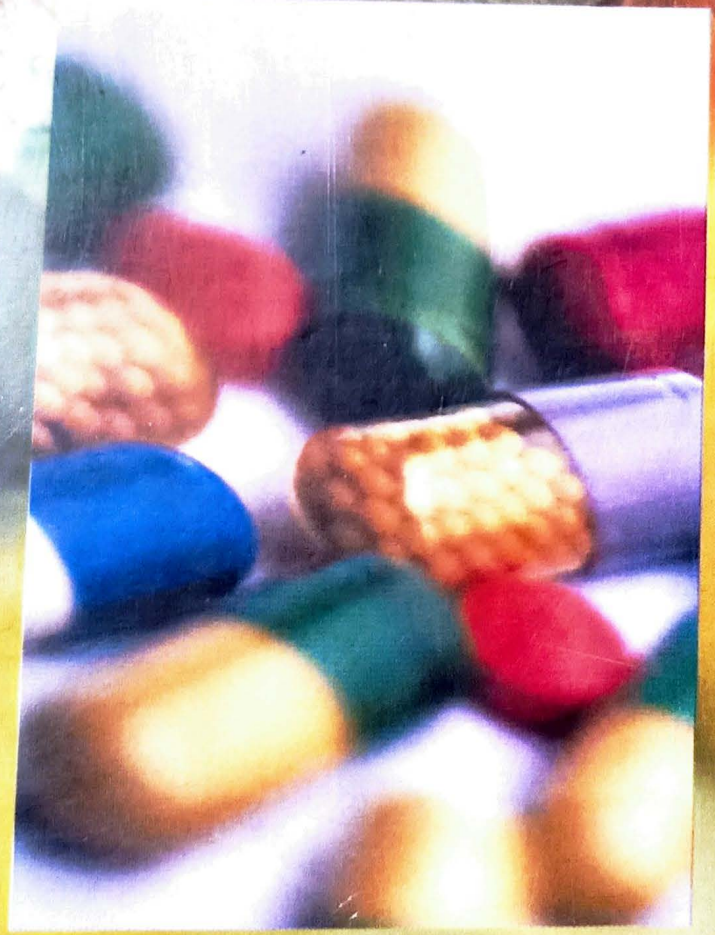
Essentials of PHARMACOTHERAPEUTICS



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2.7 NON-NARCOTIC ANALGESICS AND ANTIPYRETICS (ANTI-INFLAMMATORY AGENTS, DRUGS FOR GOUT, RHEUMATOID ARTHRITIS, AND MIGRAINE)

Pain has been defined as a characteristic sensation arising from a noxious stimulus, which includes its neurophysiological aspect. Sherrington, in his classic definition has further included the reactive component of pain, *i.e.*, the "psychical adjuvant of an imperative protective reflex". This indicates that pain also has a survival value for the species. There are two main classes of pain ***superficial*** (integumental), and ***deep***. Superficial pain is usually a quick response of sudden onset, while deep pain is more lingering and aching. Some pain receptors in the body are probably ***chemoreceptors***, as a wide variety of compounds, including autacoids like ***bradykinin***, and several of the ***prostaglandins***, can elicit pain. The main physiological pain receptors, however, are the free nerve endings.

Drugs can alter the pain experience in *three* ways (pain *reception*, *perception*, and *reaction*). The ***first step*** that can be interrupted is peripheral *pain reception* at the nerve endings. This modality is susceptible to *non-narcotic analgesics* and *local anaesthetics*. The ***second step*** which can be modified is *pain perception* at the level of the CNS. Both, *narcotic* and *non-narcotic analgesics* interfere with this level of pain integration. The ***third step*** which can be influenced is *pain reaction*. There are several constituents which make up the reaction to pain, namely, the *autonomic response* reflected by changes in blood pressure and palmer sweat; the *skeletal muscle response* manifested by muscle tension and characteristic facial expression; and the *psychic* component, or the suffering of pain. The last named component of pain reaction varies from person to person, and is affected only by narcotic analgesics (Opioids).

Terminology

The non-narcotic analgesics are a heterogeneous group of drugs which have the properties of being analgesic, antipyretic and anti-inflammatory. These agents have been variously named — *analgesic–antipyretics; aspirin-like drugs;* and ***nonsteroidal anti-inflammatory drugs (NSAIDs).*** The non-narcotic analgesics have a peripheral site of action, and have no affinity for the opioid receptors. They are considered to be ***non-addictive.*** From the clinical standpoint they relieve mild to moderate pain, and are often designated as 'mild' or 'weak' analgesics. These terms are somewhat misleading, as they do not adequately indicate, that how very effective these durgs are for relief of the most common kinds of pain and that they are capable of being abused to the point of producing some degree of ***psychological dependence***. May be it is best to characterize these agents as analgesic–antipyretics.

Classification

The non-narcotic analgesics and anti-inflammatory drugs may be classified as under :

1. *Salicylates:* Aspirin, calcium carbaspirin, choline salicylate, diflunisal, magnesium salicylate, methyl salicylate, salicylic acid, salsalate, sodium salicylate, sodium thiosalicylate, sulfasalazine, mesalazine, olsalazine.
2. *Para-aminophenol* : Paracetamol.
3. *Pyrazolones:* Phenylbutazone, oxyphenbutazone, sulfinpyrazone.
4. *Nonsteroidal anti-inflammatory drugs (NSAIDs).*
   (*a*) *Indole derivatives:* Indomethacin, sulindac, tolmetin, etodolac.
   (*b*) *Propionic acid derivatives*: Ibuprofen, fenoprofen, ketoprofen, naproxen, flurbiprofen, oxaprozin.
   (*c*) *Fenamates:* Mefenamic acid, meclofenamate.
   (*d*) *Phenylacetic acid derivative:* Diclofenac.
   (*e*) *Oxicams* : Piroxicam, tenoxicam.
   (*f*) *Sulfonanilide* : Nimesulide
   (*g*) *Alkanones:* Nabumetone
   (*h*) *Miscellaneous*: Hydroxychloroquine, penicillamine.

5. *Gold compounds*: Auranofin, aurothioglucose, gold sodium thiomalate.
6. *Antigout drugs*: Colchicine, probenecid, sulfinpyrazone, allopurinol.

The non-narcotic analgesics in certain texts have been classified as the *salicylates* (Group 1), and *non-salicylates* (Group 2–6).

Salicylates

The salicylates, the most important group of analgesic–antipyretic drugs, are derivatives of salicylic acid. Aspirin, a product developed in 1899 by Bayer, is by far the most popular analgesic, and remains the standard reference for non-narcotic analgesics. It is one of the oldest drugs in use. The layman uses aspirin as a household analgesic.

Aspirin (Acetylsalicylic Acid)

Hippocrates and other ancient physicians employed plants in the treatment of disease, now known to contain natural salicylates. These include species of willow and poplar, and a species of Gaultheria, from which *oil of wintergreen* (methyl salicylate) is obtained. Extracts of willow bark were used to treat fevers late in the eighteenth century. Actually the word *salicylate* is derived from *Salix*, the Latin name for the willow tree. The *prototype* synthetic salicylate, aspirin, was introduced as a substitute for sodium salicylate.

Pharmacological Actions and Mode of Action

The salicylates act both *centrally* and *peripherally* to produce their therapeutic and toxic effects. Aspirin exhibits analgesic, antipyretic, and anti-inflammatory activity. The results of salicylate administration are dose-related to a large extent. The analgesic and antipyretic actions are readily produced by low doses, while relatively large doses are required to bring about anti-inflammatory action in rheumatic conditions. Massive overdosage causes complex and potentially dangerous metabolic effects. The *salicylic acid* portion of the salicylate molecule is the pharmacologically active moiety. It is essential that the hydroxyl group of this molecule remains in the *ortho* position.

Analgesic/anti-inflammatory actions. The salicylates have been found to be most useful for the treatment of headache, rheumatic and muscular pain, arthritic pain and pain arising from integumental structures. They are *not* effective in acute pain of visceral origin.

The exact mechanism of analgesic action of the salicylates is not known, but evidence based on experimental animal studies has shown that the analgesic action is *mainly* a peripheral effect, in the form of *blockade of pain impulse generation*. Whether or not they have some additional minor central analgesic action is unclear. They have no effect on the reticular activating system or the limbic system, but may be they exert some action on subcortical sites like the thalamus and hypothalamus.

The peripheral analgesic action of salicylates has been extensively worked upon, and depends essentially on reducing the production of certain ***prostaglandins.*** The prostaglandins are universally released on tissue damage, and are present in the inflammatory exudate. It is evident that prostaglandins (particularly prostagladin E_2) plays an important role in several aspects of the inflammatory process. Lately, attention has been focussed on ***inhibition of prostaglandin synthesis*** as a machanism of analgesic,

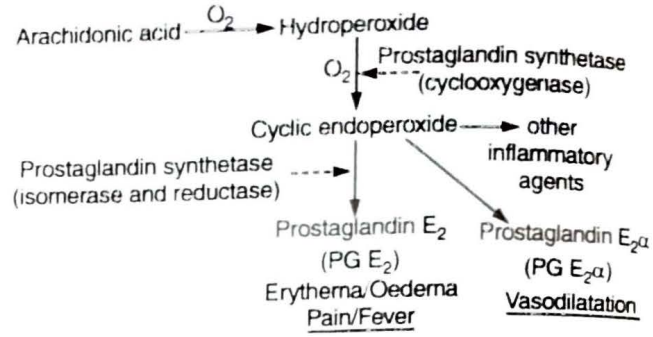

Fig. 2.7.1: The synthetic pathway of Prostaglandin E_2 and Prostaglandin $F_{2\alpha}$, the mediators of inflammation (simplified).

anti-inflammatory and antipyretic activity. The synthetic pathway of the relevant prostaglandin (PGE_2) is shown in **(Fig. 2.7.1).**

The final step in prostaglandin synthesis depends on the activity of the enzyme complex prostaglandin synthetase, and aspirin inhibits its activity. Prostaglandins play a part in the erythema, oedema, pain and fever associated with inflammation either by a direct action, or by sensitizing the receptors to other substances released by tissue damage such as ***bradykinin*** and ***histamine.*** The analgesic anti-inflammatory drugs, including aspirin, are believed to inhibit ***cyclo-oxygenase*** and thus reduce prostaglandin production. In man the turnover of prostaglandin is reduced by about 80 percent by a therapeutic dose of aspirin. Thus, in short, the salicylates have a peripheral site of analgesic anti-inflammatory action; where they interfere with the synthesis of prostaglandins, causing blockade of impulse generation in the chemoreceptors mediating pain. They have an ***anti-bradykinin*** action, which is reflected as an elevation in pain threshold. Bradykinin is one of the major mediators of the inflammatory response, and is formed through action of activated kallikrein, potentiated by fibrinopeptide B **(Fig. 2.7.2).** The analgesic and anti-inflammatory activity go hand in hand.

Antirheumatic action. Large doses of salicylates are often dramatically effective in controlling manifestations of acute and chronic connective tissue inflammatory disorders. In

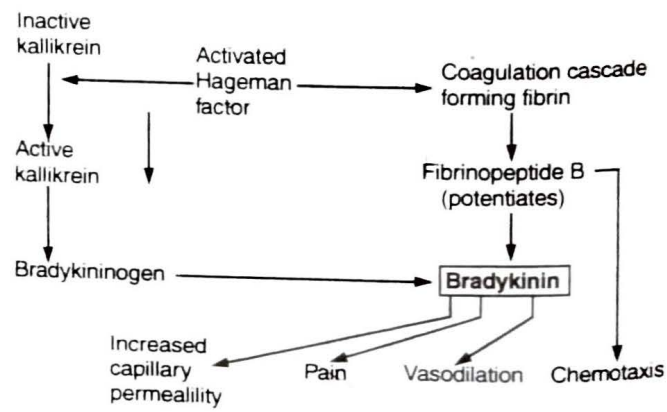

Fig. 2.7.2: Formation and role of bradykinin in inflammation (see text).

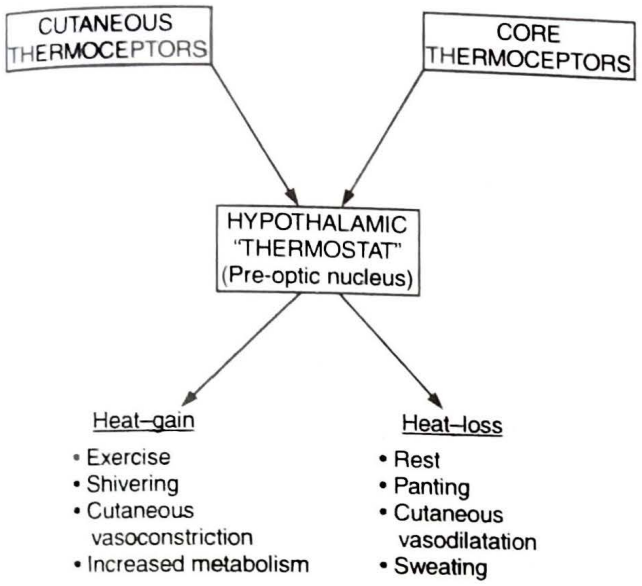

Fig. 2.7.3: Regulation of body temperature.

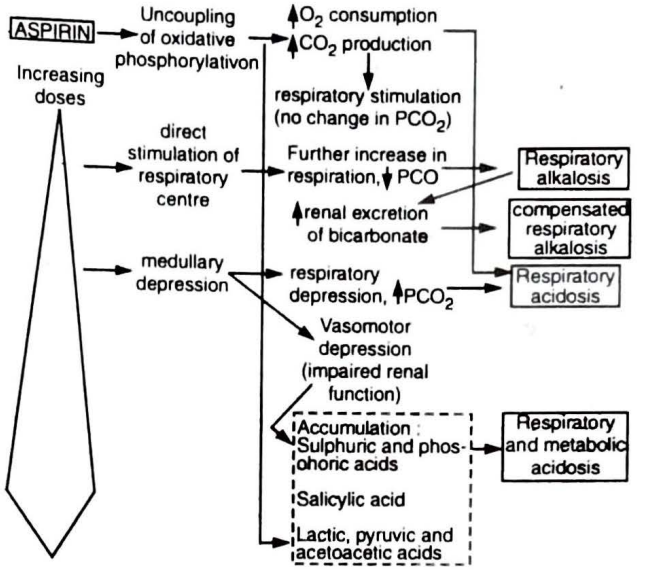

Fig. 2.7.4: Acid-base disturbances caused by increasing doses of aspirin (see text).

acute rheumatic fever the response is dramatic. The pain and fever are reduced and the joint inflammation settles down. The mechanism of antirheumatic action is unclear. It was suggested that salicylates stimulate the adrenocortical hormones *cortisone* and *hydrocortisone*, which have potent anti-inflammatory activity. However, this theory has lost favour now due to contradictory evidence. The view now held is that the salicylates directly check some steps in the sequence of the inflammatory process, *e.g.*, keeping *bradykinin* and *prostaglandin* from being released to cause vasodilation, increased capillary permeability and pain. The salicylates and other antirheumatic drugs like the corticosteroids, may also prevent the release of ***lysosomal enzymes*** which destroy the cartilage of rheumatic joints.

