enteropathy has been seen in horses and ponies. The drug has a low safety margin and care must be taken in equids to use the lower end of the dose range. Top range doses would lead to accumulation and toxicity.

**Carprofen**

Carprofen (Rimadyl) is a poor COX inhibitor, yet a potent anti-inflammatory drug. It is generally well-tolerated and can be used as a peri-operative analgesic with a reduced risk of nephrotoxicity compared to other NSAIDs.

**Ketoprofen** Ketoprofen has potent anti-inflammatory, analgesic and anti-pyretic actions. In addition to its effects on COX, ketoprofen may inhibit lipoxygenase and bradykinin to have a broader mechanism of action. The main side effect is gastro-intestinal erosion.

**Cinchophen** This drug has a primarily anti-inflammatory effect, though is analgesic and anti-pyretic at higher doses (similar to aspirin). Cinchophen also has uricosuric activity. Side effects include hepatotoxitiy and gastric ulceration.

Cinchophen is the main component of prednoleucotropin (PLT) tablets used for the treatment of osteoarthritis in a dog. These tablest also contain a very low dose of prednisolone, a [corticosteroid](http://en.wikivet.net/Steroids).

**Flunixin** Flunixin is of limited use in small animal practice due to its toxicity; however, it is commonly used in farm and equine practice. It has potent anti-inflammatory and analgesic effects and is used for such conditions as pneumonia, mastitis and endotoxic shock. Preparations are available in combination with anti-microbials (e.g. Resflor - florfenicol plus flunixin).

**Fenamates** Tolfenamic acid and meclofenamic acid are the fenamates used in veterinary medicine. In addition to the usual mechanism of action, they may provide some antagonism to the prostaglandin receptor.

**Oxicams** Meloxicam (Metacam) is commonly used in dogs and cats, and is now licensed in cattle, pigs and horses. It may have cartilage sparing effects in osteoarthritis, but this has only been tested under laboratory conditions. Other NSAIDs appear to be detrimental to cartilage.