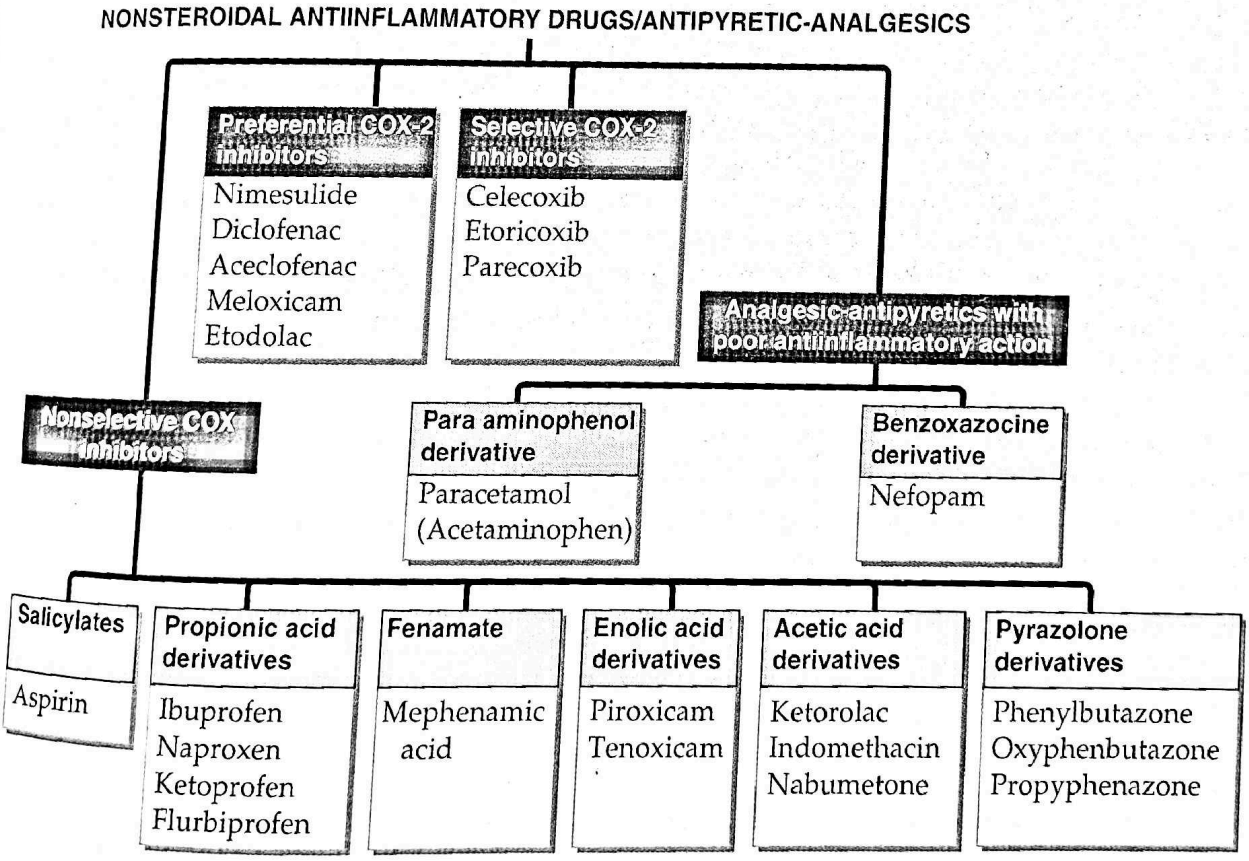
Chapter 14 Nonsteroidal Antiinflammatory Drugs and Antipyretic-Analgesics

The nonsteroidal antiinflammatory drugs (NSAIDs) and antipyretic analgesics are a class of drugs that have analgesic, antipyretic and antiinflammatory actions in different measures. In contrast to morphine they do not depress CNS, do not produce physical dependence, have no abuse liability and are particularly effective in inflammatory pain. They are also called *nonnarcotic, nonopioid* or *aspirin-like* analgesics. They act primarily on peripheral pain mechanisms, but also in the CNS to raise pain threshold. They are more commonly employed and many are over-the-counter or nonprescription drugs.

Willow bark (*Salix alba*) had been used as a medicine for many centuries. Salicylic acid was prepared by hydrolysis of the bitter glycoside obtained from this plant. *Sodium salicylate* was used for fever and pain in 1875. Its great success led to the introduction of acetylsalicylic acid (aspirin) in 1899. *Phenacetin* and *antipyrine* were also produced at that time. The next major advance was the development of phenylbutazone in 1949 having antiinflammatory activity almost comparable to corticosteroids. The term Nonsteroidal Antiinflammatory Drugs (NSAIDs) was coined to designate such drugs. *Indomethacin* was introduced in 1963. A host



of compounds heralded by the propionic acid derivative *ibuprofen* have been added since then, and cyclooxygenase (COX) inhibition is recognised to be their most important mechanism of action. Subsequently some selective COX-2 inhibitors (celecoxib, etc.) have been added.

The NSAIDs are chemically diverse, but all are weak organic acids or their active metabolites are organic acids.

NSAIDs and prostaglandin (PG) synthesis inhibition

In 1971 Vane and coworkers made the landmark observation that aspirin and some NSAIDs blocked prostaglandin (PG) generation. This is now considered to be the major mechanism of action of NSAIDs. Prostaglandins, prostacyclin (PG I_2) and thromboxane A_2 (TXA_2) are produced from arachidonic acid by the enzyme cyclooxygenase (*see* p. 198) which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological 'house keeping' functions, while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation. This leads to generation of PGs locally which mediate many of the inflammatory changes. However, COX-2 is constitutively present at some sites in brain, in juxtaglomerular cells and in the foetus; it may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced. Features of nonselective COX-1/COX-2 inhibitors (traditional NSAIDs) and selective COX-2 inhibitors are compared in Table 14.1

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme.

Beneficial actions due to PG synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyresis
- Antiinflammatory
- Antithrombotic
- Closure of ductus arteriosus in newborn

Other NSAIDs are competitive and reversible inhibitors of COX; return of activity depends on their dissociation from the enzyme which in turn is governed by the pharmacokinetic characteristics of the compound.

Analgesia PGs induce hyperalgesia (*see* p. 203) by affecting the transducing property of free nerve endings so that stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain sensitizing mechanism induced by bradykinin, TNFα, interleukins (ILs) and other algesic substances primarily by inhibiting COX-2. This constitutes the peripheral component of the analgesic action of NSAIDs. They are, therefore, more effective against inflammation associated pain.

Lately the central component of analgesic action of NSAIDs has also been shown to involve inhibition of PG synthesis in the spinal dorsal horn neurones as well as in brain, so that PG mediated amplification of pain impulses does not occur.

Antipyresis NSAIDs lower body temperature in fever, but do not cause hypothermia in normothermic individuals. Fever during infection and tissue injury is produced through the generation of pyrogens including, ILs, TNFα, interferons which induce PGE_2 production in hypothalamus—raise its temperature set point. NSAIDs block the action of pyrogens but not that of PGE_2 injected into the hypothalamus. The isoform dominant at this site appears to be COX-2 (possibly COX-3, a splice variant of COX-1 that is inhibited by paracetamol as well). However, fever can occur through non-PG mediated mechanisms as well.

Antiinflammatory The most important mechanism of antiinflammatory action of NSAIDs is considered to be inhibition of COX-2 mediated enhanced PG synthesis at the site of injury. However, there is some evidence that inhibition of the constitutive COX-1 also contributes to suppression of inflammation, especially in the initial stages. The antiinflammatory potency of different compounds roughly corresponds with their potency to inhibit COX. However, nimesulide is a potent antiinflammatory but relatively weak COX inhibitor. PGs are only one of the

Table 14.1: Features of nonselective COX inhibitors and selective COX-2 inhibitors

Action	COX-1/ COX-2 inhibitors	COX-2 inhibitors
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	–
5. Gastric mucosal damage	+	–
6. Renal salt/water retention	+	+
7. Delay/prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	–

mediators of inflammation, and inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages, and there are many targets for antiinflammatory action.