Antipyretic action. Body temperature is controlled from a hypothalamic integrating centre (thermostat), which detects changes in the deep body (core) and environmental (cutaneous) thermoceptors and then adjusts the functioning of peripheral effectors. This dynamic equilibrium is maintained through the cutaneous blood vessels, sweat glands and other peripheral structures **(Fig. 2.7.3).**

Fevers caused by bacterial endotoxins or viruses, are caused by endogenous pyrogens which act directly upon the thermoregulatory neurones in the hypothalamus to increase the set point tempterature. The effectors raise the core temperature so that it is higher than normal. In this febrile process mainly the prostaglandin (PGE_2) is involved.

Salicylates have a marked antipyretic action, and reduce elevated body temperature (normal body temperature is not reduced). This is usually accompanied by profuse sweating, and is believed to be due to inhibition of the synthesis and release of prostaglandin E in the ***pre-optic nucleus of the hypothalamus,*** which is the site of the temperature regulating area. PGE_2 has a strong pyrogenic action and is thought to be released in the brain by circulating pyrogens, as the level of this prostaglandin increases in the CSF during fever, and aspirin effectivity blocks this rise.

Respiration and acid-base balance. The salicylates cause serious acid-base imbalances. They increase respiratory rate and volume by two mechanisms: (*i*) by a ***direct*** stimulation of the respiratory centre, and (*ii*) by ***uncoupling oxidative phosphorylation*** causing increased oxygen utilization and production of carbon dioxide. Even in therapeutic doses the increased respiratory rate can be appreciated, and it becomes very obvious after aspirin overdosage. As a secondary effect respiratory alkalosis occurs. In very high doses the respiratory centre is depressed, and salicylates cause central respiratory paralysis.

As mentioned above, initially in therapeutic doses salicylates cause *respiratory alkalosis*. The kidney compensates by excretion of bicarbonate accompained by an increased excretion of sodium and potassium. As a result plasma bicarbonate falls, and blood pH returns towards normal. This is the stage of *compensated respiratory alkalosis*. Further, in toxic doses the respiratory centre in the medulla is depressed, and there is an enhanced production of CO_2; consequently the plasma PCO_2 increases and the blood pH decreases. Since the plasma bicarbonate is already low, the acid–base status at this stage is essentially an *uncompensated respiratory acidosis*. Superimposed however, is a *true metabolic acidosis* caused by accumulation of acids as a result of : (*i*) displacement of plasma bicarbonate by salicylic acid derivatives; (*ii*) vasomotor depression by toxic doses impairs renal function leading to accumulation of strong acids of metabolic origin; and (*iii*) organic acids accumulate as a result of salicylate-induced derangement of carbohydrate metabolism, like pyruvic acid, lactic and acetoacetic acids. Such a state further enhances metabolic acidosis **(Fig. 2.7.4).**

The acid–base disturbances also cause alterations of *water* and *electrolyte balance*. In addition water is lost by salicylate-induced sweating, and insensible water loss due to hyperventilation, leading to **dehydration.** High doses of salicylates also cause potassium depletion due to renal and extrarenal factors.

Gastrointestinal effects. Ingestion of aspirin can cause dyspepsia in a number of patients. The symptoms to some degree are dose-related, but can occur with minimal doses. The gastric mucosa shows gastritis with *superficial gastric ulceration*. Solid particles of the drug are particularly damaging and can cause severe gastric bleeding, which is painless, and frequently leads to blood loss in the stool and

occasionally to an iron-deficiency anaemia. In most cases blood loss is not significant, and is less than 15 ml daily. Bleeding is increased if aspirin is taken with alcohol, and reduced if taken with antacids.

The mechanism by which aspirin causes gastric erosion is not fully understood, but it may act by *precipitating the gastric mucus, thereby allowing the H^+ ions to attack the mucosa.* Further, the inhibition of prostaglandin synthetase and consequent decrease in mucosal prostaglandin levels allows ulceration to occur (Prostaglandins of the E series have an anti-secretory and anti-ulcer activity). However, gastric acidity does play an important role in causing gastric ulceration and erosion.

Cardiovascular effects. Therapeutic doses of salicylates have no important direct cardiovascular actions. The peripheral vessels dilate after large doses, due to a direct effect on the smooth muscle. Toxic amounts depress the circulation directly, and by a central vasomotor paralysis. In cases of acute rheumatic fever with carditis, very high doses of salicylates may cause congestive heart failure and pulmonary oedema.

Hepatic and renal effects. Salicylates elevate enzyme activities in the plasma which indicate hepatic dysfunction (SGOT, SGPT, alkaline phosphatase), and occasionally hepatomegaly occurs. In severe salicylate intoxication, fatty infiltration of the liver and kidney may occur. Aspirin should be avoided in patients with severe hepatic damage, hypoprothrombinaemia, vitamin K deficiency or haemophilia, because inhibition of platelet function can lead to bleeding.

Aspirin causes shedding of the renal tubular epithelial cells into the urine, which lasts for a few days with continued administraton of the drug. However, prolonged salicylate dosage can cause *permanent renal damage.*

Platelet antiaggregatory action. Platelet aggregation is inhibited by aspirin, but not to a significant extent by other salicylates. This difference is probably due to the acetyl group of aspirin, which is capable of *irreversibly inhibiting platelet cyclo-oxygenase and the subsequent synthesis of thromboxane A_2* for the entire life of the platelet (8–11 days). As thromboxane A_2 is a vasoconstrictor, and facilitates platelet aggregation, the inhibition of its synthesis *reduces platelet aggregation.* Other salicylates only have a weak and transient inhibitory effect on platelet cyclo-oxygenase, and thromboxane synthesis is only briefly interrupted.

Low doses of aspirin are more effective in reducing platelet aggregation than high doses. This is because synthesis of *platelet thromboxane* is more sensitive to inhibition by aspirin than synthesis of *vessel wall prostacyclin (PGI_2),* a substance that inhibits platelet aggregation. Doses of aspirin (40 to 80 mg/day) reduce thromboxane A_2 levels upto 95 percent, while prostacyclin levels are decreased by only 35 percent. Therefore, the *prostacyclin : thromboxane A_2 ratio* is markedly increased, and platelet aggregation is prevented. Higher doses (325 mg/day) almost completely block *both* vessel wall prostacyclin and platelet thromboxane synthesis, and the acute antiaggregatory effects of prostacyclin are lost. However, because prostacyclin activity is only temporarily interrupted, while thromboxane A_2 activity is impaired for the life of the platelet, even larger doses of aspirin can result in a favourable prostacyclin: thromboxane A_2 ratio with continued use when aspirin is given every 2 to 3 days rather than once or twice daily.

Several other non-salicylate drugs, like *dipyridamole* and *sulfinpyrazone* also exhibit platelet antiaggregatory action **(Chap. 4.5).**

Endocrine effects. High doses of salicylates release adrenaline from the adrenal medulla and very large doses stimulate ACTH secretion from the anterior pituitary, by an action on the hypothalamus. The plasma levels of adrenocorticosteroids transiently increase, mainly by displacement from plasma proteins. *However, there is ample evidence that the anti-inflammatory actions of salicylates are independent of the effect on the pituitary-adrenal axis, and corticosteroids.* The plasma protein-bound iodine (PBI) level is decreased by chronic taking of aspirin. In diabetes mellitus, *aspirin lowers the blood glucose level,* probably by an increased peripheral utilization of glucose. With large doses, however, the release of adrenaline may cause hyperglycaemia.

Metabolic effects. The salicylates affect many metabolic processes, and only a few salient aspects are presented below:

Oxidative phosphorylation. The salicylates uncouple oxidative phosphorylation in manner similar to 2, 4-dinitrophenol. This effect is evident in man in doses employed for rheumatoid arthritis. As a result of uncoupling, a number of adenosine triphosphate (ATP)-dependent reactions are inhibited. There is an increased oxygen uptake and CO_2 production. Hepatic glycogen is depleted. Salicylates in toxic doses decrease aerobic metabolism.

Carbohydrate metabolism. In large doses the salicylates may cause *hyperglycaemia* and *glycosuria* and deplete liver and muscle glycogen. These effects are partly explained by secretion of adrenaline and glucocorticoids from the adrenal gland.

Fat metabolism. The salicylates reduce lipogenesis, partly by blocking the incorporation of acetate into fatty acids. They also *antagonize adrenaline-induced lipolysis* in fat cells. The combination of these effects leads to incresed entry and enhanced oxidation of fatty acids in muscle, liver and other itssues, causing a fall in the plasma levels of free fatty acids (FFA), phospholipids and cholesterol.

Nitrogen metabolism. The salicylates in toxic doses cause a negative nitrogen balance, characterized by an aminoaciduria. Adrenocortical activation contributes to this negative nitrogen balance by enhancing protein catabolism.

Uricosuric effect. In suitable doses the salicylates increase the urinary excretion of urates, and they were once used in the treatment of acute and chronic gout. Low doses may actually decrease urate excretion, and elevate plasma urate concentrations.

Salicylates and pregnancy. There is no evidence that salicylates cause foetal damage in humans, although babies born to women who ingest salicylates chronically have a *low birth weight.* Endogenous prostaglandin release is probably partly responsible for causing uterine contractions in the process of normal labour. Drugs like aspirin and indomethacin which inhibit prostaglandin synthesis are likely to prolong normal parturition.

Local effects. Salicylic acid is an irritant to the skin and mucosa and destroys epithelial cells. The *keratolytic action* of salicylic acid is used for the local treatment of corns, warts, fungal infections and certain types of eczematous dermatitis. The tissue cells soften, swell and desquamate. Salts of

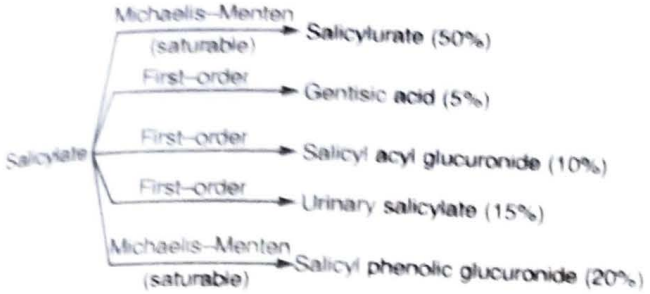

Fig. 2.7.5: The scheme of salicylate metabolism.

salicylic acid are non-irritating to the skin and mucosa, however if free acid is released, as in the stomach, the mucosa may be irritated. *Methyl salicylate* (oil of wintergreen) is irritating both to the skin and mucosa. It is only used externally, in liniments as a *counterirritant*.

Pharmacokinetics

Orally ingested salicylates (aspirin and sodium salicylate) are absorbed rapidly, partly from the stomach, but mostly from the upper small intestine. The rate and extent of absorption depends on the *disintegration and dissolution rate* of the tablets, the *pH of the mucosal surface*, and *gastric emptying time*. Appreciable plasma concentrations are reached within 30 minutes, after a single dose, and a peak is reached within 2 hours followed by a gradual decline. The pharmacokinetics of salicylate elimination is complex. The t½ of the salicylate lengthens as the dose increases; doses of 300 to 650 mg have a t½ of about 3 hours; with doses of 1 g the t½ is increased to 5 hours; and with 2 g is increased to about 9 hours (see later). In addition, as the t½ increases, urinary excretion decreases. Thus, increasing the dose without increasing the interval between doses may result in *accumulation* and *toxicity* of the drug.

After absorption, salicylates are distributed throughout most body tissues and fluids, primarily by pH dependent passive processes. Salicylates cross the blood-brain barrier slowly as a large fraction of the drug is ionized. They are considerably bound (80–85%) to plasma proteins, mainly albumin. Salicylates may also affect the protein binding of other drugs (see interactions).

Salicylates are metabolized mainly in the liver by five parallel pathways, two of which are saturable, and are also excreted unchanged by a first-order process **(Fig. 2.7.5)**. The formation of *salicylurate* is noteworthy, as it is one of the few drug metabolism mechanisms which occur in the mitochondria, and is easily saturable. Because of the saturable nature of some of the pathways, the percentage of products formed is variable, and those mentioned in the scheme are approximate.

Based on the scheme of salicylate metabolism, it has been observed that for doses lower than 4 mg/kg the plasma disappearance of salicylate follows *first-order kinetics*, and the t½ is 2 to 4 hours, but for higher doses the elimination is overall non-linear and the t½ may be 15 to 30 hours **(Chap. 1.5)**. Salicylate elimination is mainly via the urine, and is influenced by urinary pH, the loss being greater if the urine is alkaline. Optimal therapy is best achieved by individualization of dosage using plasma salicylate estimations. When used in *rheumatoid arthritis*, the effective plasma level is 200–250 mcg/ml. This is very close to the level at which salicylism (300 mcg/ml) appears. The level for adequate analgesia has not been established.

