

PHARMACOLOGY

Autacoids : Nonsteroidal Antiinflammatory Drugs, Antipyretics, Analgesics; Drugs used in Gout

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Nonsteroidal anti-inflammatory drugs, NSAIDs, aspirin, COX inhibitors, gout, colchicine, allopurinol, probenecid

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are a diverse group of chemical compounds whose mechanism of action typically involves the inhibition of one or more components of the inflammatory response. They play an important role in the symptomatic relief of the inflammation and pain such as arthritis, gout, injury. All the drugs included here have analgesic, antipyretic and anti-inflammatory actions. They are called nonsteroidal to differentiate them from the steroidal drugs which have anti-inflammatory actions. They are also called as nonopioid, nonnarcotic like analgesics to differentiate them from opioid analgesics. They do not depress the central nervous system, nor do they produce physical dependence and have no abuse liability.

Chemistry and Classification

The NSAIDs are grouped in several classes based on their chemistry as well as based on their selectivity for inhibiting the enzyme cyclooxygenase (COX). All except nabumetone are weak organic acids. The classification is as follows :

A) Non Selective COX inhibitors

1. Salicylates : Aspirin, Diflunisal
2. Propionic acid derivatives : Ibuprofen, naproxen, ketoprofen, flurbiprofen, oxaprozin
3. Indole and indene derivatives : Indomethacin, sulindac
4. Arylacetic derivatives : Diclofenac
5. Pyrrole derivatives : Ketorolac
6. Anthranilic acid derivative : mephenamic acids
7. Oxicam derivatives : Piroxicam, tenoxicam
8. Pyrazolone derivatives : Phenylbutazone, oxyphenbutazone
9. Paraminophenol derivative : Paracetamol (acetaminophen)

B) Preferential COX-2 inhibitors

Nimesulide, nabumetone, meloxicam

C) Selective COX-2 inhibitors

Celecoxib, rofecoxib, valdecoxib

Role of NSAIDs in inflammation

Inflammation represents the body's response to injury and includes products of activated mast cells, lymphocytes, leukocytes and platelets. These cells release mediators of inflammation such as prostaglandins (PGs), leukotrienes, kinins, histamine, nitric oxide, complement derived products. Many processes are involved in the promotion and resolution of the inflammatory process including migration of inflammatory cells out of the microvasculature to the site of injury, adhesion to the tissues and cells by specific adhesion molecules to the tissues in the body (for example E-, P and L selectins, intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule -1 (VCAM-1) and leukocyte integrins.

The recruitment of inflammatory cells to the sites of injury involves a number of mediators such as complement factor 5A, platelet activating factor and eicosanoid LTB₄. Cytokines like interleukin -1 (IL-1) IL-8 and tumor necrosis factor (TNF) and granulocyte macrophage colony

stimulating factor, induce gene expression and protein synthesis in many cells to mediate and promote inflammation.

Prostaglandins

One of the key events in the acute inflammatory process is the liberation of arachidonic acid (AA) from damaged cells membranes upon exposure to phospholipase A₂. AA acid is metabolized by enzyme cyclo oxygenase(COX) into prostanoids (prostaglandins, prostacyclin, thromboxanes) and lipoxygenase (leukotrienes) mainly.

COX exists in two forms. COX-1 is regarded as the constitutive or housekeeping isoform. It is the major isoform found in healthy tissues, such as the central nervous system, gastric mucosa, platelets and kidneys. In the gastric mucosa, COX-1 plays a major role in the synthesis of PGs involved in the formation of the mucous protective barrier against gastric acid. In platelets COX-1 is involved in thromboxane production and platelet aggregation. COX-2 is mostly an inducible isoform. It gets upregulated by inflammatory products such as cytokines, growth factors, mitogens in human monocytes, macrophages, endothelial cells, chondrocytes, synoviocytes and osteoblasts. It is constitutively present in the brain and kidney. COX-2 is associated with elevated concentration of PGs during inflammation, pain and fever. PGs and the intermediate endoperoxides are mediators of inflammation. In acute inflammatory reactions, PGs appear in fluids and exudates. Later other mediators such as histamine and bradykinin are formed when tissue damage and disintegration are more prominent. PGs contribute to the inflammatory response in many ways, they cause vasodilation, increase vascular permeability, increase pain sensitivity, (PGI₂, PGE₂), PGE₂ is pyrogenic. PGs stimulate certain inflammatory events, they inhibit or modulate others. A balance between enhancement and suppression of inflammatory events could be achieved by local regulation of PG metabolism, because in some systems PGs have been shown to be either stimulatory or inhibitory depending on their concentration.

Inhibition of prostaglandin biosynthesis by NSAIDs : The principal therapeutic effect of NSAIDs derives from their ability to inhibit prostaglandin biosynthesis. NSAIDs inhibit the COX enzyme, the first enzyme in prostaglandin biosynthesis. They do not inhibit the lipoxygenase pathways of arachidonic acid metabolism and hence do not suppress LT formation. Aspirin covalently modifies COX-1 and COX-2 irreversibly inhibiting the enzymes activity. It acetylates the serine moiety. Nonaspirin NSAIDs inhibit the COX enzyme in a competitive, reversible manner. This is important because the duration of aspirin's effect is related to the rate of turnover of cyclooxygenases in different target tissues. The duration of effect of other NSAIDs relates to the time course of drug disposition. This is important in the antiplatelet action of aspirin. Aspirin in low doses inhibits platelet COX-1 which lasts for the life time of the platelet. The inhibition in low doses is related to their presystemic inhibition in the portal circulation before aspirin is deacetylated to salicylate on first pass metabolism through the liver. Inhibition of platelet COX-1 dependent TXA₂ formation is cumulative and takes 8 to 12 days, the platelet turn over time to recover once therapy has been stopped.

Most NSAIDs inhibit both COX-1 and COX-2 . Nonselectivity of COX inhibition is responsible for the gastric adverse effects of NSAIDs. Since COX-1 is expressed as the constitutive isoform in gastric mucosa, responsible for cytoprotection and COX-2 expressed at

sites of inflammation, it was hypothesized that selective inhibitors of COX-2 would be associated with antiinflammatory effects with a lower ulcerogenic potential. This led to the development of NSAIDs with greater selectivity for COX-2 versus COX-1.