Activated endothelial cells express adhesion molecules (ELAM-1, ICAM-1) on their surface and play a key role in directing circulating leucocytes to the site of inflammation (chemotaxis). Similarly, inflammatory cells express *selectins* and *integrins*. Certain NSAIDs may act by additional mechanisms including inhibition of expression/activity of some of these molecules and generation of superoxide/other free radicals. Growth factors like GM-CSF, IL-6 as well as lymphocyte transformation factors and TNFα may also be affected. Stabilization of lysosomal membrane of leukocytes and antagonism of certain actions of kinins may be contributing to antiinflammatory action of NSAIDs.

Dysmenorrhoea Involvement of PGs in dysmenorrhoea has been clearly demonstrated: level of PGs in menstrual flow, endometrial biopsy and that of $PGF_{2\alpha}$ metabolite in circulation are raised in dysmenorrhoeic women. Intermittent ischaemia of the myometrium is probably responsible for menstrual cramps. NSAIDs lower uterine PG levels—afford excellent relief in 60–70% and partial relief in the remaining. Ancillary symptoms of headache, muscle ache and nausea are also relieved. Excess flow may be normalized.

Shared toxicities due to PG synthesis inhibition

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Limitation of renal blood flow : Na^+ and water retention
- Delay/prolongation of labour
- Asthma and anaphylactoid reactions in susceptible individuals

Antiplatelet aggregatory NSAIDs inhibit synthesis of both proaggregatory (TXA_2) and antiaggregatory (PGI_2) prostanoids, but effect on platelet TXA_2 (COX-1 generated) predominates. Therapeutic doses of most NSAIDs inhibit platelet aggregation and prolong bleeding time. *Aspirin is highly active*, because it acetylates platelet COX irreversibly in the portal circulation before getting deacetylated by first pass metabolism in liver. Small doses of aspirin are therefore able to exert antithrombotic effect for several days. Risk of surgical and anticoagulant associated bleeding is enhanced.

Ductus arteriosus closure During foetal circulation ductus arteriosus is kept patent by local elaboration of PGE_2 by COX-2. Unknown mechanisms switch off this synthesis at birth and the ductus closes. When this fails to occur, small doses of indomethacin or aspirin bring about closure in majority of cases within a few hours by inhibiting PG production. Administration of NSAIDs in late pregnancy has been found to promote premature closure of ductus in some cases. Risk of post-partum haemorrhage is increased. Prescribing of NSAIDs near term should be avoided.

Parturition Sudden spurt of PG synthesis by uterus occurs just before labour begins. This is believed to trigger labour as well as facilitate its progression. Accordingly, NSAIDs have the potential to delay and retard labour. However, labour can occur in the absence of PGs.

Gastric mucosal damage Gastric pain, mucosal erosion/ulceration and blood loss are caused by all NSAIDs to varying extents: relative gastric toxicity is a major consideration in the choice of NSAIDs. Inhibition of COX-1 mediated synthesis of gastroprotective PGs (PGE_2, PGI_2) is clearly involved, though local action inducing back diffusion of H^+ ions in gastric mucosa also plays a role. Deficiency of PGs reduces mucus and HCO_3^- secretion, tends to enhance acid secretion and may promote mucosal ischaemia. Thus, NSAIDs enhance aggressive factors and contain defensive factors in gastric mucosa; are therefore ulcerogenic. Paracetamol, a very weak inhibitor of COX is practically free of gastric toxicity and selective COX-2 inhibitors are relatively safer. Stable PG analogues (misoprostol) administered concurrently with NSAIDs counteract their gastric toxicity.

Renal effects Conditions leading to hypovolaemia, decreased renal perfusion and Na^+ loss induce renal PG synthesis which brings about intrarenal adjustments by promoting vasodilatation, inhibiting tubular Cl^- reabsorption (Na^+ and water accompany) and opposing ADH action. NSAIDs produce renal effects by at least 3 mechanisms:

- COX-1 dependent impairment of renal blood flow and reduction of g.f.r., which can worsen renal insufficiency.
- Juxtaglomerular COX-2 (probably COX-1 also) inhibition dependent Na^+ and water retention.
- Ability to cause papillary necrosis on habitual intake.

Renal effects of NSAIDs are not marked in normal individuals, but become significant in those with CHF, hypovolaemia, hepatic cirrhosis, renal disease and in patients receiving diuretics or antihypertensives. In them Na^+ retention and edema can occur; diuretic and antihypertensive drug effects are blunted.

Involvement of PG synthesis inhibition in analgesic nephropathy is uncertain.

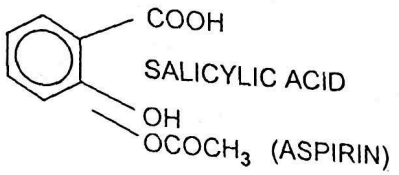
Analgesic nephropathy occurs after years of heavy ingestion of analgesics. Such individuals probably have some personality defect. Regular use of combinations of NSAIDs and chronic/repeated urinary tract infections increase the risk of analgesic nephropathy. Pathological lesions are papillary necrosis, tubular atrophy followed by renal fibrosis. Urine concentrating ability is lost and the kidneys shrink. Because phenacetin was first implicated, it went into disrepute, though other analgesics are also liable to produce similar effects.

Anaphylactoid reactions Aspirin precipitates asthma, angioneurotic swellings, urticaria or rhinitis in certain susceptible individuals. These subjects react similarly to chemically diverse NSAIDs, ruling out immunological basis for the reaction. Inhibition of COX with consequent diversion of arachidonic acid to LTs and other products of lipoxygenase pathway may be instrumental, but there is no proof.

SALICYLATES

Aspirin (prototype)

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX. It is one of the oldest analgesic-antiinflammatory drugs and has diverse uses.



Pharmacological Actions

1. *Analgesic, antipyretic, antiinflammatory actions* Aspirin is a weaker analgesic (has lower maximal efficacy) than morphine type drugs: aspirin 600 mg ≃ codeine 60 mg. However, it effectively relieves inflammatory, tissue injury related, connective tissue and integumental pain, but is relatively ineffective in severe visceral and ischaemic pain. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings. A central subcortical action raising threshold to pain perception also contributes to analgesia, but the morphine-like action on psychic processing

or reaction component of the pain is missing. No sedation, subjective effects, tolerance or dependence is produced.

Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilatation), but does not decrease heat production.

Antiinflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/ day). Signs of inflammation like pain, tenderness, swelling, vasodilatation and leucocyte infiltration are suppressed. In addition to COX inhibition, quenching of free radicals may contribute to its antiinflammatory action. However, progression of the underlying disease in rheumatoid arthritis, osteoarthritis and rheumatic fever, etc. is not affected.

2. *GIT* Aspirin, as well as salicylic acid released from it irritate gastric mucosa, cause epigastric distress, nausea and vomiting. At high doses, it stimulates CTZ. Vomiting caused by aspirin has a central component as well.

Aspirin (pKa 3.5) remains unionized and diffusible in the acid gastric juice, but on entering the mucosal cell (pH 7.1) it ionizes and becomes indiffusible. This 'ion trapping' (*see* p. 17) in the gastric mucosal cell enhances gastric toxicity. Further, aspirin particle coming in contact with gastric mucosa promotes local back diffusion of acid. This causes focal necrosis of mucosal cells and capillaries → acute ulcers, erosive gastritis, congestion and microscopic haemorrhages. The occult blood loss in stools is increased by even a single tablet of aspirin. Blood loss averages 5 ml/day at antiinflammatory doses. Haematemesis occurs occasionally: may be an idiosyncratic reaction.