Therapeutic Uses

1. ***Analgesia***. Aspirin is used for the relief of mild to moderate pain of musculoskeletal origin, *e.g.*, *headache*, *myalgia*, *neuralgia*, *toothache*, *dysmenorrhoea* and *backache*.
2. ***Antipyresis***. Aspirin lowers elevated body tempeature (pyrexia). The antipyretic response is non-specific, and offers only a symptomatic relief. Use of aspirin should be avoided in cases of very high fever (hyperpyrexia), as it may produce a *shock-like state* due to profuse sweating and a sudden fall in body temperature. In hyperpyrexic patients the temperature should first be brought down by tepid water sponging (hydrotherapy).
3. ***Anti-inflammatory activity***. Salicylates may be used for various inflammatory conditions, *e.g.*, *rheumatoid arthritis*, *osteoarthritis*, *bursitis*, and *acute rheumatic fever*. Large doses of aspirin (3 g to 7 g/day) are usually necessary, and therapy is palliative. The plasma salicylate level should be maintained between 250 and 300 mcg/ml to effecitvely suppress the rheumatic process.
4. ***Prophylaxis*** of thromboembolic complications like *venous emboli* and *cerebral ischaemia* associated with cardiovascular disorders. It does not benefit patients of completed stroke. Aspirin reduces the risk of *transient ischaemic attacks* (TIA) in men, but effectiveness in women is doubtful.
5. ***Prevention of re-infarction*** in patients with previous history of *acute myocardial infarction* or *unstable angina*.

Contraindications and Precautions

Salicylates are contraindicated in cases of *salicylate hypersensitivity*, *haemophilia*, *bleeding ulcers*, and *other haemorrhagic states*. The *Reye's syndrome*, a rare but life threatening disease, has been linked with the use of aspirin and other salicylates in children under the age of 12 years who have *influenza* or *chickenpox*. Thus, salicylates are not recommended in children with influenza or smallpox. *Cautious use* is desirable in patients with gastric ulcers, anaemia, impaired hepatic or renal functions, asthma, nasal polyp, and in pregnant or nursing mothers.

Preparations and dosage of salicylates. The various preparations and usual dosage range of salicylates are listed in **Table 2.7-1.**

Adverse Reactions

The most frequent side effects with salicylates are *heartburn*, *nausea* and *gastric distress*. These can be overcome by taking the drug with food, a full glass of water, an antacid or in one of the enteric-coated dosage forms **(Table 2.7-1)**. Serious GI reactions occur with high doses, and include bleeding and mucosal ulceration.

1. ***Salicylism***. Large doses of salicylates result in this syndrome, characterized by headache, dizziness, tinnitus, confusion, sweating, deafness, palpitation and hyperventilation. These symptoms indicate the upper limit of the tolerable dose, and can be reversed by reducing the dose.

Table 2.7-1. *Preparations and dosage of salicylates*

Drug	*Preparations*	*Dosage Range*	*Comments*
Aspirin	Tablets, Gum Tablets, Enteric-coated tablets, Timed-release tablets, Enteric-coated capsules, Suppositories	*Adults* : Pain, fever – 325 to 650 mg Inflammation 3–7 g/day Transient ischaemic attacks 40–1300 mg/day Prevention of myocardial infarction –325 mg/day *Children*: Pain, fever – 65 mg/kg/day in divided doses Inflammation – 90–130 mg/kg/day in divided doses	Keep aspirin in a cool, dry place, do not use if vinegar-like odour is detected; use suppositories for a vomiting patient
Calcium carbaspirin	Tablets	400-800 mg	Readily soluble but a less potent aspirin complex
Choline salicylate (Arthropan)	Liquid – 870 mg/5 ml	1 teaspoonful every 3 to 4 hours Rheumatoid arthritis –1 tsp to 2 tsp upto 4 times a day	Liquid preparation giving more rapid absorption and less gastric irritation
Diflunisal (Dolobid)	Tablets – 250, 500 mg	Pain – 250–500 mg initially followed by 250 mg every 8 to 12 hours Rheumatoid arthritis/osteoarthritis – 500 mg to 1 g daily in 2 divided doses (maximum 1500 mg/day)	A salicylic acid derivative *not* metabolized to salicylic acid; platelet inhibitory effect is dose related and reversible; at 1 g/day the bleeding time is only slightly increased; anti-inflammatory efficacy is equal to 2–3 g/day of aspirin, with less GI distress; not to be used in children under 12 years of age
Magnesium salicylate (Magan)	Tablets – 325, 545, 600 mg	Pain – 600 mg 4 times a day Rheumatic fever – upto 9.6 g/day	A sodium-free salicylate with lower incidence of GI upset
Methyl salicylate (oil of wintergreen)	10% to 50% in Ointment or Liniment	Applied topically as a *counterirritant* to relieve muscular and rheumatic pain	Significant absorption can occur through skin and produce untoward effects; very toxic if ingested orally
Salicylic acid	Cream – 2.5, 10% Ointment – 25, 40, 60% Gel – 6, 17% Soap – 3.5% Liquid – 13.6, 17% Plaster – 40%	Applied to the affected area at night, and wash off in the morning	Used topically as a *keratolytic* agent for psoriasis, acne, keratosis, fungal infections, or other conditions requiring removal of dead skin; skin must be hydrated for 5 minutes prior to use, may cause irritation or burning of skin; may be applied as an ether-alcohol or a colloidian solution (Freezone) for removal of corns, warts and calluses; avoid contact with eyes and mucous membranes
Salsalate (Salflex)	Tablets – 400, 750 mg Capsules – 500 mg	3 g/day in divided doses	Primarily used for rheumatoid arthritis and other rheumatic conditions; low incidence of GI upset
Sodium salicylate (Uracel)	Tablets – 325, 650 mg Enteric-coated Tablets – 325, 650 mg Injection – 1g/10ml Injection – 50 mg/ml	325 to 650 mg every 4 to 8 hrs as needed	Irritating to GI mucosa; less effective than an equal dose of aspirin
Sodium thiosalicylate (Thiocyl)	Injecton – 50 mg/ml	Analgesia – 50 to 100 mg daily Rheumatic fever – 100 to 150 mg every 4–6 hours for 3 days, then 100 mg bid Acute gout – 100 mg every 3 to 4 hours for 2 days, then 100 mg/day	Readily absorbed after IM injection, occasionally used for acute stages of rheumatic fever

2. ***Haemorrhage***. Major GI bleeding has been estimated to occur in 15 out of 100,000 chronic users of aspirin per year.
3. ***Hypersensitivity*** reactions range from rash and pruritus to bronchoconstriction, oedema and shock. Fixed drug eruptions and rhinorrhoea may occur in aspirin-sensitive persons.
4. ***Reye's syndrome***. Use of salicylates, specially aspirin in children with *influenza* or *chickenpox* has been associated with Reye's syndrome, a life-threatening condition marked by initial severe vomiting, lethargy, delirium, coma and death. Mortality rate is about 25 percent, and permanent brain damage is common in survivors. A definite causal relationship to salicylates has *not* been confirmed, but aspirin and other salicylates are not recommended in children below 12 years with influenza or chickenpox.
5. Other adverse reactions include *renal dysfunction*, delirium, hallucinations, *respiratory* alkalosis followed by *acidosis*, acid–base disturbances, hyperthermia, petechial haemorrhages, hypokalaemia, convulsions, respiratory failure, coma and death.
6. *Drug interactions*. Many interactions are likely to occur: (*i*) by competing with protein-binding sites, the metabolites of aspirin enhance the actions and toxicity of *oral anticoagulants*, *heparin*, *naproxen*, *oral antidiabetics*, *phenytoin*, *thiopental*, *indomethacin*, *methotrexate*, and *valproic acid*; (*ii*) aspirin in small doses can inhibit the uricosuric action of probenecid and sulfinpyrazone; (*iii*) the effects of aspirin are enhanced or prolonged by drugs that acidify the urine, *e.g.*, ascorbic acid, ammonium chloride, and decreased by urinary alkalinzers, *e.g.*, sodium bicarbonate; (*iv*) aspirin may increase the risk of bleeding with oral anticoagulants and antiplatelet aggregatory drugs; (*v*) *phenobarbital* may decrease the efficacy of aspirin by enzyme induction; (*vi*) the antihypertensive action of *beta-blockers* is lessened possibly due to prostaglandin inhibition; (*vii*) the incidence of GI-distress and bleeding is increased by steroids, alcohol, indomethacin, pyrazolones, and other anti-inflammatory drugs; (*viii*) *furosemide* may decrease salicylate excretion, resulting in toxicity at lower doses; (*ix*) salicylates have a hypoglycaemic action and may *potentiate* the effects of insulin and sulphonylureas; (*x*) aspirin may lower the clinical effectiveness of nonsteroidal anti-inflammatory drugs; and (*xi*) antacids and activated charcoal can reduce the oral absorption of aspirin.

Salicylate Poisoning

Because of the easy availability of salicylates in the household, salicylates are a frequent cause of intoxication in children. In adults the intoxication is generally ***accidental*** or ***suicidal***. A single dose of 10–30 g of aspirin or sodium salicylate is the usual lethal dose for adults, but at times much larger amounts have been ingested without a fatal outcome. The lethal dose of methyl salicylate is much lower, and 4 ml (4.7 g) of it may be fatal in children. ***Acute intoxication*** is manifested by early signs of CNS stimulation including hyperventilation; later complex acid–base imbalances and petechial haemorrhages occur.

Symptoms and signs. Gastrointestinal symptoms like *epigastric distress*, *nausea*, *vomiting*, *anorexia* and *abdominal pain* are often conspicuous. A more severe intoxication is characterized by CNS abnormalities and skin eruptions. *Restlessness*, *apprehension*, *vertigo*, *tremors*, *hallucinations*, *convulsions* and *coma* may occur. Fever is usually prominent, specially in children. Dehydration occurs as a result of hyperpyrexia. Disturbances of acid-base balance, and electrolytes of the plasma occur, as discussed earlier. Haemorrhagic phenomena are evident due to hypoprothrombinaemia. Dangerous hypoglycaemia may occur in children.

Treatment. The patient should be hospitalized, and blood obtained for plasma salicylate determination and electrolyte studies. *Gastric lavage*, *alkalinization*, *diuresis* and *intensive supportive measures* are necessary to treat salicylate poisoning. Because of the peculiarities of salicylate metabolism (see above), elevated plasma levels fall very slowly. ***Activated charcoal*** reduces the absorption of salicylate from the gut. Hyperthermia and dehydration need immediate management, for which external sponging with tepid water or alcohol provides quick relief, and adequate amount of intravenous fluids must be given. ***Bicarbonate solutions*** must be infused intravenously to maintain alkaline diuresis. Glucose is administered intravenously to correct ketosis and hypoglycaemia. If potassium deficiency occurs, the cation K^+ should be added to the intravenous fluids. ***Plasma transfusion*** may be beneficial. Haemorrhagic phenomena may necessitate ***whole-blood transfusion*** and vitamin K (phytonadione). In very severe intoxication, extrarenal measures like *exchange transfusion*, *peritoneal dialysis*, *haemodialysis* and *haemoperfusion* are most effective in removing the salicylate from the system. Thus, treatment of salicylate poisoning is an acute medical emergency.

Diflunisal (Dolobid). This agent (5-2, 4-difluorophenyl)-salicylic acid is a close relative of aspirin, which has analgestic-antipyretic, and anti-inflammatory properties. It probably acts by prostaglandin synthetase inhibition, and is slightly more effective than aspirin as an analgesic, and is better tolerated than aspirin in the treatment of *osteoarthritis*, *rheumatoid arthritis*, and *musculoskeletal pain*.

Sulfasalazine (Salazopyrin)

Sulfasalazine (salicylazosulfapyridine) contains two compounds–sulfapyridine and 5-aminosalicylic acid, joined by an azo bond. It was originally introduced for the treatment of *ulcerative colitis*, but was later shown to be effective in patients of *rheumatoid arthritis*. Its pharmacokinetics is complex. Its primary metabolites are 5-acetylsalicylic acid (5-ASA) and sulfapyridine. The current view held is that 5-ASA is the active agent in the inflammatory bowel disease *ulcerative colitis*, and either sulfapyridine alone or sulfapyridine with the parent drug are active in *rheumatoid arthritis*. The *mode of action* in rheumatoid arthritis is probably *not* as a dihydrofolate inhibitor, though effect on B cell function may be important. This drug is approved by the FDA, USA for use in rheumatoid arthritis, and is a frequently used drug in Europe. Efficacy may depend on the immunosuppressive properties, affinity for connective tissue, and the high concentrations reached in the intesinal wall, serous fluids and liver. *Dosage* is 2 g/day in 4 divided doses. *Adverse reactions* include dizziness, rashes, photosensitivity, anorexia, nausea, and vomiting. Rarely neutropenia, hypersensitivity pneumonitis, and sterility may occur.

Mesalazine is 5-aminosalicylic acid, and it inhibits

prostaglandin G/H synthetase and lipoxygenase. Its precise *mode of action* in ulcerative colitis is illunderstood. *Initial* adult dose is 2.4 g daily in divided doses followed by 1.2 to 2.4 g daily for maintenance of remission. *Adverse effects* include nausea, abdominal pain, watery diarrhoea, and interstitial nephritis.

Olsalazine consists of 2 molecules of mesalazine linked with an azo bond. It is activated by the colonic bacteria to mesalazine, and used in the management of *ulcerative colitis*. The usual dose for remission is 500 mg bid daily. Doses should be taken with food. *Adverse effects* include watery diarrhoea, abdominal pain, dyspepsia, headache, arthralgia, and skin rashes.

Non-salicylates

Para-aminophenols

The parent compound of this group of analgesics is *acetanilide*, but it is no longer used because of its excessive toxicity, as it causes cyanosis due to methaemoglobinaemia.

Paracetamol (Acetaminophen, N-Acetyl-para-amino-phenol, Calpol)

Paracetamol is the major metabolite of phenacetin and has similar analgesic–antipyretic actions, but it does not possess any anti-inflammatory or antirheumatic activity. It has no effect on platelets or blood-clotting mechanisms. Its site of analgesic action is incompletely understood. Paracetamol is a week inhibitor of peripheral prostaglandin synthetase, and is as potent as aspirin in inhibiting the brain prostaglandin synthetase. Thus, it has been suggested that a central site of action is probably involved. It is antipyretic presumably due to its effects on brain prostaglandins. Paracetamol is a popular analgesic, used as a substitute for salicylates in patients who have peptic ulcer disease, or who are unable to tolerate aspirin.

Pharmacokinetics. The absorption rate and relative bioavailability of paracetamol are increased by concomitant administration of metoclopramide, and there is a significant relationship between gastric emptying and absorption. Diurnal variation in absorption rate is evident with reduced absorption at night. It is bound to plasma proteins (25–50%) to a much lesser degree than the salicylates. It is evenly distributed throughout the body. The major metabolites are sulphate and glucuronide which are excreted in the urine. Paracetamol has a $t_{1/2}$ of about 2 hours.