Pain: NSAIDs are mild analgesics, they are particularly effective in pain associated with inflammation. Bradykinin, cytokines such as TNF- β , IL-1, IL-8 and other mediators liberate PGs and other mediators that promote hyperalgesia. PGs sensitize pain receptors to mechanical and chemical stimulation, resulting in a lowering of threshold of the polymodal nociceptors of C fibers. Other mechanisms for pain relief at the peripheral or central neurons are also being postulated for NSAIDs.

Fever: During fever the set point at which the body temperature is maintained by the hypothalamus is elevated. PGE₂ triggers the hypothalamus to elevate the body temperature by promoting an increase in heat generation and a decrease in heat loss. PGE₂ is synthesized in response to cytokines (IL-1B, IL-6, interferons and TNF α , Aspirin and NSAIDs suppress their response by inhibiting PGE₂ synthesis. NSAIDs do not suppress the fever response to exercise or increased ambient temperature. NSAIDs do not inhibit the pain and fever elicited by direct administration of prostaglandins suggesting thereby that they are acting by inhibiting prostaglandin synthesis in the body.

Salicylates

The salicylates are amongst the oldest drugs known. Extracts from poplar and willow bark (were used for their analgesic effect). The active principle of willow and poplar preparations was salicylic acid and was first extracted in 1835 from natural sources and later by chemical synthesis. In 1853, aspirin (acetylsalicylic acid) was first synthesized. Several additional salicylates have been marketed, Sodium salicylate, choline salicylate, magnesium salicylate (Salicylates generally act by virtue of their content of salicylic acid, although one of the unique effects of aspirin is caused by its capacity to acetylate proteins. Aspirin may be considered a prototype of the NSAIDs and is the standard of reference against which NSAIDs are compared and evaluated.

Therapeutic Uses: Aspirin has clinically useful analgesic, antipyretic, antiinflammatory and antiplatelet effects. Aspirin and NSAIDs are drugs of major importance in the treatment of numerous chronic inflammatory diseases.

Acute pain : Aspirin is an effective analgesic for almost any type of pain. Aspirin as well as other NSAIDs and acetaminophen have a ceiling or plateau effect in the treatment of acute pain i.e. analgesic effect is seen upto a certain dose, beyond which increasing the dose does not result in further enhancement of analgesic effect but may increase the toxicity.

Rheumatic fever: Aspirin markedly reduces the acute inflammatory components of the disease such as fever, joint pain, swelling and immobility. Salicylate do not alter the progression of the disease. Antibiotic therapy is the major therapeutic strategy.

Rheumatoid arthritis: Rheumatoid arthritis is a chronic, systemic disease involving multiple organ systems. It is characterized by chronic inflammation of synovial membranes. Irreversible

articular changes and extraarticular manifestations such as subcutaneous or subperiosteal nodules of granulation tissue, peripheral neuropathy and chronic skin ulcers occur to a variable extent due to a generalized focal vasculitis. Rheumatoid arthritis is considered to be an autoimmune disease. Salicylates (usually aspirin) are used. They produce a measurable reduction of inflammation in the joints and tissues, lessening the symptoms and improving mobility. If salicylates are ineffective, other NSAIDs, corticosteroids or disease modifying antirheumatic drugs may be used.

Salicylates are given in high doses 3 to 6 gm/day to control the symptoms. The anti-inflammatory actions are seen at plasma salicylate concentrations beyond toxicity levels. Patients may tolerate some side effects to obtain the anti-inflammatory effects gained by high plasma titers of salicylates. NSAIDs provide symptomatic relief from pain and inflammation associated with the disease and do not arrest the progression of pathological injury to the tissue and are also not disease modifying.

Other Inflammatory diseases: Aspirin and NSAIDs are used commonly as anti-inflammatory agents in various other inflammatory diseases including juvenile rheumatoid arthritis, ankylosing, spondylitis, psoriatic arthritis, Reiter's syndrome and osteoarthritis. NSAIDs along with rest and physiotherapy would be effective for mild arthropathies.

Fever: Aspirin other NSAIDs and acetaminophen are used as antipyretics in fever of inflammatory origin. They act by inhibiting synthesis of PGs in the hypothalamus as well as by causing vasodilation of peripheral blood vessels. Aspirin is no longer recommended to treat fever in children because of its association with Reye's syndrome

Prophylaxis against platelet aggregation

Aspirin inhibits the synthesis of TXA_2 , by irreversible acetylation of the COX enzyme in platelets. As they lack a nucleus, the platelets cannot generate new enzyme during their lifetime. The majority of platelet COX acetylation may occur presystemically as platelets pass through gut capillaries, before the hydrolysis of aspirin to salicylate in the portal circulation. PGI_2 molecule which is antiaggregatory is produced by systemic vascular endothelium. The vascular endothelium cells also possess a nucleus and hence can resynthesize COX. This may explain the relative lack of low dose aspirin on antiaggregatory PGI_2 and provides the rationale for using long term low dose aspirin therapy to prevent myocardial infarction.

Other NSAIDs only reversibly inhibit COX in platelets and are not used for antiplatelet effects.

Closure of patent ductus arteriosus

Prostaglandins are implicated in maintenance of patency of the ductus arteriosus. Indomethacin and other NSAIDs have been used in neonates to promote closure of the patent ductus.

Systemic Mastocytosis

In patients with systemic mastocytosis, there is release of prostaglandins (PGD_2) from mast cells, resulting in vasodilation and hypotension. The use of aspirin and NSAIDs provides relief along with histamine antagonists.

Bartter's syndrome

Bartter's syndrome is a rare disorder with hypokalemic, hypochloremic metabolic alkalosis with hyperplasia of the juxtaglomerular apparatus. Biosynthesis of renal PGE₂ via COX2 is increased. Indomethacin is associated with improvement in the biochemical derangements and symptoms.

Cancer chemoprevention

Aspirin and other NSAIDs are being investigated for cancer chemoprevention. The use of aspirin is associated with as much as 50% decrease in the risk of colon cancer. The mechanism for this protective effect is unclear.

Niacin Tolerability

Niacin induces intense flushing due to release of PGD₂ from the skin. This can be inhibited by treatment with aspirin.