Soluble aspirin tablets containing calcium carbonate + citric acid and other buffered preparations are less liable to cause gastric irritation, but incidence of ulceration and bleeding is not significantly lowered.

3. *Blood* Aspirin, even in small doses, irreversibly inhibits TXA_2 synthesis by platelets. Thus, it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value. This effect lasts for about a week (turnover time of platelets).

Long-term intake of large dose decreases synthesis of clotting factors in liver and predisposes to bleeding. This can be prevented by prophylactic vit K therapy.

4. *Metabolic and other effects of high (antiinflammatory/toxic) doses* Analgesic doses of aspirin (0.3–0.6 g 6–8 hourly) employed for headache, fever, etc. produce almost no other action. However, high doses (3–5 g/day or 100 mg/kg/day) needed for antiinflammatory action in rheumatoid arthritis/rheumatic fever produce several other effects.

- Cellular metabolism is enhanced, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation. Glucose utilization is increased resulting in fall in blood glucose level (especially in diabetics); liver glycogen is depleted. However, toxic doses may cause central sympathetic stimulation and rise in blood sugar.
- Respiration is stimulated by direct action on respiratory centre as well as due to increased CO_2 production. Hyperventilation followed by respiratory depression occurs at toxic doses.
- Respiratory stimulation tends to washout CO_2 and produce respiratory alkalosis. This is compensated by enhanced HCO_3^- excretion by kidney. Most adults receiving 3–5 g/day stay in a state of *compensated respiratory alkalosis.* Still higher doses depress respiration while excess CO_2 production continues to cause *respiratory acidosis.* Increased production of metabolic acids (lactic, pyruvic, acetoacetic) and dissociated salicylic acid may contribute to uncompensated *metabolic acidosis,* since plasma HCO_3^- is already low. Dehydration occurs due to excess water loss in urine, sweating and hyperventilation. Most children menifest this phase during salicylate poisoning, while in adults it is seen only in late stages of poisoning.
- Aspirin has no direct effect on heart or circulation, but doses which enhance metabolic rate, increase cardiac output indirectly. Toxic doses depress vasomotor centre, so that blood pressure may fall. CHF may be precipitated if cardiac reserve is low.

- Aspirin interferes with urate excretion and antagonises the uricosuric effect of probenecid. However, at high doses (≥ 5 g/day) it may block urate reabsorption and increase its excretion, but aspirin is not a reliable uricosuric.

Pharmacokinetics

Aspirin is absorbed from the stomach and small intestines. Its poor water solubility is the limiting factor in absorption: microfining the drug-particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption. However, higher pH also favours ionization, thus decreasing the diffusible form.

Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues to release salicylic acid which is the major circulating and active form. It is ~80% bound to plasma proteins and has a volume of distribution ~0.17 L/kg. Entry into brain is slow, but aspirin freely crosses placenta. Both aspirin and salicylic acid are conjugated in liver with glycine to form salicyluric acid (major pathway). They are conjugated with glucuronic acid as well. The metabolites are excreted by glomerular filtration and tubular secretion, only 1/10th is excreted as free salicylic acid.

The plasma t½ of aspirin as such is 15–20 min, but taken together with that of released salicylic acid, it is 3–5 hours. However, metabolic processes get saturated over the therapeutic range; t½ of antiinflammatory doses may be 8–12 hours while that during poisoning may be as long as 30 hours. Thus, elimination is dose dependent.

Adverse effects

(a) *Side effects* that occur at analgesic dose (0.5–2.0 g/day) are nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of aspirin is gastric mucosal damage and peptic ulceration.

(b) *Hypersensitivity and idiosyncrasy* Though infrequent, these can be serious. Reactions include rashes, fixed drug eruption, urticaria, rhinorrhoea, angioedema, asthma and anaphylactoid reaction. Profuse gastric bleeding occurs in rare instances.

(c) *Antiinflammatory doses* (3–5 g/day) produce the syndrome called 'salicylism'—dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement, hyperventilation and electrolyte imbalance.

Aspirin therapy in children with rheumatoid arthritis has been found to raise serum transaminases, indicating liver damage. Most cases are asymptomatic but it is potentially dangerous. An association has been noted between salicylate therapy and 'Reye's syndrome', a rare form of hepatic encephalopathy seen in children having viral (varicella, influenza) infection.

In adults also, long-term therapy with high dose aspirin can cause hepatic injury. Salt and water retention occurs in a dose related manner.

(d) *Acute salicylate poisoning* It is more common in children. Fatal dose in adults is estimated to be 15–30 g, but is considerably lower in children. Manifestations are:

Vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglycaemia, petechial haemorrhages, restlessness, delirium, hallucinations, hyperpyrexia, convulsions, coma and death due to respiratory failure + cardiovascular collapse.

Treatment is symptomatic and supportive. Most important is external cooling and i.v. fluid with Na^+, K^+, HCO_3^- and glucose according to need determined by repeated monitoring. Blood transfusion and vit K should be given if bleeding occurs.

Precautions and contraindications

- Aspirin is contraindicated in patients who are sensitive to it and in those with peptic ulcer or bleeding tendencies; in children suffering from chicken pox or influenza. Due to risk of Reye's syndrome, pediatric formulations of aspirin are prohibited in India and the UK.
- In chronic liver disease aspirin can precipitate hepatic necrosis.
- Aspirin should be avoided in diabetics, in those with low cardiac reserve or frank CHF and in juvenile rheumatoid arthritis.
- Aspirin should be stopped 1 week before elective surgery.

- Given repeatedly during pregnancy it may be responsible for low birth weight babies. Delayed or prolonged labour, greater postpartum blood loss and premature closure of ductus arteriosus are possible if aspirin is taken at or near term.
- Aspirin should be avoided by breastfeeding mothers.
- Avoid high doses in G-6PD deficient individuals—haemolysis can occur.

Interactions

1. Aspirin displaces warfarin, sulfonylureas, phenytoin and methotrexate from binding sites on plasma proteins: overdose symptoms of these drugs may occur. Its antiplatelet action increases the risk of bleeding in patients on oral anticoagulants.
2. Aspirin at analgesic doses inhibits tubular secretion of uric acid and antagonizes uricosuric action of probenecid. Tubular secretion of methotrexate is also interfered.
3. Aspirin blunts diuretic action of furosemide and thiazides and reduces K^+ conserving action of spironolactone. Competition between canrenone (active metabolite of spironolactone) and aspirin for active transport in proximal tubules has been demonstrated.

Uses

1. *As analgesic* For headache (including mild migraine), backache, myalgia, joint pain, pulled muscle, toothache, neuralgias and dysmenorrhoea; it is effective in low doses (0.3–0.6 g 6–8 hourly). Analgesic effect is maximal at ~ 1000 mg (single dose).

2. *As antipyretic* Aspirin is effective in fever of any origin; dose is same as for analgesia. However, paracetamol, being safer, is generally preferred.

3. *Acute rheumatic fever* Aspirin is the first drug to be used in all cases; other drugs are added or substituted only when it fails or in severe cases (corticosteroids act faster). In a dose of 4–5 g or 75–100 mg/kg/day (in divided portions) it brings about marked symptomatic relief in 1–3 days. Dose reduction may be started after 4–7 days and maintenance doses (50 mg/kg/day) are continued for 2–3 weeks or till signs of active disease (raised ESR) persist. Withdrawal should be gradual over the next 2 weeks.

Granulomatous lesions, nodules, cardiac complications, valvular defects, chorea and duration of disease are not altered by salicylate therapy.

4. *Rheumatoid arthritis* Aspirin in a dose of 3–5 g/day produces relief of pain, swelling and morning stiffness, but progress of the disease process is not affected. Since large doses of aspirin are poorly tolerated for long periods, it is rarely used now; newer NSAIDs are preferred.

5. *Osteoarthritis* It affords symptomatic relief, but is infrequently used now; paracetamol is the first choice analgesic for most cases.