Therapeutic uses. Paracetamol is a mild analgesic-antipyretic, with little, if any, anti-inflammatory properties. It does not irritate the gastric mucosa, and has therefore been employed as a ***substitute for aspirin***. Its use has much increased recently, because it is thought to be less toxic than the salicylates. The usual adult dose is 0.5 to 1 g (1–2 tablets) repeated 4–6 hourly to maintain analgesia.

Adverse effects include drug rashes, methaemoglobinaemia, and blood dyscrasias occasionally. Unlike aspirin, which in small doses may interfere with uric acid excretion, paracetamol does not antagonize the uricosuric action of probenecid. As paracetamol has no anti-inflammatory activity, it cannot be used as a substitute for salicylates in the treatment of acute rheumatic fever. On prolonged usage, or overdosage or abuse, ***paracetamol liver damage*** may occur. Hepatotoxicity is caused by a toxic metabolite of paracetamol, N-acetyl-p-benzoquinone, which is inactivated by conjugation with *glutathione*. Thus glutathione is ultimately depleted and the toxic metabolite causes necrosis of liver cells. Kidney tubules may also be damaged. ***Treatment*** consists of administering agents which increase glutathione in liver cells, like ***acetylcysteine;*** and agents which increase conjugation reactions like ***methionine*** and ***cysteamine***. Paracetamol has resulted in agranulocytosis in a few cases.

Analgesic Nephropathy

The non-narcotic analgesics have been in use for many years. Phenacetin was introduced in 1887, paracetamol in 1893, and aspirin in 1899. Much later in 1953 postmortem studies revealed that high consumption of non-narcotic analgesics increased the incidence of chronic renal disease manifested as ***papillary necrosis, interstitial fibrosis*** and ***tubular atrophy***. Later, this relationship between analgesic abuse and renal disease was confirmed the world over. This problem is still incompletely resolved. The difficulties being: (*i*) the usual analgesics taken are mixtures of drugs, and it is difficult to point out the culprit, and (*ii*) results of animal experiments cannot be safely projected on to man.

The *papillary necrosis* is possibly due to ischaemia caused by damage to the vasa recta. Renal tubules passing into the necrotic papillae are obstructed and undergo atrophy, and *interstitial fibrosis* follows. Originally, ***phenacetin*** was thought to be the causative agent. But more recently nephrotoxicity has also resulted in patients after taking ***aspirin*** or ***paracetamol*** for long periods. There is evidence that *analgesic mixutres* are more likely to produce renal damage than single agents.

Analgesic nephropathy occurs most commonly in middle aged individuals who have been heavy consumers of analgesics over several years. They develop a form of ***dependence*** on the drugs, usually taken for medical reasons, as for the treatment of chronic arthritis. The disease may present as progressive renal failure, hypertension and recurrent urinary infection. Anaemia due to chronic loss of blood from the gut caused by aspirin may be evident. ***Treatment*** consists of stoppage of analgesics and symptomatic therapy.

Pyrazolones

This group includes *antipyrine, aminopyrine, phenylbutazone, oxyphenbutazone* and *sulphinpyrazone*. The earliest members of this group were antipyrine and aminopyrine, but they are not used now because of their potential bone marrow toxicity in the form of *agranulocytosis*. The other safer members are discussed below.

Phenylbutazone (Butazolidin)

Phenylbutazone (originally used as a solubilizing agent for aminopyrine) was introduced in 1949 for the treatment of rheumatoid arthritis and allied disorders. It has ***analgesic–antipyretic*** and ***anti-inflammatory*** properties similar to aspirin, but is much more toxic, which limits its use in long-term therapy. In doses of about 600 mg/day, phenylbutazone has mild ***uricosuric*** effect in man, as a result of diminished tubular reabsorption or uric acid. In low doses it diminishes uric acid secretion, and causes urate retention. Its congener, ***sulphinpyrazone*** is a much more effective uricosuric agent, and is useful in the treatment of chronic gout (see later). Phenylbutazone causes

significant retention of salt and water, and oedema may result. It also inhibits iodine uptake by the thyroid gland, and myxoedema may occasionally occur.

Pharmacokinetics. Phenylbutazone is rapidly and completely absorbed from the gastrointestinal tract, but rectal absorption is erratic. Peak concentration is reached in 2 hours. It is 98 percent bound to plasma proteins. The plasma $t_{1/2}$ is 50–100 hours. The drug penetrates into synovial spaces, and reaches a concentration of about one-half of that of plasma, and may persist in the joints for upto 3 weeks after stoppage of therapy. Phenylbutazone is extensively metabolized in the liver, the most important reactions being glucuronide formation, and hydroxylation to ***oxyphenbutazone***, which has similar properties to phenylbutazone (see later). Phenylbutazone and its metabolite oxyphenbutazone are slowly excreted in urine. There is no consistent relationship between the plasma level of phenylbutazone and its clinical or toxic effects.

Therapeutic uses. Phenylbutazone is a powerful anti-inflammatory agent due to its ability to inhibit prostaglandin synthesis. It is however, a weaker analgesic, and has some uricosuric action. Serious side effects are not uncommon, and its use should be restricted to certain types of pain. The initial dose is 400 mg daily orally in divided doses with meals to lessen gastric irritation, and is reduced to a minimal dose which will control the symptoms. Suppositories containing 250 mg are also available. *Phenylbutazone is used in the following conditions, only after other drugs have failed, and after careful consideration of the risks involved (benefit: risk ratio).* Generally, use of phenylbutazone should be limited to 1 week.

1. *Acute gout.* It is an effective alternative to colchicine in acute gout as a short course.
2. *Ankylosing spondylitis.* It is probably the most effective drug to relieve pain in this condition. The minimum required dose should be given. Brief courses of the drug are safer in *ankylosing spondylitis* and *osteoarthritis.*
3. *Rheumatoid arthritis.* Numerous other agents are available for the symptomatic treatment of this disorder; many of them less toxic than phenylbutazone. Hence, it should be used only when others have failed.
4. *Superficial thrombophlebitis.* A short course relieves discomfort and possibly promotes resolution.

Adverse reactions. Phenylbutazone is poorly tolerated by many patients, and side effects are noted in upto 45 percent of cases. Nausea, vomiting, epigastric discomfort, skin rashes, diarrhoea, insomnia and haematuria may occur. Salt and water retention, oedema formation and heart failure occurs in patients with impaired cardiac function.

More serious adverse effects include ***peptic ulceration,*** or reactivation of a healed ulcer, with haemorrhage and perforation; hypersensitivity reactions like serum sickness; ulceration, stomatitis, hepatitis and nephritis ***Bone marrow depression*** leading to aplastic anaemia, leucopenia, agranulocytosis and thrombocytopenia, may occur. Bone marrow depression is usually but not always reversible on stoppage of the drug. Cases of ***fatal aplastic anaemia*** and ***agranulocytosis*** have been reported. Thus phenylbutazone is a toxic drug.

Drug interactions. Phenylbutazone is a highly protein-bound acidic drug, and it displaces *oral anticoagulants, oral hypoglycaemics, sulphonamides* and other anti- inflammatory agents from their protein-binding sites. The result being an increased pharmacologic or toxic effects of the displaced drug. In addition, phenylbutazone may cause induction of hepatic microsomal enzymes. It increases the effect of *insulin.* Oral absorption of phenylbutazone is reduced by concurrently administering *cholestyramine. Contraindications* include hypersensitivity, cardiac and renal dysfunction, first trimester of pregnancy, peptic ulcertaion, gut bleeding, oedema, hypertension and cardiac decompensation.

Oxyphenbutazone (Suganril)

Oxyphenbutazone, the hydroxy analogue of phenylbutazone, is one of the active metabolites of the parent drug. It has the same profile of pharmacological activity, therapeutic uses, toxicity, interactions and contraindications as phenylbutazone. It is claimed to be a *lesser* gastric irritant than phenylbutazone. Oxyphenbutazone has not been shown to be superior to phenylbutazone. It is available in 100 mg tablets, and the dosage is similar to that of phenylbutazone (see above).

Apazone (Azapropazone). This is a pyrazolone derivative, with aspirin-like activity, and a profile of activity and mode of action similar to that of phenylbutazone. In addition, apazone is a potent *uricosuric* agent, and may be particularly useful in the treatment of *acute gout.* It is generally well tolerated by the patient. It has been recommended for the treatment of *rheumatoid arthritis* and *osteoarthritis.* The usual dose is 1200 mg/day in 2 divided doses.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

In a search for effective anti-inflammatory drugs with *lesser* toxicity than the older established NSAIDs (salicylates and pyrazolones), several organic acids were shown to have a lower incidence of side effects like tinnitus and GI distress, than comparably effective doses of the salicylates or pyrazolones. These compounds have been termed as *nonsteroidal anti-inflammatory drugs* (NSAIDs). Out of these substances, *indomethacin* is considerably more toxic than the rest. The NSAIDs belong to various chemical classes, and display significant differences in their pharmacokinetic properties **(Table 2.7-2.)**

The relative *nephrotoxicity* among NSAIDs is indomethacin >fenoprofen >ibuprofen = mefenamic acid = naproxen >piroxicam = sulindac = tolmetin.

The NSAIDs possess *analgesic* and *antipyretic* properties, but should *not* be used for minor headaches or pyrexia in place of aspirin or paracetamol. However, with the exception of *indomethacin* and *meclofenamate,* the NSAIDs may be used for relieveing other types of mild to moderate pain like *dysmenorrhoea, postextraction dental pain, episiotomy pain* and *soft-tissue athletic injuries,* in addition to their use as anti-inflammatory drugs. Their action in inflammatory states is to reduce joint swelling, pain, stiffness, and to increase the functional capacity of the joint. However, they do not alter the course of the underlying disease. It is noteworthy that aspirin should *not* be combined with NSAIDs because it can decrease the blood level and activity of these non-aspirin drugs. Likewise, their combination with corticosteroids is not more effective than either drug alone.

Table 2.7-2. *Pharmacokinetic parameters of nonsteroidal anti-inflammatory drugs (NSAIDs)*

Drug	Peak Blood Levels (hrs)	Plasma Half-life (hrs)	Single Dosage Range (mg)	Dosage Interval (hrs)
Indole derivatives				
Indomethacin (Indocin)	1–2	4–6	25–50	6–8
Sulindac (Clinoril)	1–2	8–16	150–200	12
Tolmetin (Tolectin)	0.5–1	1–3	200–400	4–6
Etodolac (Lodine)	1–2	7	200–300	4–6
Propionic acid derivatives				
Ibuprofen (Brufen)	1–2	1.5–2.5	400–800	6–8
Fenoprofen (Nalfon)	1.5–2	2–3	300–600	6–8
Ketoprofen (Orudis)	0.5–1.5	2–4	25–50	6–8
Naproxen (Naprosyn)	2–4	12–15	250–375	8–12
Flurbiprofen (Flurofen)	0.5–4	3–8	100–150	6–12
Oxaprozin (Daypro)	3–5	40–60	1200	24
Fenamates				
Mefenamic acid (Ponstan)	2–4	2–4	250–500	4–6
Meclofenamate (Meclomen)	0.5–1.5	2–3	200–400	4–6
Phenylacetic acid derivative				
Diclofenac (Voveran)	2–3	1.5–2.5	25–75	6–12
Oxicams				
Piroxicam (Toldin)	3–5	30–75	10–20	24
Tenoxicam (Tobitil)	1–2.6	70–72	20	24
Sulfonanilide				
Nimesulide (Nimulid)	1–4	3–4	100	12
Alkanone				
Nabumetone (Nabuser)	1–2	24–34	1000	24

Indole Derivatives

Indomethacin (Indocin, Indicin)

Indomethacin is used in ***rheumatoid arthritis*** and ***ankylosing spondylitis*** for its anti-inflammatory and antipyretic effects. Contrary to earlier belief, indomethacin has analgesic properties independent of its anti-inflammatory action, and there is evidence for both central and peripheral effect. Indomethacin *inhibits prostaglandin* E_2. It inhibits the motility of polymorphonuclear leucocytes, an action similar to that of colchicine, and it uncouples oxidative phosphorylation in cartilaginous and hepatic mitochondria.

Pharmacokinetics. Indomethacin is rapidly and completely absorbed from the gut following oral adminsitration. Peak concentration in plasma is reached within 3 hours in the fasting subject, and somewhat later if the drug is taken after meals. The plasma concentration required for its anti-inflammatory activity is probably less than 1 mcg/ml. It is about 90 percent bound to plasma proteins and also extensively bound to tissues. The concentration in the CSF is low. Indomethacin undergoes extensive hepatic metabolism and both the parent substance and the metabolites take part in an ***enterohepatic circulation.*** The $t_{1/2}$ is 4 to 6 hours, but is prolonged in biliary obstruction. Indomethacin and its metabolites are excreted in the urine.

Therapeutic uses. Because of a high incidence of serious side effects associated with chronic use, indomethacin must never be used as a routine analgesic–antipyretic. However, it has proved to be useful as an antipyretic in ***Hodgkin's disease*** when fever is refractory to other agents.

Indomethacin is as effective as phenylbutazone, and more effective than aspirin in the treatment of ***ankylosing spondylitis, rheumatoid arthritis,*** and ***acute gout*** (though it does not promote uricosuria). As an anti-inflammatory agent indomethacin reduces pain, swelling and tenderness of joints, increasing grip strength, and decreases the duration of morning stiffness. In these actions it is equivalent to phenylbutazone. Indomethacin is also used to treat ***uveitis*** and inflamation following eye surgery. It has also been effective in reducing pain and inflammation of ***pleurisy, pericarditis*** and ***pericardial effusion.*** It appears to be more effective than aspirin in relieving pain of ***dysmenorrhoea.***

Indomethacin is available for oral use in capsules containing 25 or 50 mg of the drug. The initial dose is 25 mg twice daily, and can be increased by 25 mg increments weekly to a total daily dose of 100 to 200 mg. Most patients respond within a week. The drug if taken with food or after meals causes less of gastric distress.