Local use

Mesalamine (5-aminosalicylic acid) is a salicylate that is used for its local effects in the treatment of inflammatory bowel disease. The drug is not effective orally because it gets inactivated before reaching the lower intestine. Hence, it is used as a suppository and rectal retention enema, for the treatment of inflammatory bowel disease. Two oral preparations that deliver the drug to the lower intestine include sulfasalazine (sulfapyridine linked to mesalamine) and olsalazine (dimer of 5-amino salicylate). The drug is cleaved to its active components by bacteria in the colon.

Adverse Effects of Aspirin and Other NSAIDs

The severity of side effects that can accompany aspirin ingestion or other NSAIDs depends on the overall health of the patient, the length of dosing and the total daily intake of the drug.

Gastrointestinal: The most common adverse effects are gastric upset (intolerance) and gastric and duodenal ulcers. These occur due to inhibition of COX-1 by NSAIDs, which interferes with cytoprotective actions of the PGs in the gastric mucosa. This may result in serious gastrointestinal bleeding, symptomatic peptic ulcers, gastrointestinal perforations and obstructions. Selective COX-2 inhibitors have been shown to be less prone than nonselective COX inhibitors in inducing ulcers and bleeding.

Bleeding : The antiplatelet effect of aspirin can lead to increases in bleeding time with probability of hemorrhages during surgical procedures.

Cardiovascular : Selective COX-2 inhibitors depress PGI₂ formation by endothelial cells without concomitant inhibition of platelet thromboxane. Selective COX-2 inhibitors rofecoxib, valdecoxib and celecoxib are associated with an increased risk of heart attack and stroke. Patients at increased risk of cardiovascular disease or thrombosis are particularly prone to cardiovascular adverse events. Hypertensive complications occur more commonly in patients as selective COX-2 inhibitors, which inhibit renal PG synthesis.

Kidney: Normal renal function is dependent on PG synthesis. Both COX-1 and COX-2 are

important in producing PGs (PGE₂) involved in reducing water and sodium reabsorption at the ascending limb of loop of Henle and maintaining renal vasodilation. With NSAID therapy, dose dependent water and sodium retention manifested by peripheral edema, elevation in blood pressure, occurrence of congestive heart failure may occur. Acute renal failure may occur due to renal artery vasoconstriction due to inhibition of PGI₂ synthesis. Chronic renal toxicity known as analgesic associated nephropathy may occur with long term use of high doses of NSAIDs. It is characterized by papillary necrosis and chronic interstitial nephritis.

Reye's syndrome: The use of aspirin in children with viral infections has been associated with Reye's syndrome (acute illness with metabolic encephalopathy and liver disease). This may be fatal and survivors may be left with permanent brain damage. The aspirin and related salicylates are thus contraindicated for the treatment of flu like symptoms in children.

Toxicity: Toxicity due to aspirin overdose is common. Chronic toxicity caused by salicylates results in a syndrome termed salycism, which is characterized by tinnitus, nausea, vomiting, headache, hyperventilation and mental confusion. At higher doses there may be respiratory alkalosis, followed by a combined respiratory and metabolic acidosis accompanied by dehydration. Serious clinical manifestations of acute aspirin overdose occur at doses greater than 6 to 10 gm in adults or when intake exceeds 150 to 200 mg/kg of body weight.

Treatment of aspirin overdose is palliative and supportive. Chronic toxicity is treated by simply stopping the drug. Acute toxicity requires respiratory support, gastric lavage, maintenance of electrolyte imbalance, alkalinization of urine with intravenous bicarbonate.

Hypersensitivity : to aspirin and NSAIDs may occur. The symptoms may range from rhinitis to severe asthma. There may be urticaria and angioedema. Aspirin intolerance is a contraindication to therapy with any other NSAID because cross sensitivity may occur. Acetaminophen is the only antipyretic analgesic that may be used safely in patients with aspirin intolerance.

Contraindications and precautions:

1. Peptic ulcer: Serious bleeding and perforation may occur
2. Bronchial asthma : Aspirin may cause an asthmatic attack.
3. Diabetes : High doses may cause hyperglycemia or hypoglycemia. Aspirin in high doses may either raise or lower plasma glucose concentrations by stimulating epinephrine and glucocorticoid release or by depleting liver glycogen respectively. Salicylates may also increase insulin secretion, because PGE₂ inhibits insulin secretion.
4. Gout : Low doses of aspirin can increase plasma urate concentrations as a result of competition between salicylate and uric acid at the active secretion sites in the kidney. High doses lower plasma urate.
5. Viral disease (Influenza) : Reye's syndrome in children may occur
6. Hypocoagulation states : Aspirin and NSAIDs can cause bleeding

7. Pregnancy : Aspirin and NSAIDs are associated with prolongation of labour by inhibiting the synthesis of PGs involved in uterine contractions. They may increase blood loss at the time of delivery and cause premature closure of the ductus arteriosus. There is some evidence that aspirin in very high doses may have teratogenic effects. Thus pregnancy especially close to term is a relative contraindication to the use of all NSAIDs.

Drug interactions:

1. Concomitant NSAIDs and low dose aspirin; this combination may increase the gastrointestinal side effects.

2. NSAIDs and glucocorticoids may increase the severity of gastrointestinal ulceration.

3. Use of NSAIDs with anticoagulants (warfarin, heparin) may increase bleeding

4. NSAIDs may result in loss of antihypertensive effect of ACE inhibitors, B-adrenergic blockers, diuretics.

5. Many NSAIDs which are highly bound to plasma protein may displace other drugs from their binding sites, enhancing their effects. This may occur with warfarin, sulfonylureas, methotrexate. The dosage of these drug may require adjustment to prevent toxicity.

6. Alcohol sensitizes the gastric mucosa to aspirin. Hence increased gastric irritation may occur.

Pharmacokinetics of salicylates: Aspirin is rapidly absorbed from the stomach and small intestine. It is a weak acid, with a pKa of 3.5 which favors its absorption in the stomach. However most absorption takes place in the small intestine because of its much larger surface area. Although salicylate is more ionized as the pH is increased a rise in pH also increases the solubility of salicylate and thus dissolution of the tablets, increasing the absorption. Thus there may be little difference in the rate of absorption of sodium salicylate, aspirin and buffered aspirin. It is metabolized by gastric and plasma esterases to salicylate ion. Aspirin has a short half life of 15 minutes, the half life for salicylate is 2 to 3 hours. The half life of salicylate may increase to 5 to 30 hours with high doses due to capacity limited metabolism.