6. *Postmyocardial infarction and poststroke patients* By inhibiting platelet aggregation aspirin lowers the incidence of reinfarction. TXA_2 synthesis in platelets is inhibited at low doses. It has been argued that high doses can reverse the beneficial effects by concurrently inhibiting PGI_2 (antiaggregatory and vasodilatory) synthesis in vessel wall. Large studies have demonstrated that aspirin 75–150 mg/day reduces the incidence of myocardial infarction (MI): it is now routinely prescribed to post-infarct patients. 'New onset' or 'sudden worsening' angina is associated with high infarction rate. This can be reduced to half by 100–150 mg aspirin per day for 12 weeks.

Aspirin reduces 'transient ischaemic attacks' and lowers incidence of stroke in such patients. But the risk of stroke in post-MI patients is not reduced.

7. *Prevention of preeclampsia* Imbalance between synthesis of TXA_2 and PGI_2 is believed to be causative in pregnancy related hypertension and preeclampsia. Aspirin 80–100 mg/day administered from 12th week of gestation till child birth has been found to reduce the risk of

Adverse effects of NSAIDs

Gastrointestinal
Nausea, anorexia, gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagitis

Renal
Na^+ and water retention, edema, chronic renal failure, nephropathy, papillary necrosis (rare)

CVS
Rise in BP, risk of myocardial infarction (especially with COX-2 inhibitors), CHF

Hepatic
Raised transaminases, hepatic failure (rare)

CNS
Headache, tinnitus, mental confusion, vertigo, seizure precipitation

Haematological
Bleeding, thrombocytopenia, haemolytic anaemia, neutropenia

Others
Asthma exacerbation, rhinitis, nasal polyposis, skin rashes, pruritus, angioedema

preeclampsia in pregnant women with diabetes, chronic kidney disease and other predisposing conditions.

8. Other conditions in which aspirin may be used are:
   - Familial colonic polyposis: aspirin and other NSAIDs suppress polyp formation and afford symptomatic relief in this rare disorder.
   - Prevention of colon cancer: incidence of colon cancer among regular aspirin users is much lower. Colonic tumours express large quantities of COX-2. However, the rofecoxib trial (APPROVE) was prematurely terminated and the drug withdrawn due to increased incidence of cardiovascular events. The Adenoma Prevention with Celecoxib (APC) trial has also been terminated due to 2.5 fold increase in risk of major fatal/nonfatal cardiovascular events.
   - To prevent flushing attending nicotinic acid ingestion, which is due to PGD_2 release in the skin.

ASPIRIN 350 mg tab, COLSPRIN 100, 325 mg tabs, ECOSPRIN 75, 150, 325 mg tabs, DISPRIN 350 mg tab (with cal. carbonate 105 mg + citric acid 35 mg), LOPRIN 75, 162.5 mg tabs.

An injectable preparation has also been made available; BIOSPIRIN: Lysine acetylsalicylate 900 mg + glycine 100 mg/vial for dissolving in 5 ml water and i.v. injection.

PROPIONIC ACID DERIVATIVES

Ibuprofen was the first member of this group to be introduced in 1969 as a better tolerated alternative to aspirin. Many others have followed. All have similar pharmacodynamic properties but differ considerably in potency and to some extent in duration of action (Table 14.2).

All members inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency to inhibit COX does not closely parallel *in vivo* antiinflammatory potency. Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

Adverse effects Ibuprofen and all its congeners are better tolerated than aspirin. Side effects are milder and their incidence is lower. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. Gastric erosion and occult blood loss are rare.

CNS side effects include headache, dizziness, blurring of vision and tinnitus.

Rashes, itching and other hypersensitivity phenomena are infrequent. However, these drugs precipitate aspirin-induced asthma.

Fluid retention is less marked.

They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient.

Pharmacokinetics and interactions All propionic acid derivative NSAIDs are well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant—dose of oral anticoagulants and oral hypoglycaemics need not be altered. Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided. Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.

All NSAIDs of this class enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as in bile.

Drug interactions with NSAIDs

Pharmacodynamic		*Pharmacokinetic*	
Diuretics	: ↓ diuresis	Coumarin anticoagulants	Metabolism inhibited; competition for plasma protein binding
β blocker	: ↓ antihypertensive effect	Sulfonylureas	
ACE inhibitors	: ↓ antihypertensive effect	Phenytoin	
Anticoagulants	: ↑ risk of g.i. bleed	Valproate	
Sulfonylureas	: ↑ risk of hypoglycaemia		
Alcohol	: ↑ risk of g.i. bleed	Digoxin	↓ Renal excretion of interacting drug
Cyclosporine	: ↑ nephrotoxicity	Lithium	
Corticosteroids	: ↑ risk of g.i. bleed	Aminoglycosides	
Selective serotonin reuptake inhibitors	: ↑ risk of g.i. bleed	Methotrexate	

Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an 'over-the-counter' drug.
2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.
3. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively, wherein they suppress swelling and inflammation.

Ibuprofen It has been rated as the safest traditional NSAID by the spontaneous adverse drug reaction reporting system in U.K. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60 mg) in relieving dental surgery pain, but is a weaker antiinflammatory; not suitable for acute gout and other similar conditions.

Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose aspirin, because it reversibly occupies the active serine residue of COX-1 and protects it from irreversible acetylation by aspirin. Thus, the antiplatelet action of ibuprofen is short lasting, and it abolishes the antiplatelet and cardioprotective effect of low dose aspirin.

Naproxen The antiinflammatory activity is stronger and it is particularly potent in inhibiting leucocyte migration—may be more valuable in acute gout: dose 750 mg stat followed by 250 mg 8 hourly till attack subsides. It is also recommended for rheumatoid arthritis and ankylosing spondylitis. Because of longer t½, regular use can effectively suppress platelet function. Gastric bleeding is more common than with ibuprofen. Naproxen carries lower thrombotic risk than diclofenac, etoricoxib, etc. Dose should be reduced in the elderly.

Naproxen is marketed as active single S(–) enantiomer preparation, which poses less renal burden. However, some R(+) enantiomer is formed *in vivo* due to inversion.

Table 14.2: Dosage and preparations of propionic acid derivatives

Drug	*Plasma t½*	*Dosage*	*Preparations*
1. Ibuprofen	2–4 hr	400–600 mg (5–10 mg/kg) TDS	BRUFEN, EMFLAM, IBUSYNTH 200, 400, 600 mg tab, IBUGESIC also 100 mg/5 ml susp.
2. Naproxen	12–16 hr	250 mg BD–TDS	NAPROSYN, NAXID, ARTAGEN, XENOBID 250 mg tab., NAPROSYN also 500 mg tab.
3. Ketoprofen	2–3 hr	50–100 mg BD–TDS	KETOFEN 50, 100 mg tab; OSTOFEN 50 mg cap. RHOFENID 100 mg tab, 200 mg SR tab; 100 mg/2 ml amp.
4. Flurbiprofen	4–6 hr	50–100 mg BD–QID	ARFLUR 50, 100 mg tab, 200 mg SR tab, FLUROFEN 100 mg tab.

Ketoprofen An additional action to stabilize lysosomes and to inhibit LOX has been demonstrated with ketoprofen; though antiinflammatory efficacy is similar to ibuprofen, and side effects are more.

Flurbiprofen It may have some additional mechanisms of antiinflammatory action, and is more effective than ibuprofen, but gastric side effects are also more. It is used as an ocular antiinflammatory as well.

OCUFLUR, FLUR, FLURBIN, 0.03% eye drops, 1 drop 6 hourly.

Choice among different propionic acid derivatives is difficult; *naproxen* is probably more efficacious and better tolerated in antiinflammatory doses. It is longer acting and has the advantage of twice daily dosing. However, individuals vary in their preference for different members.

FENAMATE (Anthranilic acid derivative)

Mephenamic acid An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits synthesis of PGs as well as antagonises some of their actions.

