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Aspirin and Related Derivatives of Salicylic Acid

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Summary

After almost 90 years of clinical use, aspirin remains one of the world's most extensively used 'over-the-counter' drugs, and it is still recognised as the standard analgesic/antipyretic/anti-inflammatory agent by which newer drugs are assessed. However, its pre-eminent position as the analgesic of choice for mild to moderate pain has been seriously challenged with the introduction of many 'new' non-steroidal non-narcotic analgesic drugs. Indeed, there is convincing scientific evidence that many of the 'newer' non-steroidal drugs such as diflunisal, ibuprofen, flurbiprofen etc. are significantly superior analgesics and, in many cases, have a longer duration of action.

In recent years the salicylates, aspirin in particular, have been the focus of much attention regarding their side effect profiles. At usual dosages for relief of pain and during occasional use, aspirin is well tolerated by the vast majority of patients. Adverse reactions, of which there is a wide spectrum, most frequently accompany anti-inflammatory doses of aspirin, or may be the result of accidental overdosing (particularly in children and the elderly) – probably a reflection of the lay population's acceptability of aspirin's presumed safety. As with other non-steroidal analgesic drugs, gastrointestinal complaints are the most commonly reported side effects.

The existence of many shared clinical, adverse and toxic effects of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is thought to be accounted for by a common mechanism – inhibition of the ubiquitous cyclo-oxygenase enzyme. Thus, suppression of prostaglandin biosynthesis is widely considered to explain the common properties of NSAIDS, although further research is still necessary to clarify some inconsistencies and to complete our understanding of the processes involved.

Aspirin and salicylates have been reported to have a wide range of drug interactions but only relatively few seem to be clinically important. Many of the interactions are pharmacokinetic in nature. Drugs considered to produce the most significant interactions with salicylates include anticoagulants and thrombolytic agents, uricosuric agents, corticosteroids, methotrexate and sulphonylurea hypoglycaemic agents.

Numerous historical accounts of the use of plant materials containing salicin, extraction of the active material salicylic acid, and the synthesis of active derivatives, especially acetylsalicylic acid (aspirin), have been published (e.g. Hanks, 1982; Miller, 1982; Starmer, 1983). Aspirin was first administered clinically at the turn of the century and now, almost 90 years later, it still remains the world's most extensively used 'over-the-counter' drug. In the United States alone, it has been esti-

mated that approximately 20,000 million aspirin tablets are consumed per annum and this represents about 100 tablets/year for every man, woman and child (Taylor, 1980-81). The fact that aspirin has remained so popular for so long highlights its acceptability to the general public and, presumably, is a good indication of its therapeutic usefulness for treating minor aches and pains.

Although aspirin is generally considered safe by most people, it is certainly not innocuous; side effects, especially gastrointestinal disturbances, do occur (see Ivey, this issue). Additionally, aspirin is a common cause of analgesic poisoning in both adults and children. Accidental overdosing, particularly in the elderly and in children, is probably a reflection of the drug's popularity and wide availability, and the lay population's acceptability of its efficacy and presumed safety.

It is against this background that the search for safer and more effective salicylates has been carried out. This review will focus on the pharmacodynamic properties (analgesic and anti-inflammatory activity), pharmacokinetic characteristics and therapeutic efficacy (including adverse effects and drug interactions) of aspirin, the standard non-narcotic analgesic by which newer salicylates are assessed. Where appropriate, some perspective of how other derivatives of salicylic acid (such as diflunisal, fendosal, fosfosal and salsalate) compare with aspirin will be presented. (For structural formulae of these compounds, see fig. 1.)

1. Pharmacodynamic Properties

1.1 Mechanism of Action

Although aspirin is the most widely used non-narcotic analgesic, it was not until the early 1970s that a major discovery was made regarding its mechanism of action. The demonstration in 1971 that aspirin inhibited the enzymatic production of prostaglandins initiated intense investigation of the physiological role of these autacoids (Ferreira et al., 1971; Smith and Willis, 1971; Vane, 1971). It is now widely accepted that many of the therapeutic and unwanted effects of aspirin (and other salicylates) can be attributed to a reduction in the bio-