About 80% to 90% of the salicylate in the plasma is bound to proteins, especially albumin. Salicylate is distributed throughout most body fluids and tissues. It freely crosses the placenta from mother to fetus.

The salicylates are excreted in the urine by glomerular filtration and by active proximal tubular secretion. They are secreted as free salicylic acid (10%) salicyluric acid (75%), salicylic phenolic (10%), acylglucuronides (5%) and gentistic acids (less than 1%)

Therapeutic Drug Monitoring of salicylates : Aspirin is one of the NSAIDs for which plasma salicylate concentrations can be used to monitor therapy and toxicity. Intermittent analgesic-antipyretic doses of aspirin produce plasma salicylate levels of less than 60 mcg/ml. The does of 4 to 5 gm. of aspirin produces plasma salicylate levels in the range of 120 to 350 µg/ml. Significant adverse effects may be seen at levels of more than 300 µg/ml. For antiinflammatory

effects in rheumatic diseases a plasma salicylate concentration between 150 to 300 µg/ml are required.

Diffenunisal

Diffenunisal is a difluorophenyl derivative of salicylic acid with anti-inflammatory, analgesic and antipyretic activity. Although structurally related to salicylates, diffenunisal is not hydrolyzed in vivo to salicylates. It is more potent than aspirin in suppressing PG formation. It has a long plasma half life of 8 to 12 hours versus 2.5 hours for salicylates, which permits twice a day dosing. The incidence of gastrointestinal side effects and bleeding are lesser in comparison to aspirin. Diffenunisal does not penetrate the blood brain barrier as well as aspirin and although causing fewer CNS side effect, including tinnitus, it is not useful as an antipyretic.

Other NSAIDs

Many NSAIDs unrelated to salicylates are now available. They all inhibit COX, but vary in their relative potencies against COX-1 and COX-2. Some NSAIDs may have other anti-inflammatory actions in addition to inhibiting COX. Most of these drugs are arylalkanoic or heteroarylalkanoic acid derivatives. They will be discussed according to their chemical classification and COX inhibiting selectivity.

Pharmacokinetics of other NSAIDs : All NSAIDs are rapidly and completely absorbed from the gastrointestinal tract. Food does not substantially change their bioavailability. Most NSAIDs are highly metabolized by phase I, followed by phase II reactions and others by direct glucurodination (phase II) alone. Metabolism occurs by CYP2A or CYP2C families of P450 enzymes. Most NSAIDs are extensively protein bound (90% to 95%). Nearly all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation). The degree of lower gastrointestinal tract irritation correlates with the amount of enterohepatic circulation. Renal excretion is the most important route for the final elimination. NSAIDs are not recommended in advanced hepatic and renal disease.

Propionic acid derivatives

The substituted phenylpropionic acid derivatives constitute the largest group of aspirin alternatives. Ibuprofen the first member of this group is amongst the most commonly sold NSAIDs in the market.

All are nonselective COX inhibitors with effects and side effects common to other NSAIDs. Some unique characteristics exist among individual drugs. Naproxen has prominent inhibitory effects on leukocyte function in inflammation and ketoprofen appears to prevent lysosomal enzyme release by stabilizing the membranes of lysosomes. Propionic acid derivatives as a group are less likely than aspirin to cause gastrointestinal bleeding disturbances, they have been used in place of aspirin. They are approved as analgesic, antiinflammatory and antipyretic drugs.

Ibuprofen : Dose for analgesic effect is 400 mg every 4 to 6 hours Doses up to 800 mg 4 times daily can be used for rheumatoid arthritis and osteoarthritis. Rare side effects include blurred vision and toxic amblyopia. Patients who develop ocular disturbances should discontinue the use of ibuprofen.

Naproxen : It is the only NSAID manufactured as the active (S) enantiomer. It is available as both the free acid and as the sodium salt, which is absorbed more rapidly from the gastrointestinal tract and is the preferred form. It is more irritating to the gastrointestinal tract than ibuprofen.

Ketoprofen :In addition to PG synthesis inhibition ketoprofen has also been shown to inhibit leukotriene synthesis. It stabilizes lysosomal membranes and has an antibradykinin effect. It is more potent than ibuprofen with 25 to 50 mg as effective as 400 mg of ibuprofen for mild to moderate pain. Ketoprofen has been reported to be more irritating to the gastrointestinal tract.

Flurbiprofen :It does not possess an analgesic indication.

Oxaprozin : It has a half life of 50 hours. It produces a significant incidence of photosensitivity manifested as vesicular eruptions on sun exposed skin. It causes prolongation of bleeding time, which may persist for more than 8 days after the last dose because of its long half life.

Indole and Indene derivatives (Acetic acid derivatives)

Indomethacin : Is a methylated indole acetic acid with powerful antiinflammatory properties. It is a potent inhibitor of COX and a more potent antiinflammatory drug than aspirin. Although it produces antipyretic, analgesic action because of its toxic potential, however, indomethacin should not be used as an antipyretic or simple analgesic.

Indomethacin is approved for closure of persistent patent ductus arteriosus. It is administered intravenously. Such therapy is indicated primarily in premature infants who weigh between 500 and 1750 gm. Treatment with indomethacin may also decrease the incidence and severity of intraventricular hemorrhage in low birth weight neonates.

Adverse effects are common. The drug can cause severe gastrointestinal disturbances, with perforation and bleeding. CNS effects including severe headache and confusion with psychosis is possible. In addition dermatologic, allergic reactions, leukopenia, aplastic anemia, thrombocytopenia and hepatitis may occur.

Etodolac :Although classified as a nonselective NSAID, etodolac appears to be approximately threefold more selective for the inducible COX-2 isoenzyme than for the constitutive COX-1 isoenzyme. This may account for the lower incidence of gastrointestinal side effects with long term dosing compared with other nonselective NSAIDs.

Sulindac : Is an indene derivative. It is also a sulfoxide. Sulindac is a prodrug that must be reduced to the sulfide before it becomes an active NSAID. It has a long half life of 15 hours, probably because the drug undergoes enterohepatic circulation

Arylacetic derivatives

Diclofenac: The pharmacokinetic properties and mechanism of action are similar to other NSAIDs. Diclofenac undergoes significant first pass metabolism in the liver. And in addition to inhibiting COX, may reduce the concentration of arachidonic acid in some inflammatory cells. It has greater selectivity for inhibiting COX-2 Diclofenac accumulates in synovial fluid after oral

administration, thus the duration of its therapeutic effect is considerably longer than the plasma half life. Diclofenac is also used topically for ocular inflammation.