Adverse effects Diarrhoea is the most important dose-related side effect. Epigastric distress is complained, but gut bleeding is not significant. Skin rashes, dizziness and other CNS manifestations have occurred. Haemolytic anaemia is a rare but serious complication.

Pharmacokinetics Oral absorption is slow but almost complete. It is highly bound to plasma proteins, partly metabolized and excreted in urine as well as bile. Plasma t½ is 2–4 hours.

Uses Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain where strong antiinflammatory action is not needed. It is quite effective in dysmenorrhoea. It may be useful in some cases of rheumatoid and osteoarthritis but has no distinct advantage.

Dose: 250–500 mg TDS; MEDOL 250, 500 mg cap; MEFTAL 250, 500 mg tab, 100 mg/5 ml susp.

PONSTAN 125, 250, 500 mg tab, 50 mg/ml syrp.

Comorbid condition aggravated by NSAIDs

- Peptic ulcer
- Hypertension
- Congestive heart failure
- Renal insufficiency
- Hemostatic disorders

ENOLIC ACID DERIVATIVES (Oxicams)

Piroxicam It is a long-acting potent NSAID with antiinflammatory potency similar to indomethacin and good analgesic-antipyretic action. It is a nonselective, reversible inhibitor of COX; lowers PG concentration in synovial fluid and inhibits platelet aggregation—prolonging bleeding time. In addition, it decreases the production of free radicals and IgM rheumatoid factor. Leucocyte chemotaxis is inhibited. Thus, it can inhibit inflammation in diverse ways.

Pharmacokinetics Piroxicam is rapidly and completely absorbed: 99% plasma protein bound; largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile; enterohepatic cycling occurs. Plasma t½ is long—nearly 2 days. Single daily administration is sufficient, and steady-state concentrations are achieved in a week.

Adverse effects The g.i. side effects are more than ibuprofen, but low doses are better tolerated and less ulcerogenic than indomethacin. However, ulcer and g.i. bleeding are frequent with higher doses. Rashes and pruritus are seen in ~ 1% patients, and serious skin reactions are possible. Edema and reversible azotaemia have been observed.

Uses Due to slow onset of action piroxicam is suitable for use as long-term antiinflammatory drug in rheumatoid and osteoarthritis, ankylosing spondylitis, etc., but is not a first choice drug for any condition because of relatively higher toxicity. It has also been used for acute gout, musculoskeletal injuries and in dentistry.

Dose: 20 mg BD for two days followed by 20 mg OD:

DOLONEX, PIROX 10, 20 mg cap, 20 mg dispersible tab, 20 mg/ml inj in 1 and 2 ml amps; PIRICAM 10, 20 mg cap.

Tenoxicam A congener of piroxicam with similar properties and uses.

TOBITIL 20 mg tab; dose 20 mg OD.

ACETIC ACID DERIVATIVES

Ketorolac This arylacetic acid NSAID has potent analgesic but modest antiinflammatory activity. In postoperative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects. Like other NSAIDs, it inhibits PG synthesis and relieves pain primarily by a peripheral mechanism. In short-lasting pain, it has compared favourably with aspirin.

Ketorolac is rapidly absorbed after oral and i.m. administration. It is highly plasma protein bound and 60% excreted unchanged in urine. Major metabolic pathway is glucuronidation; plasma t½ is 5–7 hours.

Adverse effects Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.

Ketorolac has been used concurrently with morphine to keep its dose low. However, it should not be given to patients on anticoagulants.

Use Injected ketorolac is used in postoperative, dental and acute musculoskeletal pain: 15–30 mg i.m. or i.v. every 4–6 hours (max. 90 mg/day). It may also be used for renal colic, migraine and pain due to bony metastasis.

Orally it is used in a dose of 10–20 mg 6 hourly for short-term management of moderate pain, but not for osteo- or rheumatoid arthritis. Continuous use for more than 5 days is not recommended due to risk of g.i. and renal toxicity. It should not be used for preanaesthetic medication or for obstetric analgesia. Topical ketorolac is quite popular for noninfective ocular conditions.

KETOROL, ZOROVON, KETANOV, TOROLAC 10 mg tab, 30 mg in 1 ml amp.

KETLUR, ACULAR 0.5% eye drops; 1–2 drops 2–4 times a day for noninfective ocular inflammatory conditions.

Indomethacin This indole acetic acid derivative is a potent antiinflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory or tissue injury related pain. It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility. In toxic doses it uncouples oxidative phosphorylation (like aspirin).

Pharmacokinetics Indomethacin is well absorbed orally, rectal absorption is slow but dependable. It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney. Plasma t½ is 2–5 hours.

Adverse effects A high incidence (up to 50%) of gastrointestinal and CNS side effects is produced.

Gastric irritation, nausea, anorexia, gastric bleeding and diarrhoea are prominent.

Frontal headache (very common), dizziness, ataxia, mental confusion, hallucination, depression and psychosis can occur.

Leukopenia, rashes and other hypersensitivity reactions are also reported.

Increased risk of bleeding due to decreased platelet aggregability.

Indomethacin is contraindicated in machinery operators, drivers, psychiatric patients, epileptics, kidney disease, pregnant women and in children.

Dose: 25–50 mg BD-QID. Those not tolerating the drug orally may be given nightly suppository.

IDICIN, INDOCAP 25 mg cap, 75 mg SR cap, ARTICID 25, 50 mg cap, INDOFLAM 25, 75 mg caps, 1% eye drop. RECTICIN 50 mg suppository.

Uses Because of prominent adverse effects, indomethacin is used as a reserve drug in conditions requiring potent antiinflammatory action like ankylosing spondylitis, acute exacerbations of destructive arthropathies, psoriatic arthritis and acute gout or rheumatoid arthritis that are not responding to better tolerated NSAIDs.

Malignancy associated fever refractory to other antipyretics may respond to indomethacin.

It has been the most common drug used for medical closure of patent ductus arteriosus: three 12 hourly i.v. injections of 0.1–0.2 mg/kg achieve closure in majority of cases.

Bartter's syndrome responds dramatically, as it does to other PG synthesis inhibitors.

Nabumetone It is a prodrug—generates an active metabolite 6-methoxy naphthyl acetic acid (6-MNA) which inhibits both COX-1 and COX-2. It possesses analgesic, antipyretic and antiinflammatory activities; effective in the treatment of rheumatoid and osteoarthritis as well as in soft tissue injury. Nabumetone has caused a lower incidence of gastric erosions, ulcers and bleeding, probably because the active COX inhibitor is produced in the tissues after absorption. However, abdominal cramps and diarrhoea can occur. Rashes and photosensitivity are reported. The plasma t½ is 24 hours.

NABUFLAM 500 mg tab; 1–2 tab OD.

SECTION 3

PYRAZOLONES

Antipyrine (phenazone) and amidopyrine (aminopyrine) were introduced in 1884 as antipyretic and analgesic. Their use was associated with high incidence of agranulocytosis: are banned globally. *Phenylbutazone* was introduced in 1949 and soon its active metabolite *oxyphenbutazone* was also marketed. These two are potent antiinflammatory drugs, inhibit COX, but have slow onset. Their gastric toxicity is high; edema due to Na^+ and water retention is frequent and CNS side effects, hypersensitivity reactions, hypothyroidism are reported. They have gone out of use due to residual risk of bone marrow depression and other toxicity.

Propyphenazone This is the only pyrazolone still avilable in India, though prohibited in many countries for risks similar to other drugs in this group. It has fast onset short duration analgesic-antipyretic-antiinflammatory action. Marketed only as 'over-the-counter' analgesic-antipyretic FDCs, it is mostly used by people for self medication of headache, bodyache, toothache, fever, etc.

SARIDON: propyphenazone 150 mg + paracetamol 250 mg + caffeine 30 mg tab.