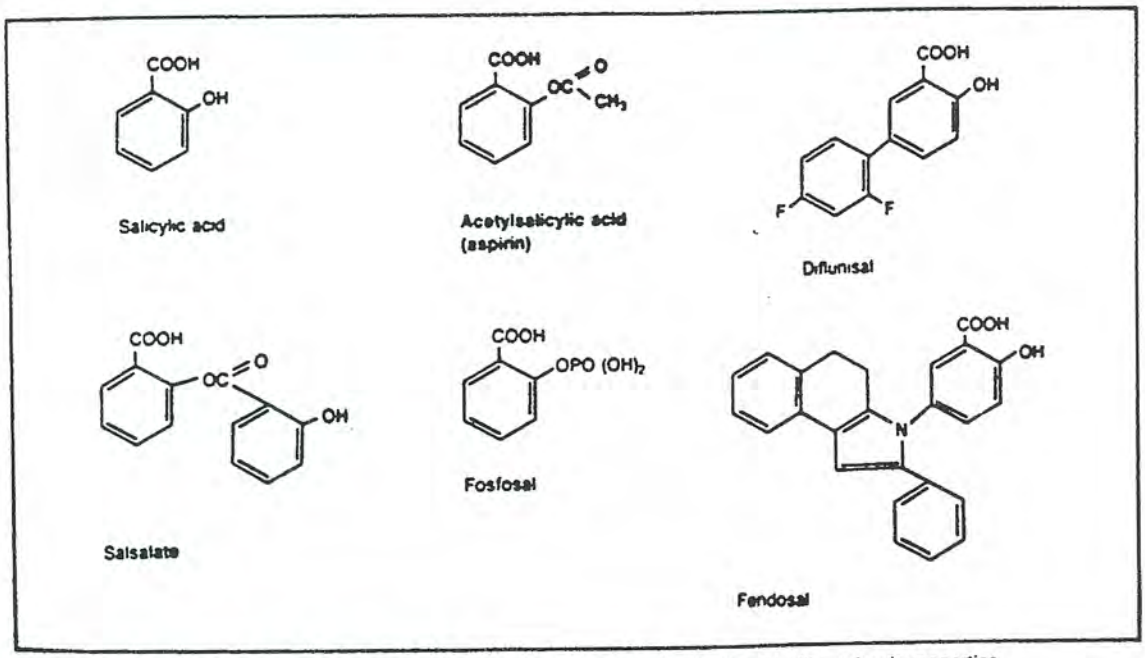

Fig. 1. Structural formulae of salicylic acid, aspirin and other derivatives of salicylic acid with analgesic properties.