The adverse effects are similar to NSAIDs, however elevation of hepatic enzymes in the plasma is more common. The drug is not recommended for children, pregnant or nursing mothers.

Pyrrole derivatives

Ketorolac : Has more than 400 fold selectivity for inhibiting COX-1 over COX-2. It was the first injectable NSAID approved. It is also available in tablet form for oral use but only after initial intramuscular or intravenous injection. The total course of therapy with ketorolac should not exceed 5 days. The drug has a relatively high incidence of gastrointestinal ulceration and bleeding complications compared with other NSAIDs

Parenteral ketorolac may be as effective as standard doses of intramuscular morphine or meperidine, longer lasting and with fewer adverse effects. Injectable ketorolac has an important application in postoperative pain management. The drug is contraindicated before surgery because its intense antiplatelet effect due to COX-1 blocking activity may result in increased intraoperative bleeding. A topical preparation for ocular use is available to treat ocular itching associated with seasonal allergic conjunctivitis.

Fenmates (anthranilic acid derivatives)

Mefenamic acid, meclofenamic acid, flufenamic acids: These drugs have therapeutically no advantages over other NSAIDs and frequently cause gastrointestinal side effects and serious blood dyscrasias. The drugs may produce severe diarrhoea, associated with steatorrhea and inflammation of the bowel. Autoimmune hemolytic anemia is a potentially serious but rare side effect.

Oxicams (Enolic acid derivatives)

Piroxicam, meloxicam, tenoxicam: Piroxicam has antiinflammatory actions, in addition to its inhibition of PG synthesis. It can inhibit activation of neutrophils and the inhibition of the enzymes proteoglycanase and collagenase in cartilage . It undergoes considerable enterohepatic recycling and has a plasma half life of 50 hours. This permits once a day dosing. It also requires 2 weeks for full therapeutic concentrations to be achieved after the initiation of therapy, hence it cannot be used for acute analgesia.

Pyrazolones

Phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine: These drugs are not used now because of their propensity to cause irreversible agranulocytosis.

Para-aminophenol Derivatives

Acetaminophen : Acetaminophen (N-acetyl - p- aminophenol) is an aniline derivative. Other aniline derivatives include acetanilid and phenacetin, whose active metabolite is acetaminophen. Phenacetin, was used very commonly as a constituent of analgesic preparations, but is not used now because of data linking long term administration of such combinations with renal damage. Phenacetin can also produce CNS disturbances (sedation), hemolytic anemia and methemoglobinemia.

Pharmacological Effects: Acetaminophen has both analgesic and antipyretic activity equivalent to aspirin. It has weak antiinflammatory effects. This may be because it has a poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation. Other proposed mechanisms of action for acetaminophen do not involve PGs and include the activation of spinal serotonergic pathways and the inhibition of nitric oxide synthase.

Acetaminophen exerts relatively few important effects on specific organs or systems. It does not inhibit platelet aggregation, cause occult bleeding or gastric irritation, affect uric acid excretion.

Acetaminophen is well absorbed orally in the small intestine. The drug is evenly distributed throughout the body fluids and tissues. It crosses the placenta freely. The drug has a half life of 2 to 4 hours and is metabolized in the liver. A highly reactive and hepatotoxic metabolite, N-acetyl-p benzoquinoneimine (NAPQ1) may cause serious hepatic toxicity in overdose. The drug is bound to plasma proteins to the extent of 40%. Elimination is through kidneys by glomerular filtration and active proximal tubular secretion. Acetaminophen does not compete with organic acids for secretion.

Uses: Acetaminophen is the antipyretic of choice in children and teenagers, because unlike aspirin, it is not associated with the development of Reye's syndrome. It may be used as a mild analgesic. Acetaminophen is not preferred as an antiinflammatory drug. The oral dose of acetaminophen is 325 to 1000 mg. Total daily doses should not exceed 4000 mg. In children a dose of 10 mg/kg may be used.

Adverse Effects : Acetaminophen usually is well tolerated at recommended therapeutic doses. At therapeutic doses, acetaminophen does not cause gastric disturbances, inhibit platelet aggregation, prolong prothrombin time or produce other side effects associated with the use of NSAIDs. Rarely it may cause neutropenia, thrombocytopenia, pancytopenia, methemoglobinemia. Rash and allergic reactions occur occasionally. Patients who are hypersensitive to salicylates are rarely sensitive to acetaminophen.

The potential for adverse effects are confined to acute overdose or an interaction with alcohol.

Hepatotoxicity : is the most serious adverse effect of overdosage of acetaminophen. It may result in potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma may also occur. Hepatotoxicity appears to result from the formation of the highly reactive metabolite NAPQ1, which normally reacts rapidly with glutathione and is neutralized. In acetaminophen overdose, this metabolite depletes glutathione and accumulates resulting in the alkylation of liver proteins and cellular injury. This is a life threatening situation. And management is a medical emergency. N-acetyl cysteine(NAC) is effective treatment in many cases of toxicity if administered on time. It enables the formation of new glutathione and reduces mortality rates. To be effective N-acetylcystiene (NAC) must be administered as soon as possible but usually not more than 36 hours after ingestion. N- acetylcysteine is administered orally or intravenously. In addition to NAC therapy, aggressive supportive care must be given.

Alcohol consumption and acetaminophen may result in a complex interaction. In patients who

consume alcohol regularly, CYP2E1 is highly induced. CYP2E1 promotes the conversion of acetaminophen to NAPQ1, also hepatic glutathione tends to be depleted in chronic alcohol consumers. Thus when patients are consuming alcohol, CYP2E1 is preferentially bound by alcohol and not acetaminophen which limits production of NAPQ1. However, when they stop consuming alcohol, they are at a greater risk for acetaminophen toxicity, as CYP2E1 is induced, alcohol is not available and increased amounts of NAPQ1 are formed.

Preferentially selective COX inhibitors

Meloxicam: Meloxicam is a weak preferential blocker of COX-2. Meloxicam may be considered as 'preferentially selective rather than “highly” selective COX-2 inhibitor. Meloxicam appears to produce a lower incidence of serious gastrointestinal side effects, probably as a result of its relative sparing of COX-1 activity. It has an elimination half life of 15 to 20 hours, which supports once a day dosing. Meloxicam is metabolized primarily through hepatic CYP2C9 enzymes, There is a possibility that inhibitors of this enzyme system such as metronidazole or fluconazole could cause meloxicam concentrations to increase in the blood.