PREFERENTIAL COX-2 INHIBITORS

Nimesulide This NSAID is a relatively weak inhibitor of PG synthesis and moderately COX-2 selective. Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation 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. It has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.

Nimesulide is almost completely absorbed orally, 99% plasma protein bound, extensively metabolized and excreted mainly in urine with a t½ of 2–5 hours.

Adverse effects of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and central (somnolence, dizziness). Gastric tolerability of nimesulide is better, though ulcer complications are as prevalent as with other NSAIDs.

Instances of *fulminant hepatic failure* have been associated with nimesulide and it has been withdrawn in Spain, Ireland, Singapore and Turkey; use in children is banned in Portugal, Israel and now in India as well. Considering that it has not been marketed in many countries like the UK, USA, Australia, Canada, the overall safety of this drug, especially in children, has been questioned. However, most asthmatics and those who develop bronchospasm or intolerance to aspirin and other NSAIDs do not cross react with nimesulide. Its specific usefulness appears to be only in such patients.

Dose: 100 mg BD; NIMULID, NIMEGESIC, NIMODOL 100 mg tab, 50 mg/5 ml susp.

Diclofenac sodium An analgesic-antipyretic-antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and is somewhat COX-2 selective. The antiplatelet action is not appreciable due to sparing of COX-1, and the cardioprotective effect of low dose aspirin is not blocked. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

Diclofenac is well absorbed orally, 99% protein bound, metabolized and excreted both

in urine and bile. The plasma t½ is ~2 hours. However, it has good tissue penetrability and concentration in synovial fluid is maintained for 3 times longer period than in plasma, exerting extended therapeutic action in joints.

Adverse effects of diclofenac are generally mild: epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common. Some comparative trials have found its gastric toxicity to be similar to celecoxib and etoricoxib. Like many NSAIDs, diclofenac can increase the risk of heart attack and stroke, probably reflecting lack of antiplatelet action. Reversible elevation of serum amino-transferases has been reported more commonly. Renal blood flow and g.f.r may be reduced, especially at higher doses.

Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, renal colic, post-traumatic and postoperative inflammatory conditions—affords quick relief of pain and wound edema.

Dose: 50–75 mg TDS, then BD oral, 75 mg deep i.m.
VOVERAN, DICLONAC, MOVONAC 50 mg enteric coated tab, 100 mg S.R. tab, 25 mg/ml in 3 ml amp. for i.m. inj. DICLOMAX 25, 50 mg tab, 75 mg/3 ml inj., DYNAPAR AQ, JUSTIN AQ: diclofenac sod. 75 mg in 1 ml for i.m./i.v. injection; This more concentrated parenteral formulation of diclofenac can be given i.m. (less painful, because propylene glycol is not used) as well as by bolus i.v. injection without dilution.
Diclofenac potassium: VOLTAFLAM 25, 50 mg tab, ULTRA-K 50 mg tab; VOVERAN 1% topical gel.
DICLONAC, VOVERAN OPHTHA 0.1% eye drops.

Aceclofenac A moderately COX-2 selective congener of diclofenac having similar properties. Enhancement of glycosaminoglycan synthesis may confer chondroprotective property to aceclofenac.

Dose: 100 mg BD;
ACECLO, DOLOKIND 100 mg tab, 200 mg SR tab.

Meloxicam This newer congener of piroxicam has a COX-2/COX-1 selectivity ratio of about 10. Since measurable inhibition of platelet TXA_2 production (a COX-1 function) occurs at therapeutic doses of meloxicam, it has been labelled 'preferential COX-2 inhibitor'. Efficacy of meloxicam in osteo- and rheumatoid arthritis is comparable to piroxicam. Plasma t½ is 15–20 hours permiting single daily dose. In short-term studies, gastric changes with the lower dose (7.5 mg/day) were found to be similar to placebo, but at the higher dose (15 mg/day) they were intermediate between placebo and piroxicam. Gastric side effects of meloxicam are milder, but ulcer complications (bleeding, perforation) have been reported on long-term use. There is no convincing evidence that meloxicam is safer than other NSAIDs.

Dose: 7.5–15 mg OD;
MELFLAM, MEL-OD, MUVIK, M-CAM 7.5 mg, 15 mg tabs.

Etodolac This newer indole-acetic acid NSAID is moderately COX-2 selective with properties similar to diclofenac. At lower doses, gastric tolerance is better than older NSAIDs. It is metabolized by hydroxylation and glucuronide conjugation, and excreted in urine with a t½ of 7 hours. Postoperative analgesia with etodolac lasts for 6–8 hours. Side effects are abdominal pain, rashes and dizziness. It is approved for use in osteo- and rheumatoid arthritis as well as in acute musculoskeletal pain.

Dose: 200–400 mg BD–TDS;
ETOVA 200, 300, 400 mg tabs, ETOGESIC 400 mg tab.
Etodolac 400 mg/2 ml for i.m. injection has been approved for postoperative orthopedic pain.

SELECTIVE COX-2 INHIBITORS (Coxibs)

Because of the theoretical advantage of inhibiting COX-2 which is induced at the sites of inflammation without affecting the 'house keeping' COX-1 function, some highly selective COX-2 inhibitors have been introduced over the past 3 decades. They cause less gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than that with traditional NSAIDs. They do not depress TXA_2 production by platelets, because it is COX-1 dependent; do not inhibit platelet aggregation or prolong bleeding time, but reduce PGI_2 production by vascular endothelium. Thus, they lack the cardioprotective property of aspirin.

Currently, 3 selective COX-2 inhibitors (also called coxibs) *Celecoxib*, *Etoricoxib* and *Parecoxib* are available in India. *Rofecoxib* and

Selective COX-2 inhibitors and cardiovascular risk

COX-2 inhibitors reduce endothelial PGI_2 production without affecting platelet TXA_2 synthesis. This appears to exert prothrombotic influence and enhance CV risk.

- VIGOR (VIOXX gastrointestinal outcomes research) study in over 8000 patients found 4-fold higher incidence of myocardial infarction (MI) in rofecoxib (VIOXX) recipients compared to those on naproxen.
- APPROVE (adenomatous polyp prevention on VIOXX) a placebo controlled trial among subjects with history of colorectal adenomas was stopped prematurely at 3 years because it confirmed higher risk of heart attack and stroke: rofecoxib was withdrawn globally in 2004.
- A metaanalysis of 18 trials with rofecoxib for musculoskeletal disorders has also inferred that it increases incidence of MI.
- Valdecoxib increased occurrence of MI in patients undergoing coronary bypass surgery. There were reports of severe skin reactions as well. It was withdrawn in 2005.
- Though CLASS (celecoxib long-term safety study) did not find any increase in CV events, the APC (adenoma prevention with celecoxib) trial has been terminated prematurely due to 2.5 fold higher risk of the same.
- There is no clear evidence as yet that etoricoxib also increases CV risk.
- A joint committee in USA (2005) concluded that enough evidence to withdraw all selective COX-2 inhibitors is lacking, but that their labelling should include a warning of CV risk.

Valdecoxib were withdrawn within few years of marketing for increasing cardiovascular (CV) risk. *Lumiracoxib* marketed only in Europe has been suspended due to hepatotoxicity.

It has been concluded that *selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeds.* If selected, they should be administered in the lowest dose for the shortest period of time. Moreover, they should be avoided in patients with history of ischaemic heart disease/hypertension/cardiac failure/cerebrovascular disease, who are predisposed to CV events. Combination of low-dose aspirin with COX-2 inhibitors for reducing cardiovascular risk increases gastroduodenal injury, and is not advised.

Concerns, other than cardiovascular, have also been expressed about selective COX-2 inhibitors (*see* box).