Toxicity. A high percentage of patients (35 to 50%) receiving indomethacin in therapeutic doses experience adverse effects, and upto 20 per cent may have to discontinue its use. The most common adverse effects are headache, light-headedness confusion or hallucinations. Gastric bleeding is not common but can occur. Gastrointestinal complaints consist of anorexia, nausea and abdominal pain. Gastrointestinal ulceration with perforation has been reported. Occult blood loss in stools may lead to anaemia. *Haemopoietic reactions* like *neutropenia, thrombocytopenia,* and rarely *aplastic anaemia* may occur. *Hypersensitivity reactions* have been reported. Patient sensitive to aspirin exhibit cross-sensitivity to indomethacin. It is contraindicated in pregnant women, psychiatric disorders, epilepsy, or parkinsonism. Also contraindicated in patients with renal disease or ulcerative lesions of the gut, and blood dyscrasias.

Drug interactions. Antagonism between indomethacin and aspirin regarding the anti-inflammatory activity are possibly of little clinical significance. But the question remains unanswered whether concurrent administration of

the two drugs in rheumatoid arthritis is beneficial or not. ***Probenecid***, 1 g/day, inhibits the renal tubular secretion of indomethacin. When both are given together, plasma levels of indomethacin are almost doubled. There is an improved antirheumatic effect, but unfortunately side effects are increased. Therefore, indomethacin dosage must be reduced when combined with probenecid. Indomethacin does not interfere with the uricosuric effect of probenecid, and it does not modify the effect of *oral anticoagulants*. Indomethacin antagonizes the natriuretic effect of *furosemide*.

Sulindac (Clinoril)

It is closely related to indomethacin, and has analgesic-antipyretic and anti-inflammatory activity, which depends on its active sulphide metabolite. Thus sulindac is another example of a *prodrug*. The sulphide metabolite is 500 times more potent than sulindac as an inhibitor of cyclo-oxygenase.

It is well absorbed when given orally, and is half as potent as indomethacin on a weight basis, but the safety ratio (as determined in animals) is much higher than indomethacin. ***Enterohepatic recycling*** of sulindac followed by conversion back to the active sulphide metabolite contributes to the maintenance of high plasma levels of the active compound.

Sulindac is used in ***rheumatic conditions*** of all types and *gout*, in a dosage of 100–200 mg twice daily. It is generally well tolerated, and the main adverse effects are gastrointestinal disturbance, hypersensitivity reactions, and vertigo. The use of this drug must be avoided in the presence of active peptic ulceration.

Tolmetin (Tolectic)

Chemically tolmetin resembles indomethacin, but its properties are more like the propionic acid derivatives (ibuprofen, neproxen). It is a relatively new anti-inflammatory and analgesic–antipyretic agent, and is equivalent in efficacy to moderate doses of aspirin, but is less potent than indomethacin or phenylbutazone. It is more active than aspirin in its ability to inhibit prostaglandin synthetase. On oral administration it is almost completely absorbed, and peak plasma levels are attained within 1 hour. It is extensively bound (99%) to plasma proteins. Its $t_{1/2}$ in plasma is between 1 and 3 hours.

Therapeutic uses of tolmetin are the same as for other NSAIDs. It is used in the treatment of *rheumatoid arthritis*, specially the juvenile form of the disease; *osteoarthritis* and *ankylosing spondylitis*. *Adverse effects* include headache, tinnitus, vertigo, peptic ulcer and sodium retention. Incidence of gastrointestinal bleeding is lesser than that of aspirin. It is available as 200 mg tablets for oral use, and the recommended dose is 400 mg 3 times daily.

Etodolac (Lodine)

Etodolac is an inhibitor of cyclo-oxygenase and possesses anti-inflammatory activity. It is rapidly and well absorbed from the gut, and is highly protein bound (99%). The drug undergoes *enterohepatic circulation* in man. Etodolac is effective in the treatment of *osteoarthritis* and *rheumatoid arthritis*. It may also be used to provide *postoperative analgesia* in a single oral dose of 200–400 mg. *Adverse effects* include GI irritation and gastric ulceration. It is a well tolerated drug and side effects occur less frequently than with other NSAIDs.

Propionic Acid Derivatives

These drugs represent a new group of effective aspirin-like agents. All of them are analgesic–antipyretics, and are *potent inhibitors of cyclo-oxygenase*. The members of this group offer significant advantages over aspirin, phenylbutazone, and indomethacin, as they are better tolerated by the patients.

Ibuprofen (Brufen)

Like aspirin, ibuprofen has analgesic, anti-inflammatory, and antipyretic actions. It is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations are reached in 1 to 2 hours. It is rapidly metabolized and eliminated in the urine. The plasma $t_{1/2}$ is about 2 hours. It is extensively (99%) and firmly bound to plasma proteins.

Clinically it is used in the treatment of *rheumatoid arthritis* (including *Still's disease*), *osteoarthritis*, *ankylosing spondylitis*, *dysmenorrhoea*, *cervical spondylosis*, and *ophthalmic*, *dental* and *ENT inflammations*. Ibuprofen is available as 200, 300 and 400 mg tablets, and also as a suspension. The usual adult dose is 400 mg tid or 300 mg qid. Side effects include gastrointestinal disturbances, headache, dizziness and fluid retention.

Fenoprofen (Nalfon). Fenoprofen is chemically and pharmacologically similar to ibuprofen. It is as effective as aspirin for *rheumatoid arthritis*, and as effective as phenylbutazone for *osteoarthritis*. It is said to be as potent as naproxen, and more potent than ibuprofen and ketoprofen. *Dosage* ranges between 1.2 and 1.8 g per day in three to four divided doses.

Ketoprofen (Orudis). Peak plasma level of 2 to 5 mcg/ml is reached in 1 hour after a single 50 mg oral dose of ketoprofen. It is virtually completely absorbed from the gut. The recommended daily dose is 100 to 150 mg per day in divided doses.

Naproxen (Naprosyn)

Like aspirin, it has analgesic–antipyretic and anti-inflammatory actions. It is fully absorbed when adminsistered orally. It is almost completely bound (98 to 99%) to plasma proteins following therapeutic doses. Naproxen crosses the placenta, and appears in the milk of lactating women. It has a long plasma $t_{1/2}$ of 12 to 15 hours. Clinically it is used in the treatment of *rheumatoid arthritis*, *osteoarthritis*, and *ankylosing spondylitis*. The recommended dosage is 250 mg given twice daily with meals if gastric discomfort is experienced.

Flurbiprofen (Flurofen)

Flurbiprofen is a newer propionic acid derivative, and shares the same mechanism of action as other NSAIDs. It is considered to be one of the potent inhibitors of prostaglandin synthesis. It *suppresses both* PGE_2 and PGF_2 *alpha* through inhibition of the cyclo-oxygenase enzyme. *In vitro* studies it has been found to be more potent in this respect than aspirin, indomethacin, ibuprofen, naproxen, diclofenac and piroxicam. Flurbiprofen also is a potent ***inhibitor of leucocyte migration*** into inflamed tissues. It *does not inhibit lipoxygenase activity*, except at high concentrations.

Flurbiprofen is well absorbed orally; peak blood levels occur 0.5 to 4.0 hours after administration. The average

elimination half-life is 5.7 hours. No accumulation of the drug occurs; upto 98 per cent is excreted within 24 hours after the last dose. It is highly bound (99%) to plasma proteins, and is extensively hydroxylated (50%), and primarily excreted in the urine.

Flurbiprofen is used in the treatment of ***rheumatoid arthritis, osteoarthritis*** and ***ankylosing spondylitis***, and the daily dosage is 200 to 300 mg in 2 to 4 divided doses. *Adverse reactions* include GI disturbances like diarrhoea, dyspepsia and vomiting. GI bleeding and ulceration is rare. Rashes and angioedema may occur. Headache, dizziness, fatigue and insomnia also have been reported. It is *contraindicated* in patients with a history of asthma, bronchospasm, anaphylactic reactions and other hypersensitivity type reactions with the use of aspirin or other NSAIDs.

Oxaprozin (Daypro)

Oxaprozin is one of the newest propionic acid derivatives. It is unique in that it can be effectively administered once daily, as it has a long half-life (40–60 hrs). Its pharmacological profile is similar to other propionic acid derivatives. It is well absorbed orally, metabolized in the liver, and primarily excreted by the kidney. It has been used in doses of 1.2 g daily by mouth in patients of *osteoarthritis* and *rheumatoid arthritis*.

Fenamates

The *anthranilic acid derivatives* (fenamates) are aspirin-like drugs, but have not gained widespread clinical acceptance, because of the side effects (severe diarrhoea) they are likely to cause. Therapeutically they have no clear advantage over other aspirin-like drugs.

Mefenamic Acid (Ponstan)

It is another NSAID, and may be useful in the relief of pain in conditions which do not ordinarily require strong analgesics. It is absorbed rather slowly from the gut, reaching peak concentrations in 2–4 hours. It is 98.5 percent bound to plasma proteins. It has the property of inhibiting cyclo-oxygenase, to which possibly it owes its activity. It is used as a mild analgesic, and the usual dose is 500 mg 3 times daily.

Gastrointestinal symptoms are the most common adverse effects. *Diarrhoea* occurs in a large number of patients. Other infrequent side effects include dizziness, rashes, haemolytic anaemia, agranulocytosis, thrombocytopenic purpura, and megaloblastic anaemia. It is contraindicated in gastrointestinal inflammation or ulceration, and impairment of renal function. Like other drugs inhibiting prostaglandin synthesis, mefenamic acid also prolongs induction of labour by hypertonic saline.

Flufenamic Acid (Arlef)

This is another fenamate, which is perhaps slightly more rapidly absorbed than mefenamic acid. It is used in a dose of 400–600 mg orally daily in divided doses.

Meclofenamate (Meclomen)

Meclofenamate should not be used as initial therapy for rehumatoid arthritis or osteoarthritis, due to the high incidence of diarrhoea (10–30%), vomiting (10–12%), and other GI disorders (10%). It is not recommeded in children under 14 years. It should be taken with meals, milk or antacids. Periodic haematocrit determinations are recommended during prolonged therapy. Meclofenamate (capsules 50, 100 mg) is given in a dose of 200–400 mg/day tid or qid.

Phenylacetic Acid Derivative

Diclofenac (Voveran)

Diclofenac has analgesic, antipyretic, and anti-inflammatory activities. It is an *inhibitor of cyclo-oxygenase* and its potency is appreciably greater than that of indomethacin, naproxen, and several other NSAIDs. It is completely absorbed on oral administration; peak plasma levels occur in 2 to 3 hours; and the drug undergoes *first-pass* metabolism and only 50 percent is bioavailable. Its average half-life is 2 hours; 65 percent of the dose is eliminated in the urine, while 35 percent is found in bile, largely as conjugates of both the unchanged drug and its metabolites. Diclofenac is 99 percent bound to plasma proteins.

Diclofenac is approved for long-term treatment of ***rheumatoid arthritis, osteoarthritis,*** and ***ankylosing spondylitis***. Also used in short-term treatment of acute musculo-skeletal injury, acute painful shoulder, postoperative pain, and dysmenorrhoea. The usual daily dosage is 100 – 200 mg bid or tid. *Adverse reactions* include GI disturbances and headache, and a reversible elevation of serum transaminases occurs in 15 percent of patients. Skin rashes, allergic reactions, fluid retention and oedema, and impairment of renal function can occur.

Oxicams

Piroxicam (Toldin)

Piroxicam possesses anti-inflammatory, analgesic and antipyretic activity. It is the NSAID offered for *once-a-day treatment* of ***rheumatoid arthritis*** and ***osteoarthritis,*** and this helps patient compliance. In therapeutic doses, piroxicam equals the efficacy of indomethacin and naproxen for the long-term treatment of rheumatoid arthritis and osteoarthritis.

Piroxicam is an inhibitor of prostaglandin biosynthesis, comparable to indomethacin. It also inhibits activation of neutrophils, which is an additional mode of its anti-inflammatory action. It is well absorbed on oral administration, and peak plasma levels are attained in 3 to 4 hours. The average plasma half-life is 50 hours (range 30–75 hours), and as such piroxicam is likely to accumulate in the body. Steady-state levels are reached in 7 to 12 days. Piroxicam is extensively metabolized to inactive compounds and excreted in urine (two-thirds) and faeces (one-third). Concurrent administration of aspirin causes a 20 percent reduction in plasma levels of piroxicam. *The use of piroxicam (or any other NSAID) in conjunction with aspirin is not recommended*, as such combinations *do not* increase efficacy, but may increase the potential for adverse reactions. Adverse GI reactions are most common, but oedema, dizziness, headache, rash, and haematological changes can occur in 1 to 6 percent of patients. Serious GI toxicity in the form of bleeding, peptic ulceration, and perforation have been reported. Piroxicam is available in 10 and 20 mg capsules. The usual dose is 20 mg daily as a single dose. Maximal therapeutic response should not be expected before 2 weeks.

Tenoxicam (Tobitil)

Tenoxicam is an orally effective anti-inflammatory agent, and a *potent inhibitor of prostaglandin synthesis by blocking the enzyme cyclo-oxygenase*. Additionally, it inhibits leucocyte function including phagocytosis and chemotaxic, and scavenging of free oxygen radicals. It has an exceptionally long half-life (70 hrs), and steady-state levels are reached in about 2 weeks. The drug is completely bioavailable on oral administration, and is metabolized in the liver. It is effective in *rheumatoid arthritis, osteoarthritis,* short-term treatment of *soft tissue injuries, gout* and nonarticular conditions like *tendinitis, bursitis,* and *backache.*

Dosage. Usual dose is 20 mg once daily. For *gout* it is given in a dose of 40 mg/day for 2 days, followed by 20 mg/day for 5 days. In usual doses it is fairly well tolerated, and does not effect renal function.

Other oxicam derivatives under study include *meloxicam, lornoxicam, cinnoxicam,* and several *prodrugs* of piroxicam *(ampiroxicam, droxicam and pivoxicam).*

Nimesulide (Nimulid, Orthobid)

Nimesulide is a sulfonanilide compound. Its action is rather different than that of the classic NSAIDs. It is a relatively *weak* inhibitor of prostaglandin synthesis, but has a potent anti-inflammatory action. It acts as an *inhibitor of histamine release,* and *reduces in vitro superoxide anion formation by the activated neutrophils.*There is evidence that nimesulide also inhibits release of tumour necrosis factor alpha, and thus reduces the formation of cytokines. It also blocks the metalloproteinase activity of articular chondrocytes. Nimesulide is rapidly and extensively absorbed on oral administration. The average half-life is 3 hours. It is metabolized to a 4-hydroxy derivative, and excreted by the kidney. Its usual dose is 100 mg bid.