Nabumetone: Nabumetone is a prodrug that is converted to the active naphthylalkanone metabolite 6 methoxy-2 naphthylacetic acid (6MNA) in vivo. It was originally thought to be a preferential COX-2 inhibitor, but is actually three to five fold potent blocker of COX-1 than COX-2. Nabumetone may be associated with crampy lower abdominal pain and diarrhoea but the incidence of gastrointestinal ulceration appears to be lower than with other NSAIDs.

Nimesulide: Nimesulide is a sulfonanilide compound It is a preferential COX-2 inhibitor. It is a relatively weak inhibitor of PG synthesis and may exert antiinflammatory actions by other mechanisms such as reduced generations of superoxide by neutrophils, inhibition of PAF synthesis, and TNF α release, free radical scavenging, inhibition of metalloproteinase activity in cartilage. The analgesic antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs. The overall safety of nimesulide is not established Reports of cases of fulminant hepatic failure, has lead to its withdrawal from many countries.

Selective Cyclooxygenase -2 Inhibitors (Coxibs)

Cyclooxygenase 2 inhibitors are drugs that selectively inhibit the inducible COX-2 isoforms. of the COX enzyme systems while sparing the constitutive COX-1 isoform. Unlike preferential COX-2 inhibitors such as diclofenac, etodolac, meloxicam, nimesulide whose COX-2 selectivity does not exceed twofold to threefold, selective COX-2 inhibitors display COX-2 selectivity in the range of eightfold to 35 fold in whole blood assay systems. But COX-2 inhibitors have analgesic, antipyretic and anti-inflammatory effects similar to those of nonselective NSAIDs. The selectivity of these coxibs has lead to a reduction in serious gastrointestinal complications, including symptomatic ulcers, gastrointestinal bleeds, perforations and obstructions in comparison with other NSAIDs. Also COX-2 inhibitors at usual doses have been shown to have no impact on platelet aggregation, which is mediated by the COX-1 isoenzyme. As a result COX-2 inhibitors do not offer the cardioprotective effects of traditional nonselective NSAIDs. Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib. These have been withdrawn from the market. Since COX-2 is constitutively present in the kidneys, COX-2 inhibitors may cause renal toxicity.

Pharmacokinetics:

Celecoxib : Is a novel diaryl substituted pyrazole that possesses a sulfonamide group and is about 10-20 times more selective for COX-2 than for COX-1. It has been approved for use in familial adenomatous polyposis, where its use reduced the number of polyps by roughly 25% after 6 months of therapy. This could be because COX-2 is known to be over expressed in human colorectal adenomas and adenocarcinomas. Probably because it is a sulfonamide, celecoxib may cause rashes. Patients who require low doses aspirin, must continue to do so in addition to their anti arthritic dosages of COX-2 inhibitors. Since it is metabolized by CYP2C9, it may result in significant drug interactions when used with other drugs that are metabolized by (warfarin) or inhibit (metronidazole, fluconazole) CYP2C9.

Rofecoxib: Is a diaryl substituted furanone with COX-2 selectivity of approximately 35 fold. The drug is well absorbed orally, with an elimination half life of 17 hours. The cytochrome P450 system plays a minor role in the biotransformation of rofecoxib and hence inhibitors of this system should not affect the drug's metabolism.

Valdecoxib: Is a diaryl substituted isoxaole. Serious side reactions have been reported in sulfonamide sensitive individuals. It has been withdrawn from many countries because of cardiovascular risks.

Newer COX-2 inhibitors

Paracoxib is a prodrug that is available for parenteral use. Etoricoxib has the highest selectivity ratio of any coxib for inhibition of COX-2 relative to COX-1. Since it has structural similarities to diclofenac, it is appropriate to monitor hepatic function in patients using this drug.

Pharmacokinetics: Most coxibs are well absorbed orally, with peak concentrations reached in 1 to 4 hours. They are all extensively protein bound (90 to 99%) Most are widely distributed in the body' celecoxib is highly lipophilic and so tends to accumulate in fat and is readily transported into CNS. Luminacoxib is more acidic, which favors its accumulation at sites of inflammation. The coxibs are metabolized by a variety of cytochrome P450 enzymes including CYP3A, CYP2C9, CYP2D6 and CYP1A2. This may result in drug interactions, as the predominant enzyme system is CYP2C9 which metabolizes 20% of all drugs.

Clinical use of NSAIDs

All NSAIDs are about equally efficacious, with a few exceptions. The choice of an agent for use as an antipyretic or analgesic is based on onset and duration of action.

For fevers acetaminophen is the drug of choice in children and teenagers. Drugs with more rapid onset of action are preferred for analgesia. A drug with a longer duration of action would be preferred, especially for post operative management. The requirement of a parenteral route of drug administration may determine the choice of the NSAID.

Anti inflammatory : The choice of NSAIDs for inflammatory conditions is empirical and may be based on safety and cost considerations. There are inter individual variations in response to NSAIDs, and within an individual treated with different NSAIDs. Once a NSAID is selected, the patient should be given a short therapeutic trial to check for tolerance and response. Only if

the above are found to be satisfactory, should the drug be continued, with appropriate dose adjustments. If the patients does not achieve therapeutic benefit with one NSAID, another should be tried. For patients with renal insufficiency, non acetylated salicylates may be chosen. Diclofenac and sulindac are associated with more hepatotoxicity. Selective COX-2 inhibitors are to be preferred for patients at high risk for gastrointestinal bleeding but may have a higher risk of cardiovascular toxicity.

The choice of an NSAID requires a balance of efficacy, safety, cost and individual factors. There is no single best NSAID for all patients. The choice has to be individualized.

NSAIDs

NSAIDs act by inhibiting the activity of arachidonate cyclooxygenase and thus inhibit the synthesis of prostaglandins and thromboxanes.

There are two COX enzymes: COX-1 and COX-2. COX-1 is a constitutive housekeeping enzyme and COX-2 is induced in inflammatory cells.