Other concerns with selective COX-2 inhibitors

- COX-1 generated PGs may also play a role in inflammation: COX-2 inhibitors may not have as broad range of efficacy as traditional NSAIDs.
- Ulcer injury and *H. pylori* induce COX-2 in gastric mucosa, which may contribute to gastroprotective PG synthesis; COX-2 inhibition may delay ulcer healing. Moreover, part of gastric mucosal COX-2 activity may be constitutive.
- Juxtaglomerular COX-2 is constitutive; its inhibition can cause salt and water retention. Pedal edema, precipitation of CHF and rise in BP can occur with all coxibs.

Celecoxib The COX-2 selectivity of celecoxib is modest (about 10 times). It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential. Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX-1 activity in gastroduodenal mucosa. Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB_2 levels were not reduced. Though tolerability of celecoxib is better than traditional NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the usual side effects. Rashes, edema and a small rise in BP have also been noted.

Celecoxib is absorbed slowly, 97% plasma protein bound and metabolized primarily by CYP2C9 with a t½ of ~10 hours. It is approved for use in osteo- and rheumatoid arthritis in a dose of 100–200 mg BD.

CELACT, REVIBRA, COLCIBRA 100, 200 mg caps.

Etoricoxib This newer COX-2 inhibitor has the highest COX-2 selectivity. It is suitable for once-a-day treatment of osteo/rheumatoid/acute gouty arthritis, ankylosing spondylitis, dysmenorrhoea, acute dental surgery pain and similar conditions, without affecting platelet function or damaging gastric mucosa. The t½ is ~ 24 hours. The rate of thrombotic cardiovascular events with etoricoxib use has been found similar to that with diclofenac. However, it should be considered as a treatment option only as per conditions stated above for all

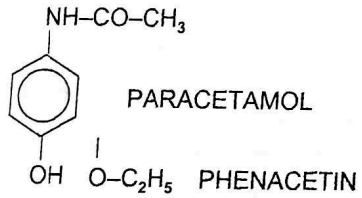
COX-2 inhibitors. Side effects are dyspepsia, abdominal pain, pedal edema, rise in BP, dry mouth, aphthous ulcers, taste disturbance and paresthesias.
Dose: 60–120 mg OD; ETOSHINE, TOROCOXIA, ETOXIB, NUCOXIA 60, 90, 120 mg tabs.

Parecoxib It is a prodrug of valdecoxib suitable for injection, and to be used in postoperative or similar short-term pain, with efficacy similar to ketorolac. It shares the same risk of serious cutaneous reactions as valdecoxib; should be stopped at the first appearance of a rash.
Dose: 40 mg oral/i.m./i.v., repeated after 6–12 hours.
REVALDO, VALTO-P 40 mg/vial inj, PAROXIB 40 mg tab.

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but was banned when it was implicated in analgesic abuse nephropathy (*see* p. 212)

Paracetamol (acetaminophen) It is the deethylated active metabolite of phenacetin that was also introduced in the last century, but has come into common use only since 1950.



Actions The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral antiinflammatory component. Analgesic action of aspirin and paracetamol is additive. Paracetamol is a good and promptly acting antipyretic.

Paracetamol has negligible antiinflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and antiinflammatory actions is its inability to inhibit COX in the presence of peroxides which are generated at sites of inflammation, but are not present in the brain. The ability of paracetamol to inhibit COX-3 (an isoenzyme so far located in dog brain) could also account for its analgesic-antipyretic action.

In contrast to aspirin, paracetamol does not stimulate respiration or affect acid-base balance; does not increase cellular metabolism. It has no effect on CVS. Gastric irritation is insignificant—mucosal erosion and bleeding occur rarely only in overdose. It does not affect platelet function or clotting factors and is not uricosuric.

Pharmacokinetics Paracetamol is well absorbed orally, only about 1/4th is protein bound in plasma and it is uniformly distributed in the body. Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are excreted rapidly in urine. Plasma t½ is 2–3 hours. Effects after an oral dose last for 3–5 hours.

Adverse effects In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally, leukopenia is rare.

Acute paracetamol poisoning It occurs especially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur. Fatality is common with > 250 mg/kg.

Early manifestations are just nausea, vomiting, abdominal pain and liver tenderness with no impairment of consciousness. After 12–18 hours centrilobular hepatic necrosis occurs which may be accompanied by renal tubular necrosis and hypoglycaemia that may progress to coma. Jaundice starts after 2 days. Further course depends on the dose taken. Fulminating hepatic failure and death are likely if the plasma levels are high. If the levels are lower —recovery with supportive treatment is the rule.

Mechanism of toxicity N-acetyl-p-benzoquinoneimine (NABQI) is a highly reactive arylating minor metabolite of paracetamol which is detoxified by conjugation with glutathione. When a very large dose of paracetamol is taken, glucuronidation capacity is saturated, more of the minor metabolite is formed—hepatic glutathione is depleted and this metabolite binds covalently to proteins in liver cells (and renal tubules) causing necrosis. Toxicity thus shows

a threshold effect manifesting only when glutathione is depleted to a critical point.

In chronic alcoholics even 5 g taken in one day can result in hepatotoxicity because alcoholism induces CYP2E1 that metabolises paracetamol to NABQI.

Paracetamol is not recommended in premature infants (< 2 kg) for fear of hepatotoxicity.

Note: Exercising abundant caution, because paracetamol is an over-the-counter drug, the US-FDA (2009) has recommended to reduce the amount of this drug in any single dosage form (tab./cap.) to 650 mg (in place of 1000 mg earlier limit), and the total daily dose for an adult to 2600 mg (in place of 4000 mg earlier).

Treatment If the patient is brought early, vomiting should be induced or gastric lavage done. Activated charcoal is given orally or through the tube to prevent further absorption. Other supportive measures, as needed, should be taken.

Specific antidote: N-acetylcysteine (MUCOMIX, MUCARE 200 mg/ml inj in 2, 5 ml amps, ACETINE 1 g/5 ml inj.) MUCOMYKS 1 g/5 ml inj, 600 mg tab.) 150 mg/kg should be infused i.v. in 200 ml 5% glucose solution over 15 min, followed by the same dose given i.v. over the next 20 hours. Alternatively, 75 mg/kg may be given orally every 4–6 hours for 2–3 days. It replenishes the glutathione stores of liver and prevents binding of the toxic metabolite to other cellular constituents.

Ingestion-treatment interval is critical; earlier the better. It is practically ineffective if started 16 hours or more after paracetamol ingestion.

Uses Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea, etc. but is relatively ineffective when inflammation is prominent as in rheumatoid arthritis. Paracetamol is recommended as first choice analgesic for osteoarthritis by many professional bodies. It is one of the best drugs to be used as antipyretic for fever due to any cause, especially in children (no risk of Reye's syndrome). However, antipyretics are not useful in fever due to *heat stroke*, in which only external cooling lowers body temperature.

Dose to dose paracetamol is equally efficacious to aspirin for noninflammatory conditions. It is much safer than aspirin in terms of gastric irritation, ulceration and bleeding (can be given to ulcer patients), does not prolong bleeding time. Hypersensitivity reactions are rare; no metabolic effects or acid-base disturbances. Paracetamol can be used in all age groups (infants to elderly), pregnant/lactating women, in presence of other disease states and in patients in whom aspirin is contraindicated. It does not have significant drug interactions. Thus, it may be preferred over aspirin for most minor conditions.

Dose: 325–650 mg (children 10–15 mg/kg) 3–4 times a day.
CROCIN 0.5 g tab, 120 mg/5 ml oral susp., 100 mg/ml oral drops; METACIN, PARACIN 500 mg tab, 125 mg/5 ml syrup, 150 mg/ml paed. drops, ULTRAGIN, PYRIGESIC, CALPOL 500 mg tab, 125 mg/5 ml syrup, NEOMOL, FEVASTIN, FEBRINIL 300 mg/2 ml inj., CROCIN PAIN RELIEF: 650 mg + Caffeine 50 mg tab.
KABIPARA: paracetamol 1g/100 ml for slow i.v. injection; AEKNIL: 150 mg/ml inj in 2,3,15 ml amps, for slow i.v. inj. JUNIMOL-RDS 80, 170, 250 mg suppository (for children), PARACETAMOL RECTAL SUPPOSITORY 80, 170 mg.