Nimesulide is used in the short-term treatement of inflammatory conditions of the musculoskeletal system, *dysmenorrhoea, thrombophlebitis, postoperative dental pain,* and *inflammations of the ear, nose and throat. Side effects* are observed in about 5% of patients, and involve the GI tract and the skin.

Nabumetone (nabuser)

Nabumetone is a weak inhibitor of cycloxygenase *in vitro,* but has substantial *anti-inflammatory, antipyretic,* and *analgesic* activity. It is effective in the treatment of *rheumatoid arthritis, osteoarthritis,* and in the short-term treatment of *soft tissue injuries.* The usual *dose* is 1 g given once daily. Nabumetone is a *prodrug,* and is converted to its main active metabolite *6-methoxy-2-naphthylacetic acid* in the liver, which inhibits cycloxygenase. *Adverse effects* include diarrhoea, nausea, dyspepsia, flatulence, constipation, skin rashes, and pruritus. The incidence of GI ulceration is much lower with nabumetone than with other NSAIDs.

Miscellaneous Anti-inflammatory Agents

Hydroxychloroquine (Plaquenil)

Hydroxychloroquine, a 4-aminoquinoline used primarily as an antimalarial, has also been employed in the treatment of ***rheumatoid arthritis*** and ***systemic lupus erythematosus.*** Hydroxychloroquine is preferred over chloroquine, as it is slightly less toxic, although not an innocuous drug.

The antiarthritic mechanism of action of the 4-aminoquinolines is not exactly known, but they *stabilize lysosomal membranes, inhibit nucleic acid synthesis, interfere with replication of viruses,* and *suppress formation of antigens* that cause hypersensitivity reactions.

Initial dosage is 200 mg bid or tid. Several weeks are required for optimal response, when the dosage can be reduced to 200 to 400 mg/day. Salicylates, other NSAIDs, and corticosteroids can be combined with hydroxychloroquine. Untoward ophthalmic reactions involving the cornea, retina, and ciliary body can occur, and periodic ophthalmic examinations are mandatory during prolonged therapy **(Chap. 10.5)**

Penicillamine (Cuprimine)

Penicillamine is a ***chelating agent*** used to remove excess copper in patients with ***Wilson's disease*** (hepatolenticular degeneration), and to increase cystine excretion in cystinuria. It is also approved for the treatment of ***severe forms of rheumatoid arthritis,*** but the use is restricted to patients unresponsive to other less toxic anti-inflammatory agents.

The antiarthritic *mode of action* of penicillamine is not precisely known. But it *inhibits lysosomal enzyme release in connective tissue; interferes with DNA synthesis, collagen, and mucopolysaccharides; suppresses T-cell activity, and lowers the titre of IgM rheumatoid factor.*

In rheumatoid arthritis, penicillamine is administered initially in a dose of 125 to 250 mg/day orally for 4 weeks. Dosage may be increased at 4 to 12 week intervals. Adverse reactions include stomatitis, pruritus, loss of taste, nausea and proteinuria. Leucopenia, thrombocytopenia, bone marrow depression, agranulocytosis, and aplastic anaemia may occur **(Chap. 14).**

Compound Analgesic Preparations

Combinations of analgesic agents, or analgesics with drugs of another class are among the most widely used (or abused) pharmaceutical products. Most of them are formulated on a theoretical basis that they would: (*i*) produce greater analgesic effect (synergism); (*ii*) provide broader therapeutic uses; and (*iii*) cause fewer or less severe adverse effects. Although products containing aspirin and aspirin-like agents have a relatively low abuse potential compared to the narcotic analgesics, yet some people with personality problems have abused these over-the-counter (OTC) products by consuming them in excessively high doses for prolonged periods. In such situations these drugs can cause serious chronic toxicity affecting the liver, kidneys and the blood.

Compound analgesic preparations containing aspirin, paracetamol, and codeine are not recommended for use. Single ingredient preparations should be prescribed in preference, because compound preparations rarely have any advantage. Moreover, they increase the cost of treatment, and make the treatment of overdosage more difficult.

Caffeine is a mild psychomotor stimulant that is often included in small doses in various analgesic preparations. It does not contribute to the analgesic or anti-inflammatory activity of the preparation, but it may aggravate the gastric irritation caused by aspirin. Many analgesic mixtures in spite of the drawbacks, are available as OTC products, and self-medication is common among the people.

Table 2.7-3. *Pharmacokinetic parameters of injectable and oral gold preparations*

Drug	Gold Content	Peak Effect (hrs)	Protein Binding (%)	Serum Half-life (days)	Excretion
Injectable					
Aurothioglucose	50%	4–6	95–100	5–25*	70% urine/ 30% faeces
Gold sodium Thiomalate	50%	2–6	95–100	3–27*	70% urine/ 30% faeces
Oral					
Auranofin	29%	1–2	50–60	20–30	15% urine/ 85% faeces

* Half-life increases after repeated dosage; upto 40 days after 3 to 5 doses, and upto 175 days after 10 doses.

Gold Compounds
Auranofin (Ridaura)
Aurothioglucose (Solganal)
Gold Sodium Thiomalate (Myochrysine)

Preparations containing elemental gold have been used over many years for treating severe rheumatoid arthritis. *Aurothioglucose* and *gold sodium thiomalate* contain 50 percent gold and are used intramuscularly (1M). In addition, *auranofin* is an orally effective compound containing 29 percent gold. These gold compounds can temporarily ***arrest the progression*** of bone destruction in the involved joints, but there is no evidence that they can induce remission of rheumatoid arthritis (see later).

The antiarthritic mode of action of gold is not completely known. Several actions are throught to contribute to the beneficial effects: (*i*) *inhibition of lysosomal activity* in macrophages; (*ii*) *decreased phagocytic action* of macrophages; (*iii*) *reduced histamine release* from mast cells; and (*iv*) *blockade of formation of glucosamine-6-phosphate* in connective tissue. The importance of the above actions remains to be determined.

Dosage. The injectable forms (aurothioglucose, gold sodium thiomalate) are available in concentrations of 10 mg/ml, 25 mg/ml and 50 mg/ml. The oral preparation (auranofin) is used as 3 mg capsules.

Aurothioglucose. Weekly IM injections (preferred site is intraguteal); first week, 10 mg; second and third weeks, 25 mg; there after, 50 mg/week.

Gold sodium thiomalate. Weekly IM injections; first week, 10 mg, second week, 25 mg; thereafter 25–50 mg/week until clinical improvement or toxicity occurs.

Auranofin. Administered orally 6 mg a day, as a single or 2 divided doses. If response is not adequate after 6 months, increase to 9 mg/day in 3 divided doses.

The pharmacokinetic properties of gold preparations are presented in **Table 2.7-3.** Gold is well distributed in the body, and major sites of localization are bone marrow, liver, skin, and bone. *Arthritic joints appears to concentrate more gold than non-involved joints.* No definite correlation exists between plasma concentrations of gold and efficacy or safety.

Adverse reactions to gold therapy can occur during treatment, or for several months after stoppage of therapy. Most common side effects are dermatitis, stomatitis, pruritus, metallic taste, flushing, sweating, and proteinuria. Diarrhoea occurs in over 50 percent of patients on gold therapy. Other adverse reactions include alopecia, grayish blue skin pigmentation, gingivitis, pharyngitis, vaginitis, blood dyscrasias (rarely), glomerulitis, haematuria, tubular necrosis, nephritis, angioedema and anaphylactic shock. *Thus, gold compounds are potentially highly toxic substances.*

Antigout Drugs

Gout is a *purine metabolism disorder* resulting from an excess of uric acid in the blood (hyperuricaemia), due to either its overproduction or faulty elimination. Crystals of *monosodium urate* begin to precipiatate and get deposited in joints, skin, kidney and other tissues. ***Gouty arthritis*** usually involves a single joint (monoarticular), but may involve many joints (polyarticular) specially in the later course of the disease. Classically the great toe is involved, characterized by pain (podalgia), swelling, tenderness, and other signs of *inflammation*. At the site there is *infiltration of granulocytes that phagocytose the urate crystals.* The granulocytes ultimately break down and liberate *lactic acid* and other acidic products, which lower the regional pH, and favour *further precipitation* of urate crystals **(Fig. 2.7.6)**. The acute phase of gout is thus a cyclic and self-perpetuating process.

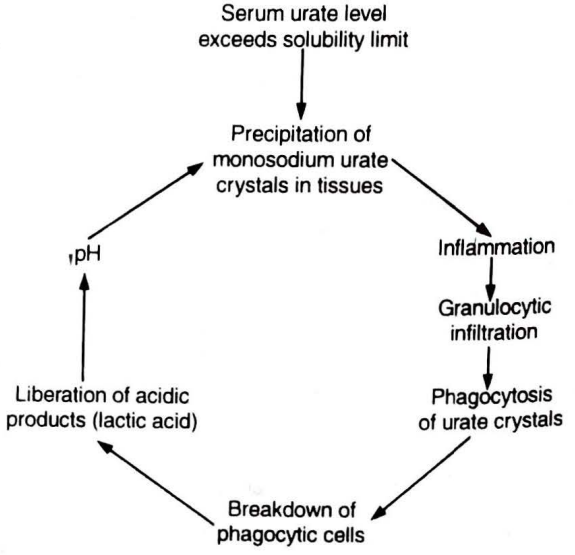

Fig. 2.7.6: The cycle of events occurring during an attack of gout.

Hyperuricaemia may also be an endogenous, *primary* disorder as seen in ***primary gout***, or it can be ***secondary*** to disease (leukaemia, polycythaemia vera, psoriasis, multiple myeloma); renal damage; use of drugs (thiazide diuretics, cytotoxic agents); or during starvation.

Production of uric acid. Uric acid is formed by the metabolism of nucleoproteins from two sources; the body's own cells and cell-rich food. The nucleic acids from these cells are first converted to the purine bases *hypoxanthine* and *xanthine*. The enzyme, xanthine oxidase, then catalyses the metabolic breakdown of these purines to uric acid **(Fig. 2.7.7)**. Thus, uric acid is the end product in the metabolism of the purines ***adenine*** and ***guanine.***

Uric acid is filtered by the glomerulus, but 98 percent is actively reabsorbed in the proximal tubule. It is also excreted into the distal tubule via an active transport system. It is more soluble in an alkaline urine, and a factor in the development of ***uric acid stones*** is an impaired ability to excrete alkaline urine. Thus, about two-thirds of urinc acid is excreted in the urine, and the remainder is excreted into the gut and is broken down by the intestinal bacteria.

Blood ordinarily contains uric acid in a concentration of 3 to 7 mg/dl of serum. The solubility of urates in tissue fluids is limited. When the saturation point is exceeded, microcrystals of ***monosodium urate*** are precipitated. Urate crystals also trigger the biosynthesis of ***bradykinin,*** a mediator of inflammation. Thus, gouty inflammation occurs.

Classification

Three types of drugs are employed in the treatment of gout:

1. Drugs used in *acute gout* to terminate the inflammatory process and prevent its recurrence: *Colchicine, phenylbutazone, oxyphenbutazone, naproxen, sulindac, indomethacin, corticotrophin, corticosteroids.*
2. Drugs used for long-term control of gout, acting by *increasing* the excretion of uric acid by the kidneys, *i.e.*, uricosuric agents: *Probenecid, sulphinpyrazine.*
3. Drugs for prevention of urate synthesis in the body: *Allopurinol.*

Acute Gout

The acute attack of gout is due to the precipitation of ***monosodium urate*** crystals in the joint. These are irritant and an acute inflammatory response occurs which is exceedingly painful. The acute reaction is usually treated by *anti-inflammatory analgesics* (phenylbutazone 100 mg tid; or oxyphenbutazone 200 mg tid; or naproxen 750 mg initially; then 250 mg 8-hourly; or indomethacin 50 mg tid) for a short time. An altenative is *colchicine* which is specific in relieving the symptoms of acute gout, but is probably not as effective as phenylbutazone or indomethacin, and its use is limited by its toxicity. In resistant cases of acute gout *corticotrophin* (ACTH) is very effective and is given in a dose of 80 units 1M, repeated after a day or two if necessary. The newer agent *sulindac* may also be used to treat acute gout in a dose of 200 mg orally twice daily till relief is obtained.

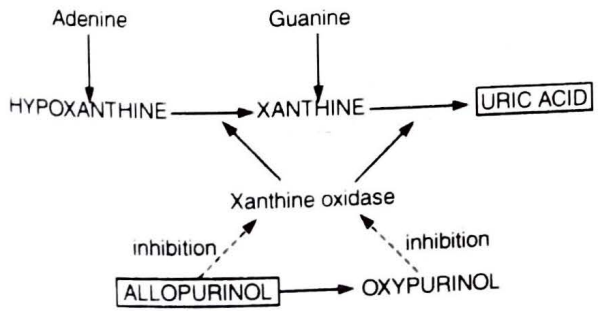

Fig. 2.7.7: Purine metabolism by xanthine oxidase, and its inhibition by allopurinol (see text).

Colchicine

Colchicine is an alkaloid derived from the corm and seeds of *Colchicum autumnale*, known for centuries for its medicinal qualities. It has *no anti-inflammatory or analgesic activity*, but is very effective in suppressing inflammation and pain in gouty joints when taken promptly in adequate amounts. It does not enhance renal excretion of uric acid or reduce its concentration in the blood.

Mode of action. The mechanism of action of colchicine in acute gout is incompletely understood. It ***inhibits the migration*** of granulocytes to inflamed joints, and ***phagocytosis is checked.*** It checks the leucocytes which get into the joint from releasing lactic acid and lysosomal enzymes (see above), and urate crystal deposition in the joint is reduced. *Bradykinin* biosynthesis also ceases. Thus, it breaks the cycle and reduces inflammation and pain.

Colchicine also is an *antimitotic* agent, arresting cell division in metaphase by blocking spindle formation. Although this phenomenon is not used therapeutically, it is a useful tool in research.