NSAIDs have three major pharmacological actions. They are:

- Anti-inflammatory, due to decrease in vasodilator prostaglandins
- Analgesic, decrease in prostaglandin generation results in less sensitization of nociceptive nerve endings to inflammatory mediators
- Antipyretic, due to decrease in the prostaglandin responsible for elevating the hypothalamic set point for temperature control

The main uses are as anti inflammatory, antipyretics and analgesic agents.

The main adverse effects include gastric damage (ulceration with risk of hemorrhage), skin reactions, reversible renal insufficiency, analgesic associated nephropathy, bronchospasm in (aspirin sensitive), less commonly liver disorders, bone marrow depression

Drugs Used To Treat Gout

Gout is metabolic disorder which results from elevated concentrations of uric acid in blood and other body fluids. The elevation in uric acid may be the result of either 1) increased synthesis caused by a primary defect in purine metabolism or hematologic disorders leukemias, cancer chemotherapy etc 2) decreased excretion of uric acid in the kidney.

All the clinical manifestations of gout result from the precipitation of sodium urate from extracellular fluids when it exceeds the limits of solubility. Gout may be categorized into 4 categories 1) acute gouty arthritis 2) tophaceous deposits (sodium urate deposits in cartilage, bone, bursae, subcutaneous tissue, around joints, 3) uric acid nephrolithiasis and 4) gouty kidney with impairment of renal function. The most common presentation is gouty arthritis. It is characterized by severe inflammation of the joint and periarticular tissues. One or more joints may be involved with swelling, redness, heat and intense pain. There may be systemic signs of inflammation including fever and leukocytosis. Attacks may occur resulting in increasing

disability.

Urate crystals are initially phagocytosed by synoviocytes which then release PGs, lysosomal enzymes, interleukin, bradykinin. Large numbers of neutrophils then accumulate in the synovium, which phagocytize urate crystals, thus leading to amplification of the inflammatory process. Subsequently mononuclear phagocytes appear, ingest urate crystals and release more inflammatory mediators.

The aims of treatment are 1) to decrease symptoms of an acute attack 2) decrease the risk of recurrent attacks

Treatment of an acute attack

The treatment of an attack of acute, gouty arthritis involves the use of drugs that inhibit inflammation. These are NSAIDs, colchicine and in rare cases glucocorticosteroids.

NSAIDs: These effectively relieve the pain, tenderness and swelling in affected joints. Several NSAIDs are effective as in addition to inhibiting prostaglandin synthesis they may also inhibit urate crystal phagocytosis.

Indomethacin, naproxen, sulindac have been approved for the treatment of gout. Aspirin should not be used because it can inhibit urate excretion at low doses, and by its uricosuric action increase the risk of renal calculi at higher doses. Aspirin can also inhibit the action of other uricosuric agents. Oxaprozin lowers serum uric acid, it should not be given to patients with uric acid stones because it increases uric acid excretion in the urine.

NSAIDs should be given at relatively high doses for 3 to 4 days and then tapered for a total of 7 to 10 days

Glucocorticoids

Glucocorticoids may need to be used in severe cases, for rapid relief of symptoms. High doses are used initially and then tapered rapidly off, prednisolone 30 to 60 mg/day for 3 days, then tapered over 12- to 14 days depending on the size and number of affected joints.

Colchicine

Colchicine is one of the oldest and most widely used drugs for acute gout. It is a plant alkaloid.

Mechanism of action : The anti-inflammatory effects of colchicine are believed to be due to its antimitotic action. It arrests mitosis in metaphase by binding to microtubular proteins and preventing spindle formation. This effect is maximum on cells with a rapid turnover such as neutrophils and the cells of the gastrointestinal tract. Colchicine disrupts fibrillar microtubules in neutrophils and other motile cells. Since the microtubular system is involved in cell locomotion, colchicine inhibits the migration of neutrophils and their phagocytic activity in inflamed joints.

Pharmacokinetics : Colchicine is absorbed rapidly from the gastrointestinal tract. The drug is partially metabolized in the liver and the metabolites and unchanged drug are excreted in the feces for upto 10 days after a single dose. There is significant enterohepatic circulation.

Uses : I) **Acute gout.** Within a few hours of its administration, colchicine results in decreasing the signs and symptoms of arthritis including pain. Colchicine is relatively specific for this condition and has little effect on other inflammatory conditions as it does not have inherent analgesic properties. The common oral dose is 0.6 mg each hour for a total of three doses. The dose should not be exceeded, nor repeated within 7 days to avoid cumulative toxicity. In patients with diseases of the cardiac, renal, hepatic or gastrointestinal system, NSAIDs or glucocorticoids may be preferred.

ii) **Prevention of Acute Gout :** The prevention of acute gout may be the main indication for the use of colchicine. The common dose is 0.6 mg once to twice a day, which should be decreased for patients with impaired renal function.

Adverse effects : The most common adverse effects of colchicine are nausea, vomiting and diarrhoea and these may be the earliest signs of impending toxicity. Diarrhea may signal more serious toxic reactions such as hemorrhagic gastroenteritis. Long term use of colchicine may lead to bone marrow depression, myopathy and alopecia.

Allopurinol

Allopurinol and its metabolite alloxanthine (oxypurinol) inhibit the enzyme xanthine oxidase. Xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and then to uric acid. Allopurinol thus lowers the blood and urine concentrations of uric acid. Most the effect in uric acid appears to be caused by alloxanthine because it is longer acting. Allopurinol is a competitive inhibitor, whereas alloxanthine is a non-competitive inhibitor of xanthine oxidase. The concentration of uric acid is decreased in plasma, and purine excretion is increased. By decreasing the uric acid levels in the body, allopurinol facilitates the dissolution tophi and prevents the development or progression of chronic gouty arthritis. The dissolution and prevention of formation of uric acid stone prevents development of nephropathy. The incidence of acute attacks of gouty arthritis may increase during the early months of allopurinol therapy due to mobilization of tissue stores of uric acid. These acute attacks may be suppressed by co administration of colchicine, initially.

Pharmacokinetics : Allopurinol is absorbed rapidly after oral administration. About 50% of the drug is metabolized to oxypurinol and the rest is excreted unchanged in the urine and feces. The plasma half life of allopurinol is 1 to 2 hours, and of oxypurinol 18 to 30 hours. This allows for once daily dosing.