BENZOXAZOCINE DERIVATIVE

Nefopam It is a nonopioid analgesic which does not inhibit PG synthesis but relieves traumatic, postoperative and short-lasting musculoskeletal pain. It may be used if pain is persistent and is not adequately relieved by other analgesics.

Nefopam produces anticholinergic (dry mouth, urinary retention, blurred vision) and sympathomimetic (tachycardia, nervousness) side effects, and nausea is often dose limiting. It is contraindicated in epileptics.

Dose: 30–60 mg TDS oral, 20 mg i.m. 6 hourly.
NEFOMAX 30 mg tab, 20 mg in 1 ml amp.

Topical NSAIDs

Many NSAIDs have been marketed in topical formulations (mostly as gels) for application over painful muscles or joints. These preparations are being used for osteoarthritis, sprains, sports injuries, tenosinovitis, backache, spondylitis and other forms of soft tissue rheumatism. It is presumed that the drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles/joints, while maintaining low blood levels. Consequently, the g.i. and other systemic adverse effects would be

minimised and first pass hepatic metabolism would also be avoided.

While there is no doubt about their safety, doubt has been raised about their actual efficacy over and above a strong placebo effect of local application, massaging and that due to presence of counter irritants like menthol, methyl salicylate, etc. in most of them. Often they are used in addition to oral NSAID medication. Guidelines of several professional bodies recommend topical NSAIDs in mild-to-moderate osteoarthritis of knee and hand as initial or adjunctive therapy.

Measurement of drug concentration attained in tissues underlying the site of application, as well as concurrent blood levels has shown that systemic absorption from topical NSAID preparations is slow taking ~10 times longer time to attain peak concentration compared to oral dosing. Highest blood levels remain below 15% of that attained after the same dose given orally. This is consistent with their lack of systemic toxicity. Local concentrations are high upto a depth of 4–6 mm, i.e. in dermis, but at 25 mm depth in muscles, the concentration is low and nearly the same as in blood. Marked variation has been noted in the concentration attained in muscles and joints depending on the type of formulation, depth and distance from site of application as well as among different individuals. Reports on the clinical efficacy of topical NSAIDs are also variable. Better responses have generally been obtained in short lasting musculoskeletal pain. Clinical trials in osteoarthritis of knee have generally rated topical formulations of NSAIDs, notably those of diclofenac and ketoprofen to be superior to placebo. Though overall efficacy of topical NSAIDs in musculoskeletal pain is low, it appears to be clinically valuable.

Preparations

Diclofenac 1% gel : VOLINI GEL, RELAXYL GEL, DICLONAC GEL
Ibuprofen 10% gel : RIBUFEN GEL
Naproxen 10% gel : NAPROSYN GEL
Ketoprofen 2.5% gel : RHOFENID GEL
Flurbiprofen 5% gel : FROBEN GEL
Nimesulide 1% gel : NIMULID TRANS GEL, ZOLANDIN GEL, NIMEGESIC-T-GEL
Piroxicam 0.5% gel : DOLONEX GEL, MOVON GEL, PIROX GEL, MINICAM GEL

Choice of nonsteroidal antiinflammatory drug

Efficacy differences among different NSAIDs are minor, but they have their own spectrum of adverse effects. They differ quantitatively among themselves in producing different side effects and there are large inter-individual differences. At present NSAIDs are a bewildering array of strongly promoted drugs. No single drug is superior to all others for every patient. Choice of drug is inescapably empirical.

The cause and nature of pain (mild, moderate or severe; acute or chronic; ratio of pain: inflammation) along with consideration of risk factors in the given patient (age, concurrent disease and drug therapy, history of allergy) govern selection of the analgesic. Also to be considered are the past response of the patient, acceptability and individual preference. Patients differ in their analgesic response to different NSAIDs. If one NSAID is unsatisfactory in a patient, it does not mean that other NSAIDs will also be unsatisfactory. Some subjects 'feel better' on a particular drug, but not on a closely related one. It is inthis context that availability of such a wide range of NSAIDs may be welcome. Some guidelines are:

1. Mild-to-moderate pain with little inflammation: paracetamol or low-dose ibuprofen.
2. Postoperative or similar acute but short- lasting pain: injectable ketorolac, or diclofenac or oral propionic acid derivative/nimesulide.
3. A parenteral NSAID may be employed for renal colic, acute gout, acute back pain, dental pain, fractures and other grievous trauma. Three NSAIDs, *viz.* Ketorolac, diclofenac and parecoxib are available for i.m./i.v. use. Paracetamol can be given by slow i.v. infusion.
4. Exacerbation of rheumatoid arthritis, ankylosing spondylitis, acute gout, acute rheumatic fever: naproxen, piroxicam, indomethacin, high dose aspirin.

5. Gastric intolerance to traditional NSAIDs or predisposed patients: a selective COX-2 inhibitor or paracetamol. Arthritis patients who are dependent on NSAIDs and have developed peptic ulcer must receive concurrent proton pump inhibitor as gastroprotective.
6. Patients with history of asthma or anaphylactoid reaction to aspirin/other NSAIDs: nimesulide, COX-2 inhibitor.
7. Patients with hypertension or other risk factor for heart attack/stroke: avoid selective COX-2 inhibitor; a propionic acid derivative or aspirin may be used at the lowest dose for the shortest period.
8. Paediatric patients: Only paracetamol, aspirin, ibuprofen and naproxen have been adequately evaluated in children.One of these should be preferred in children. Due to risk of Reye's syndrome, aspirin should be avoided.
9. Elderly patients: use lower dose of the chosen NSAID.
10. Fast acting drug formulation is suitable for fever, headache and other short lasting pain, while longer acting drugs/sustained release formulations are appropriate for chronic arthritic pain.
11. Pregnancy: paracetamol is the safest; low-dose aspirin is probably the second best.
12. Hypertensive, diabetic, ischaemic heart disease, epileptic and other patients receiving long-term regular medication: possibility of drug interaction with NSAIDs should be considered.

SECTION 3

Analgesic combinations

Combination of aspirin and paracetamol is additive (not supra-additive) and a ceiling analgesic effect is obtained when the total amount of aspirin + paracetamol is ~ 1000 mg. The same is true of combinations of paracetamol with other NSAIDs like ibuprofen, diclofenac, etc. There is no convincing evidence that such combinations are superior to single agents, either in efficacy or in safety. If at all used, such combinations should be limited to short periods.

Combination of codeine (an opioid analgesic) with aspirin or paracetamol is also additive, but in this case combination provides additional analgesia beyond the ceiling effect of aspirin/paracetamol. However, this is true only when each is given in full dose which will produce opioid side effects (nausea, vomiting, constipation, drowsiness, risk of dependence) as well. The mechanisms of pain relief by these two classes of drugs are different. Such combination should be considered only for pain refractory to single agent.

To obviate inadvertent misuse and chance of producing dependence, the fixed dose combinations of analgesics with hypnotics/sedatives/anxiolytics is banned in India.

PROBLEM DIRECTED STUDY

14.1 A 65-year-old lady presented with pain in both knees, more on the left side. The pain is worsened by walking or standing for some time. X-ray of knee shows narrowing of joint space, mild effusion and osteophytic projections. A diagnosis of osteoarthritis of knee is made. She gave history of suffering a heart attack one year back which was treated by angioplasty and a stent was placed. She regularly takes aspirin 75 mg daily for prophylaxis of further myocardial infarction.

(a) Which analgesic/NSAID will be suitable for relieving her knee pain?
(b) Which analgesic/NSAIDs should not be prescribed for her?
(c) Whether any locally applied medication can be helpful in relieving her knee pain?
(see Appendix-1 for solution)