Pharmacokinetics. Colchicine is rapidly absorbed from the gastorintestinal tract. Its plasma $t_{1/2}$ is 30 minutes. It is partly metabolized, and a major portion is excreted via the bile and undergoes ***enterohepatic*** circulation, which may account for its toxic effects on the gastrointestinal tract. Its half-life is prolonged in renal disease as 20 to 30 percent of the drug is excreted via the urine.

Therapeutic uses. Colchicine is a major drug for reduction of inflammation and relief of pain of ***acute gouty arthritis.*** It may be used as a short-term prophylaxis during initial therapy with allopurinol and uricosuric agents.

Dosage. For *acute attacks* 0.5 or 0.6 mg is administered orally every hour; or alternatively 1 or 1.2 mg may be given initially followed by 0.5 or 0.6 mg every 2 hourly until pain subsides, or nausea, vomiting and diarrhoea develop. A total dose of 4 to 10 mg may be required. Joint pain and swelling disappear within 48 to 72 hours after initiation of therapy. After the acute attack, 0.5 or 0.6 mg should be administered every 6 hourly for a few days to prevent relapse.

For *prophylaxis* 0.5 or 0.6 mg orally is given every 2 to 3 days depending on the frequency of attacks.

To avoid gastrointestinal distress, colchicine may be administered intravenously in a dose of 1 or 2 mg initially, followed by 0.5 mg every 3 to 6 hours until a satisfactory response is achieved. When given promptly one or two injections terminate the attack.

Toxicity. Colchicine causes nausea and vomiting or abdominal pain in about 80 percent of patients. Diarrhoea is considered as the therapeutic end point, and as soon as it occurs, administration should be stopped irrespective of the symptoms. Black tarry stools or light red blood in stools indicates gastrointestinal bleeding. Antidiarrhoeal agents like ***diphenoxylate*** (Lomotil) or ***paregoric*** may be needed to control severe diarrhoea. Gastrointestinal distress is uncommon after IV administration, but extravasation must be avoided as dangerous tissue necrosis may occur. ***Bone***

marrow depression (agranulocytosis, thrombocytopenia, aplastic anaemia), peripheral neuritis, myopathy, renal damage, hepatocellular failure and alopecia may occur. Colchicine should be given with special caution to the elderly and debilitated patients and those with renal, cardiovascular, hepatic and gastrointestinal disease.

Drugs that precipitate Acute Gout

The following drugs may precipitate an acute attack of gout, particularly in patients with a gouty diathesis:

1. ***Diuretics.*** The *thiazides* by their action on the distal tubule inhibit urate secretion and precipitate gout. Other diuretics like *ethacrynic acid, furosemide,* and *bumetanide* also precipitate gout. Triamterene, amiloride and spironolactone *do not* precipitate gout.
2. ***Other drugs.*** *Pyrazinamide, clofibrate, aspirin* in low doses, and *cytotoxic drugs* used for leukaemia and lymphomas may precipitate gout.

Chronic Gout

Chronic gouty arthritic processes may continue in the absence of acute attacks. Continued deposition of uric acid crystals may destroy cartilage, joints and bone epiphyses. Thus, although continued administration of small daily doses of colchicine helps to prolong the periods between acute attacks, other drugs are needed for preventing *tophaceous structural changes* in the intervals between attacks.

There are two possible approaches to the long-term control of gout: (*i*) the ***uricosuric*** drugs ***probenecid,*** *sulphinoyrazine,* or *ticrynafen* may be used to increase excretion of uric acid in urine; and (*ii*) the ***xanthine oxidase inhibitor*** allopurinol may be used to *suppress biosynthesis of uric acid* from purines. Both types of therapy should be continued indefinitely with an aim to prevent an acute attack of gout by keeping the level of blood uric acid below 7 mg/dl, and to reduce the pool of uric acid in tophaceous gout, and secondary hyperuricaemia. The salicylates antagonize the uricosuric drugs, but do not antagonize the action of allopurinol.

Uricosuric Drugs

Probenecid (Benemid)

Probenecid is a sulphonamide derivative, which was developed during World War II in the search for a drug to maintain blood levels of penicillin by interfering with its excretion, because penicillin was then expensive and in short supply. Since 1950, probenecid has been known to be a very *useful uricosuric agent* in gout.

Mode of action. Probenecid acts by inhibiting renal tubular reabsorption of uric acid, thereby greater amounts of uric acid are eliminated in the urine **(Fig. 2.7.8)**. The concentration of urates in the plasma falls gradually towards normal; and the size of tophaceous deposits is gradually reduced. The drug-induced movement of uric acid from deposits in tissues back into the blood may at first increase the number of acute attacks, for the prevention of which probenecid is initially combined with small amounts of colchicine. Probenecid is ***ineffective in acute gout.*** Probenecid also blocks the secretion of weak organic acids into the proximal and distal renal tubules. This activity is taken advantage of clinically for *blocking the secretion of penicillins*

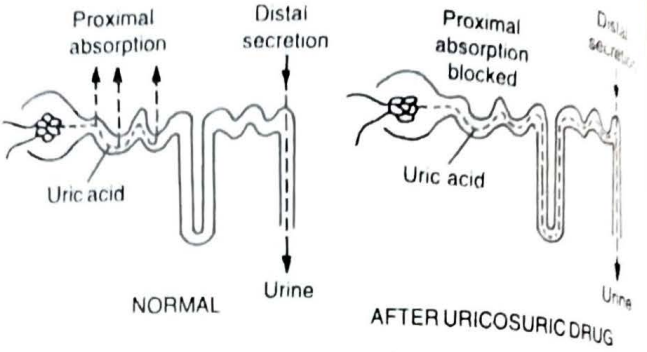

Fig. 2.7.8: Action of uricosuric drugs (probenecid, sulphinpyrazone) on uric acid elimination by the renal tubules (diagrammatic).

and *cephalosporins* into the urine. The plasma levels of these antibiotics are maintained at higher levels for a longer duration.

Pharmacokinetics. After oral administration, probenecid is rapidly absorbed within an hour, and peak plasma levels are attained in 2 to 4 hours. In the blood 85 to 90 percent of the drug is plasma protein bound; the plasma $t_{1/2}$ is 6 to 12 hours. The excretion of the drug is substantially increased in alkaline urine. About 90 to 95 percent of the metabolites are also lost in the urine. To prevent the precipitation of uric acid in the urinary tract during its increased excretion under the influence of a uricosuric drug like *probenecid* or *sulphinpyrazone,* the following precautions are necessary:

(*i*) The uricosuric drugs should be given in *repeated low doses,* rather than in single high doses;

(*ii*) *Fluids are forced* to produce a large volume of less concentrated urine; and

(*iii*) The solubility of uric acid in this dilute urine may be further increased by *alkalinizing* it by concurrent administration of small amounts of sodium bicarbonate, or potassium citrate several times daily.

Therapeutic uses. Probenecid is used for the *prophylaxis of gout;* hyperuricaemia; and for the reduction of tubular excretion of penicillins and cephalosporins.

Dosage. For uricosuric therapy, initially 250 mg twice daily orally, is administered preferably after meals, increased after a week to 500 mg twice daily, then upto 2 g daily according to serum uric acid levels. During initial therapy prophylactic colchicine should be given.

For maintaining high levels of penicillin and cephalosporin, probenecid is administered in a dose of 1 to 2 g daily.

Toxicity. Occasionally nausea, vomiting, urinary frequency, headache, flushing, dizziness and rashes may occur. Rarely hypersensitivity reactions, nephrotic syndrome, hepatic necrosis and aplastic anaemia occur. *Contraindications* are concurrent salicylate therapy, blood dyscrasias, nephrolithiasis and acute gout.

Probenecid interacts with many drugs. It reduces the renal excretion of nitrofurantoin. It may prolong the half-life of oral hypoglycaemics, and reduction of dosage is required to avoid hypoglycaemia. Probenecid blocks the renal excretion of *indomethacin, sulphipyrazone, dapsone* and *para-aminosalicylic acid (PAS),* increasing the possibility of adverse reactions. Salicylates inhibit the uricosuric activity of probenecid. During *antineoplastic therapy* which elevates serum uric acid levels, probenecid should not be adminsitered, as uric acid stones may develop in the kidneys.

Sulphinpyrazone (Anturan)

Sulphinpyrazone is an analogue of phenylbutazone, but it *lacks the latter's anti-inflammatory, analgesic* and *sodium retaining* properties. Sulphinpyrazone, like probenecid, markedly inhibits the tubular reabsorption of uric acid from the proximal renal tubules, increasing the urinary excretion of uric acid, and decreasing serum urate levels **(Fig. 2.7.8)**. In a dose of 300 to 400 mg, sulphinpyrazone produces uricosuria equivalent to 1.0 to 1.5 g of probenecid. It can serve as an alternative to probenecid for patients who cannot tolerate probenecid.

Sulphinpyrazone also *inhibits platelet adhesiveness and prolongs platelet life*. It is effective in the prevention of thromboembolic diseases like *angina pectoris, transient ischaemic attacks*, and *myocardial infarction* (also see **Chap. 4.5**).

Pharmacokinetics. Sulphinpyrazone is rapidly and completely absorbed on oral administration, and peak blood levels occur in about 1 to 2 hours. It is about 98 percent bound to plasma proteins. Its plasma $t_{1/2}$ is 1 to 3 hours. Most of the drug is excreted unchanged in the urine. The remainder is metabolized in the liver to parahydroxyl analogue which also has uricosuric activity.

Therapeutic uses. Sulphinpyrazone is used for gout prophylaxis, and in hyperuricaemia.

Dosage. Initially, 100 to 200 mg orally 2 times daily is given with milk or after meals, increasing over 2–3 weeks according to the serum uric acid levels to about 600–800 mg daily in divided doses.

Toxicity. Gastrointestinal disorders, occasionally hypersensitivity reactions, and rarely blood dyscrasias may occur. Patients who are hypersensitive to phenylbutazone or oxyphenbutazone should not be put on to sulphinpyrazone therapy, as *cross-sensitization is a rule with the pyrazolone derivatives*. The frequency of gouty attacks may increase during the first 6–12 months. During these attacks the sulphinpyrazone therapy is to be continued, and the acute attacks may be treated by colchicine or other anti-inflammatory analgesics. Salicylates inhibit the uricosuric action of sulphinpyrazone. Caution should be observed in nephrolithiasis and renal impairment.

Xanthine Oxidase Inhibitor

Allopurinol (Zyloric, Zyloprim)

In a search for an ideal antitumour drug, it was found that allopurinol is a potent xanthine oxidase inhibitor **(Fig. 2.7.7)**. Chemically it is a hypoxanthine analogue. In contrast to the uricosuric agents, allopurinol *inhibits the enzyme xanthine oxidase, reducing the formation of uric acid from xanthine and hypoxanthine*. Thereby xanthine and hypoxanthine are excreted unchanged in the urine. Precipitation of uric acid in joints and elsewhere is minimal, and uric acid is actually mobilized from deposits. It is of no use in the treatment of acute gout, or rather may precipitate acute gout initially.

Pharmacokinetics. Allopurinol is rapidly and completely absorbed from the intestine. Its plasma $t_{1/2}$ is about 3 hours. It is largely converted to oxypurinol, which itself is a weak xanthine oxidase inhibitor **(Fig. 2.7.7)**.

Therapeutic uses. Allopurinol is used for *gout prophylaxis*, and for *long-term treatment of hyperuricaemia* and *its complications*. In early uncomplicated gout there is little to choose between uricosurics and allopurinol, but allopurinol alone, or in combination with uricosurics is particularly useful in: (*i*) gout uncontrolled by uricosurics; (*ii*) severe tophaceous gout; (*iii*) urate renal stones; (*iv*) gout with renal failure; (*v*) gouty nephropathy; (*vi*) intolerance to uricosurics; and (*vii*) treatment of leukaemias and lymphomas with cytotoxic drugs.

Dosage. Initially, 100 mg as a single dose is given after meals, gradually increased to 300 my daily, over 1–3 weeks depending on the serum uric acid levels. Usual maintenance dose is 200–600 mg daily. Allopurinol can be *safely combined* with all other antigout drugs including, colchicine, probenecid and sulphinpyrazone. Doses over 300 mg/day should be preferably administered in 2 or 3 divided doses.

Toxicity. Adverse effects are infrequent. Gastrointestinal disorders, drowsiness and hypersensitivity reactions may occur. Rarely vertigo, headache, taste disturbances, hypertension, alopecia, hepatitis and symptomless xanthine deposits in muscles may occur. Rarely it may also cause myelosuppression. However, *it increases the frequency of bone marrow depression in patients receiving cyclophosphamide*. It prolongs the $t_{1/2}$ of chlorpropamide and warfarin. Allopurinol decreases the rate of breakdown of 6-mercaptopurine and azathioprine, and a lower dose of the two cytotoxic drugs should be given to avoid toxicity.

Antirheumatic Drugs

Rheumatic diseases are inflammatory or degenerative disorders that affect mainly the musculoskeletal system, *i.e.*, the joints, muscles, ligaments, tendons and bursae. The term "rheumatism" is used by the layman to lump together all the different, about 80 chronic and acute disorders, which involve the musculoskeletal system, and include *rheumatoid arthritis, rheumatic fever, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, fibrositis*, and *myositis*. We shall mainly discuss the drug therapy of rheumatoid arthritis. The primary aim of treatment is reduction of *pain* and *inflammation, maintenance of joint mobility*, and *prevention of deformity*. Except for the *gold compounds, chloroquine, penicillamine*, and *immunosuppressants*, which are said to affect the disease process in rheumatoid arthritis and related conditions, the rest of the agents just provide symptomatic relief of pain and inflammation. *The above mentioned drugs differ from the NSAIDs in a number of ways*: (*i*) they do not produce immediate effect, but elicit a *response in 4 to 6 months*; (*ii*) they improve not only the signs and symptoms of joint disease, but also *extra-articular manifestations* of rheumatoid arthritis like nodules; and (*iii*) they also reduce erythrocyte sedimentation rate and IgM *rheumatoid factor*. Penicillamine may retard the radiological progression of the disease.