Drug interactions : Allopurinol increases the half life of probenecid and enhances its uricosuric effect. Probenecid increases the clearance of oxypurinol. This will increase the dose requirements of allopurinol. Allopurinol increases the concentration of mercaptopurine and azathioprine by inhibiting their metabolism. The dosages of these drugs will have to be reduced significantly. There is increased incidence of a rash when allopurinol and ampicillin are given together.

Uses : Allopurinol provides effective therapy for the primary hyperuricemia of gout and hyperuricemia secondary to hematological malignancies, polycythemia vera, myeloid

metaplasia, other blood dyscrasias and acute tumor lysis syndrome. Allopurinol therapy should be anteceded by colchicine therapy. Allopurinol should not be started during an acute attack of gouty arthritis. Fluid intake should be increased to maintain a urine volume of more than 2 liters. The initial dose is 100 mg, increased weekly to about 300 mg/day. Those with more severe gout may require higher doses and dose above 300 mg should be given in divided doses. The doses needs to be reduced in patients with renal dysfunction. Patients with hematological malignancies may require high doses of 800 mg/day, beginning 2 to 3 days before start of chemotherapy.

ii)Allopurinol is also useful in lowering the high plasma concentrations of uric acid in patients with Lesch Nyhan syndrome.

Adverse effects : Allopurinol is well tolerated. Hypersensitivity reactions are the most common. They are usually reversible. Skin reactions, rarely toxic epidermal necrolysis, Stevens Johnson syndrome occurs which may be fatal. Serious reactions preclude further use of the drug. Leukopenia, thrombocytopenia, agranulocytosis may occur.

Febuxostat

Febuxostat is the first nonpurine inhibitor of xanthine oxidase,. It is a potent, selective inhibitor of xanthine oxidase and reduces the formation of xanthine and uric acid. It is orally absorbed and highly metabolized. It is awaiting approval at a dose of 80 to 120 mg/day for treatment of chronic gout.

Rasburicase

Rasburicase is a recombinant urate oxidase that catalyzes the enzymatic oxidation of uric acid into the soluble and inactive metabolite allantoin. It is indicated for pediatric patients with hematological malignancies who are receiving anticancer therapy at a dose of 0.15 to 0.2 mg/kg as a single daily dose for 5 days with chemotherapy initiated 4 to 24 hours after infusion of the first rasburicase dose. Adverse effects include hemolysis in G6PD deficiency, methemoglobinemia, anaphylaxis and antibody production.

Uricosuric Agents

Uricosuric agents increase the rate of excretion of uric acid. Urate is filtered, secreted and reabsorbed by the kidneys. Reabsorption predominates and this process is mediated by a specific transporter which can be inhibited. Uricosuric drugs are organic acids which compete with urate for the brush border transporter in the renal tubules. Thus inhibiting its reabsorption via the urate anion exchanger system. This transport is bidirectional and dose dependent. Drugs may compete for the transporter. Uricosuric drugs include probenecid, sulfapyrazone and benzbromarone

Probenecid

Probenecid is a highly lipid soluble benzoic acid. It inhibits the transport of organic acids across epithelial barriers. It inhibits the reabsorption of uric acid in the renal tubule. Probenecid inhibits the tubular secretion of most other substances such as methotrexate, clofibrate, inactive, metabolites of NSAIDs. Salicylates blunt the uricosuric action of probenecid. Probenecid also inhibits the transfer of monoamines and drugs such as Penicillin G from the CSF to the plasma. It inhibits biliary excretion of rifampicin. The plasma concentrations of all these agents will

increase.

Pharmacokinetics : Probenecid is absorbed completely after oral administration. The half life is dose dependent over the therapeutic range. It is metabolized into active products which have uricosuric activity. Majority of the drug is secreted actively by the proximal tubule activity.

Uses : I) Gout : Probenecid is used to increase urinary excretion of uric acid. It should not be used in patients with nephrolithiasis. Concomitant production of colchicine or NSAIDs are indicated early in the therapy to avoid precipitating an attack of gout. The starting dose is 250 mg twice daily, increasing over 1 to 2 weeks to 500 to 1000 mg twice daily.

ii) Combination with penicillin : Probenecid is used along with penicillin to prolong the concentration of penicillin by decreasing its secretion.

Adverse effects : Probenecid is well tolerated. The most common adverse effects are gastrointestinal disturbances and allergic reactions ranging from dermatitis to anaphylaxis. It is ineffective in patients with renal insufficiency.

Sulfinpyrazone

Sulfinpyrazone is a strong organic acid, which potently inhibits the renal tubular reabsorption of uric acid. It also inhibits renal tubular secretion of many other organic cations. It inhibits the metabolism of oral hypoglycemic sulfonylureas and warfarin.

Pharmacokinetics: Sulfinapyrazone is well absorbed orally. It is highly protein bound (98% to 99%). It has a short half life of 3 hours but its uricosuric effect may persist for as long as 10 hours. Sulfinpyrazone is secreted by proximal tubule secretion.

Uses : Chronic Gout. Sulfinpyrazone is administered at a dose of 100 to 200 mg given twice daily. The dose may be increased gradually to a maximum of 800 mg/day. It is in effective in patients with renal insufficiency. Colchicine may have to be administered concomitantly early to avoid precipitating an attack of gout.

Adverse effects : Hypersensitivity and gastrointestinal reactions are the most common. Depression of hematopoiesis requires periodic blood counts.

Benzbromarone

Benzbromarone is a potent uricosuric agent. It is absorbed orally. It is metabolized into active metabolites and is excreted primarily in the bile. The uricosuric action is antagonized by aspirin or sulfinpyrazone. It is effective in patients with renal insufficiency at a single daily dose of 40 to 80 mg. It may be used in patients allergic to other drugs used for the treatment of gout.

Suggested readings

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3. K.D.Tripathi. Essentials of Medical Pharmacology, 5th edition. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 2003

4. LL. Brunton, JS Lazo, KL. Parker editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics 11th edition. McGraw Hill, Medical Publishing Division., USA, 2006.

Gout

Gout is a metabolic condition characterized by an increase in uric acid levels in the body. The characteristic feature is inflammation of joints associated with pain.

Treatment involves the use of drugs which either i)inhibit the synthesis of uric acid such as allopurinol ii) increases uric acid excretion (probenecid) iii)reduces leukocyte migration into joints (colchicine) and anti inflammatory drugs (NSAIDs) which also reduce pain.