Classification

The drugs used in the treatment of rheumatic diseases fall into the following categories:

1. *Non-steroidal anti-inflammatory drugs:* Salicylates and non-salicylates.
2. *Gold compounds:* Gold sodium thiomalate.
3. *Chelating agent:* Penicillamine.
4. *Antimalarials:* Chloroquine and hydroxychloroquine.
5. *Adrenocorticosteroids* and *ACTH*.

6. *Immunosuppressants:* Azathioprine, chlorambucil.

Alternatively, the antirheumatics may be broadly grouped into two: (*i*) the *non-steroidal anti-inflammatory drugs (NSAIDs);* and (*ii*) the *slow-acting antirheumatic drugs (SAARDs).* The latter group includes *gold sodium thiomalate, penicillamine, hydroxychloroquine,* the *immunosuppressives* and the *corticosteroids.*

Drug Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is still an important agent in the medical management of rheumatoid arthritis. Many arthritis patients find it difficult to believe that this familiar over-the-counter pain reliever is the safest and usually the most effective drug for treating chronic joint disorders. For full anti-inflammatory effectiveness, aspirin must be taken in much larger amounts than for ordinary analgesia. Patients should be advised to keep on taking aspirin even when they are not having much pain, as the peripheral anti-inflammatory effect of the drug helps to keep the disease under control and prevents sudden exacerbations. To avoid gastrointestinal irritation the dose of aspirin (4–5 g/day) should be taken after meals or with milk **(Table 2.7–4).**

The ***non-salicylate anti-inflammatory agents*** used in the management of rheumatoid arthritis and related disorders include *indomethacin, ibuprofen, fenoprofen, naproxen, sulindac* and *tolmetin.* Their antirheumatic activity probably stems from the resulting reduction of prostaglandins in the arthritic joints. However, the drug induced deficiency of prostaglandin E in the gastric mucosa may be responsible for the ulcerogenic activity of antirheumatic drugs. These drugs are detailed in the beginning of this Chapter. Phenylbutazone is *no longer* recommended because of its serious toxicity.

Gold compounds. Chrysotherapy, *i.e.,* treatment with gold salts, sometimes suppresses the rheumatic process in patients. Gold was first used clinically for rheumatoid arthritis in 1927, and by 1934 its use was much popularized.

Gold sodium thiomalate. It is used in severe active or progressive *rheumatoid arthritis, palindromic rheumatism* and *juvenile chronic arthritis.* It is given by IM injection, and usually the treatment is begun with a 10 mg test dose to detect hypersensitive patients. Thereafter, if indicated, doses of 50 mg are given at weekly intervals until response is obtained. Benefit is expected after about 8 doses have been administered. Then the interval between injections is gradually increased to 2 and then to 4 weeks, or even 6 weeks. If a relapse occurs, dosage should be immediately increased to 50 mg weekly. Treatment is to be continued indefinitely.

Penicillamine. The chelating agent used in the treatment of Wilson's disease, and heavy metal poisoning **(Chap. 14)** is also effective in rheumatoid arthritis. Penicillamine has a similar action to gold. *Comparative studies indicate that penicillamine is as effecive as gold or azathioprine.* Because of its potentially hazardous adverse effects, penicillamine is reserved for patients with long-standing disease refractory to standard therapy.

Penicillamine is used for severe active or progressive rheumatoid arthritis, juvenile chronic arthritis, Wilson's disease and cystinuria. An initial dose of 125 to 250 mg orally daily is given, increased after 4 to 6 weeks to 250 to 500 mg daily. Improvement is expected after 6 to 12 weeks of therapy. *Caution is to be observed in renal and hepatic impairment, and concurrent gold, chloroquine, hydroxychloroquine and immunosuppressive therapy should be avoided.*

Antimalarials. Chloroquine and hydroxychloroquine may be used in *active rheumatoid arthritis, systemic lupus erythmatosus,* and *discoid lupus erythematosus.* They have a similar action to gold and are better tolerated than either gold or penicillamine, but their use is limited by their ocular toxicity. However, *retinopathy* is rare if the dosage mentioned below is not exceeded. Nevertheless the patients must have an ophthalmic examination before starting treatment and then at 3-monthly intervals. Ocular toxicity is reduced if these drugs are not given continuously for periods over 1 year, and the patients are advised to stop treatment for 2 months each year.

Chloroquine is administered initially in a dose of 150–300 mg daily after meals; maintenance 150 mg daily. *Hydroxychloroquine* is given initially 400–800 mg daily in divided doses after meals; maintenance 400 mg daily. These drugs are further detailed in **Chapter 10.5.**

Adrenocorticosteroids and ACTH. In 1950 when Hench and his associates administered compound E (cortisol) to their patients with rheumatoid arthritis, they observed striking clinical improvement, with disappearance of pain and tenderness of the affected joints. Initially the corticosteroids were hailed as a "cure" for rheumatoid arthritis. In the succeeeding years many patients suffered the adverse effects of corticosteroids, and now they are *held in reserve,* and used when absolutely necessary to keep the patient from being incapacitated.

Dosage. Patients are started on small doses of prednisone or prednisolone as 5, 7.5 upto 10 mg per day. This is added to the existing drug regimen of salicylates, non-salicylates, gold salts or antimalarials; and physical measures like heat, hydrotherapy and splints continue. On remission of the active disease process, the steroid dosage is reduced or gradually completely tapered off. Arthritic patients do not respond very well to *alternate day thereapy* (ADT), because they develop servere joint symptoms on the "off" day **(Chap. 7.5)**

Intra-articular steroid therapy. In inflammatory conditions of the joints, particularly in rheumatoid arthritis, corticosteroids are given by *intra-articular injection* to relieve pain, increase mobility, or reduce deformity in one or a few joints. Full aseptic precautions are essential. *Hydrocortisone acetate* 5–50 mg, according to the joint size is injected intra-articularly. Not more than three joints should be treated in one day. Other synthetic analogues like *triamcinolone acetonide* (Kenalog), *triamcinolone hexacetonide* (Lederspan), *dexamethasone sodium phosphate* (Decadron), and *methylprednisolone acetate* may be used intra-articularly for pain relief. Intra-articular steroid injections must be employed sparingly, as aseptic necrosis, particularly of the weight-bearing joints is likely to occur as a result of osteoporosis.

Corticotrophin (ACTH) has also sometimes been employed in rheumatoid arthritis. Its advantages are that it stimulates the production and release of endogenous steroids, and does not suppress adrenal function; and there is less of osteoporosis and muscle weakness. The disadvantage is that ACTH has to be administered IM and

Table 2.7-4. *Drugs used for rheumatoid arthritis*

Drugs	Total dose per day (mg)	Average Half-life (hrs)	Frequency of administration (hrs)
NSAIDs			
Salicylates			
Aspirin	4000–5000	3–30 (dose dependent)	4–6
Propionic acid derivatives			
Ibuprofen	1200–2400	2	3–6
Naproxen	500–1000	13	8–12
Fenoprofen	1200–3200	3	6–8
Ketoprofen	100–200	3	12
Flurbiprofen	150–200	4	3–4
Suprofen	800	3	3–6
Indoles			
Indomethacin	50–200	4	3–6
Sulindac	300–400	8	12
Tolmetin	600–1200	1	3–6
Para-aminophenol derivative			
Paracetamol	2000–3000	2	4–6
Fenamates			
Mefenamic acid	1000	3	4–6
Meclofenamate	200–400	2	4–6
Oxicams			
Piroxicam	10–20	45	24
Slow acting antirheumatics (SAARDs)			
Gold	25/weeek	–	Weekly
Penicillamine	250–750	–	24
Hydorxychloroquine	200	–	24
Immunosuppressives			
Methotrexate	7.5–15/week	–	Weekly
Azathioprine	75–200	–	24
Cyclophosphamide	75–150	–	24
Chlorambucil	4–8	–	24

has a relatively short half-life (even the repository form).

Immunosuppressants. These agents, when used in rheumatoid arthritis have a similar action to gold, and are useful alternatives in cases that have failed to respond to gold, penicillamine and chloroquine. *Azathioprine* (1.5 to 2.5) mg/kg per day in divided doses), and chlorambucil (5 mg/day) may be used.

Cyclophosphamide is too toxic for use in rheumatoid arthritis. The immunosuppressive agents are detailed in **Chapter 10.10.** The use is based on the concept that rheumatoid arthritis is an *autoimmune disease,* and the immunosuppressants block antibody biosynthesis.

Other measures employed for the management of rheumatoid arthritis include *lymphopheresis, plasmapheresis* and *total lymphoid irradiation. Sulphasalazine* (salicylazo-sulphapyridine) is a sulphonamide, poorly absorbed from the gut, and primarily used for the treatment of *ulcerative colitis,* has also been used in the treatment of *rheumatoid arthritis* and *ankylosing spondylitis.*

Antimigraine Drugs

Headache is the most common complaint of patients seen by the physician. It may be a serious symptom of intracranial structural changes caused by *brain tumours,* cerebrovascular disorders like *aneurysms* and *angiomas.* Other organic disorders causing headache include *glaucoma, hypertension* and *chronic sinusitis.* The nerve cells of the brain itself are not sensitive to the pain-producing stimuli, but arteries coursing the membranes covering the brain contain pain-sensitive nerve endings. When these *intracranial* arteries are distended pain is perceived. Nerve impulses also arise from *extracranial* structures like skin, blood vessels, and muscles of the scalp and neck, which become a source for pain. In addition, personality factors (psychic causes) may also cause a kind of chronic headache. Thus, headache may be divided into two: (*i*) ***tension*** or ***muscle contraction headaches;*** and (*ii*) ***vascular headaches.*** The tension headaches are difficult to manage, but respond to non-narcotic analgesics like *aspirin* or *paracetamol.* These may sometimes be combined with weak opioid analgesics like codeine or oxycodone. The analgesic remedies with or without addition of opioid analgesics should be prescribed cautiously as they are likely to produce psychic dependence.

Vascular headaches are the result of dilatation of the intracranial and extracranial arteries, and are sometimes classed as ***migraine*** and ***non-migraine*** types. Hypertensive vascular headaches with which the patient wakens in the morning are best dealt by controlling blood pressure by antihypertensive agents. Migraine headaches are classified on the basis of differences in the pattern of individual attacks, and they are : (*i*) classic migraine; (*ii*) common migraine; and (*iii*) cluster headaches (a unilateral vascular headache). Chemical substances that are possibly released locally, and play a part in the perpetuation of migraine are, a polypeptide called *neurokinin,* which resembles *bradykinin,* which causes both vasodilatation and stimulation of pain receptors; and *serotonin* which induces certain local tissue changes.

Drug Therapy

Drugs used to treat migraine may be discussed under two heads: (*i*) treatment of acute migraine attack; and (*ii*) prophylaxis of migraine.

Acute migraine attack. Most migraine headaches respond to analgesics like *aspirin* and *paracetamol*, but as peristalsis is reduced during migraine attacks, these drugs may bot be effectivey absorbed. Soluble preparations are therefore preferable. Other drugs used are *ergotamine tartrate* (Gynergen); *ergotamine tartrate 1 mg, plus caffeine* 100 mg (Cafergot); or *dihydroergotamine mesylate* (DHE-45). These drugs are detailed in **Chapter 3.5.**

Other drugs include *metoclopramide*, or the *phenothiazine* and *antihistamine* antiemetics. These drugs relieve the nausea associated with migraine attacks and metoclopramide promotes gastric emptying and peristalsis. A newer drug is *isometheptene mucate* (Midrid), which is as effective as ergotamine, and has much fewer side effects. It is a sympathomimetic, sedative, and an analgesic agent. *Diazepam* or other anxiolytics may be useful adjuncts to counteract muscle spasm and anxiety which is often present in a migraine attack.

Prophylaxis of migraine. The drugs which are helpful in preventing attacks are : (*i*) *Clonidine* (Dixarit) in a dose of 50 mcg bid, increased after 2 weeks to 75 mcg bid, if necessary, (*ii*) *Propranolol* (Inderal) 20–40 mg bid or tid for prevention of severe recurrent migraine; (*iii*) *Prochlorperazine* (Stemetil) in a dose of 5 mg tid; (*iv*) *Methysergide* (Deseril), an antiserotonergic drug, in a dose of 1.0 mg at bedtime; (*v*) *Pizotifen* (Sanomigran), another antiserotonerigc drug, in a dose of initially 500 mcg daily, increased to 3 mg/day in divided doses, if necessary; and (*vi*) *Cyproheptadine* (Periactin), an older antihistamine-antiserotonergic drug in a dose of 4–20 mg/day in divided doses.

Drugs for Central Pain Syndromes

Central pain syndromes are caused by diseases or injuries affecting portions of the CNS, *e.g., tabes dorsalis, postherpetic neuralgia*, but the aetiology of others, *e.g., trigeminal neuralgia* remains unexplained.

Carbamazepine (Tegretol). It is chemically related to tricyclic antidepressants, but it does not have antidepressive activity. It is primarily employed as an antiepileptic **(Chap. 2.5)**. Carbamazepine is the drug of choice for the treatment of *trigeminal* and *glossopharyngeal neuralgia*, and *tabes dorsalis*. It is usually administered in a dose of 200 mg to a maximum of 1.2 g daily. Small doses are used initially and increased gradually.

Phenytoin (Dilantin). It is sometimes used in the treatment of *trigeminal neuralgia*, but is less effective than carbamazepine. Phenytoin is also reported to be effective in several other pain syndromes, *e.g., peripheral neuralgia, phantom limb pain, thalamic pain* and *postherpetic neuralgia*. Phenytoin also is an antiepilpetic, and is further detailed in **Chapter 2.5.** For trigeminal neuralgia it is employed in a dose of 300–400 mg daily, and the dose may be increased, if necessary. Recently ***amitriptyline*** and ***fluphenazine*** are under controlled studies for relief of pain of *peripheral diabetic neuropathy*.

In this Chapter mainly the nonsteroidal anti-inflammatory drugs have been discussed. They cause reduction of oedema, erythema, and resulting tissue damage associated with inflammatory conditions, and may also induce analgesia, and antipyresis. This triad of action ***anti-inflammatory, analgesic–antipyretic*** – is possessed by the classic, and most widely used NSAID, aspirin. Aspirin has been commonly used since the turn of the century, and even today is the drug of first choice for mild pain, fever and arthritis (osteoarthritis and rheumatoid arthritis).

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