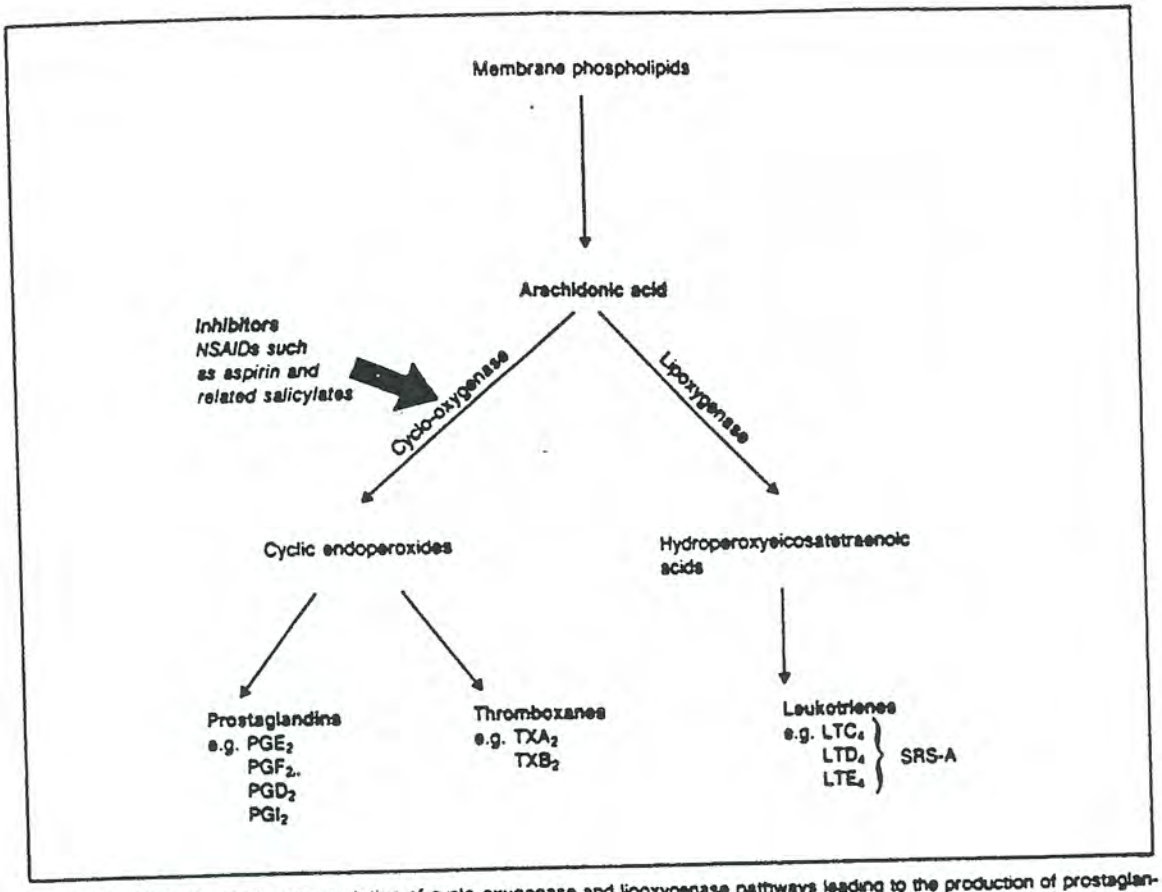

Fig. 2. Simplified schematic representation of cyclo-oxygenase and lipoxygenase pathways leading to the production of prostaglandins, thromboxanes and leukotrienes from arachidonic acid (adapted from Brune and Lanz, 1984; Farah and Rosenberg, 1980; Kay, 1983; Moncada et al., 1980).

synthesis of prostaglandins and related autacoids from arachidonic acid. In the multiplicity of steps leading to the production of prostaglandins, NSAIDs such as aspirin prevent the synthesis of cyclic endoperoxides by the prostaglandin synthetase enzyme cyclo-oxygenase (fig. 2).

Certain intermediates and end products of the arachidonic acid cascade, in combination with other local mediators such as bradykinin, histamine and 5-hydroxytryptamine, may cause erythema, oedema, pain, etc. associated with the inflammatory response. Because the prostaglandins are among the most prevalent of autacoids, inhibition of cyclo-oxygenase probably explains, at least in part, the anti-inflammatory activity of aspirin as well as its actions on gastric mucosa, platelets, kidney, uterus, etc. (Vane, 1975).

In vivo aspirin is rapidly hydrolysed to salicylic acid and acetate and many of its pharmacodynamic actions are attributable to the salicylate moiety. However, hydrolysis is not a prerequisite for pharmacological activity and aspirin itself has some unique properties (for a detailed review see Flower et al., 1980). Interestingly, aspirin inhibits cyclo-oxygenase by acetylation, whereas salicylic acid, which has no acetylating capacity, has little effect on the enzyme *in vitro*. Nevertheless, the 2 drugs produce comparable inhibition of prostaglandin biosynthesis *in vivo*. These findings not only suggest a different mechanism of action for aspirin

compared with the salicylate moiety; they also indicate that aspirin probably possesses a dual means of inhibiting cyclo-oxygenase. Early studies found aspirin to be a superior analgesic to sodium salicylate (Lasagna, 1961; Lim, 1966) and presumably this implies that acetylation of cyclo-oxygenase is an important mechanism for its analgesic properties. Recent evidence from Seymour et al. (1984) appears to support this contention, although further study is obviously needed to clarify how other non-acetyl-containing non-steroidal drugs produce their analgesic effects.

Inhibition of prostaglandin production does not seem to explain all of the pharmacodynamic actions of aspirin and additional mechanisms have been postulated (for reviews see Brune and Lanz, 1984; Hanks, 1982). It has been speculated that high doses of aspirin may inhibit hydroperoxy fatty acid peroxidase in the lipoxygenase pathway of arachidonic acid metabolism and this may contribute to some of the effects of aspirin in man (McDonald-Gibson et al., 1984). Of course, unknown peripheral and/or central mechanisms of action may also be involved. Further research is clearly needed to explain some of the inconsistencies in the literature, to clarify the exact mechanism of action of aspirin and other derivatives of salicylic acid, and to fully elucidate our understanding of the involvement of the end products of the arachidonic acid cascade in various physiological systems.

1.2 Analgesic Effects

Aspirin and related drugs can alleviate pain of mild to moderate severity. These effects appear to be mediated through peripheral and central mechanisms, although the work of Lim et al. (1964) suggests that aspirin acts mainly peripherally (see also Bowman and Rand, 1980; Flower et al., 1980).

Prostaglandins seem to sensitise peripheral pain receptors to mechanical or chemical (bradykinin, histamine, etc.) stimulation at a local level. Most data are consistent with the theory that aspirin and other cyclo-oxygenase inhibitors avert the sensitisation of peripheral nociceptors to such stimulation by preventing production and consequently release of the intermediates and/or end products of the arachidonic acid cascade. These drugs do not affect the sensitisation or pain caused by the direct action of prostaglandins, which is in agreement with this hypothesis. Additionally, cyclo-oxygenase inhibitors are most effective against dull, throbbing pain associated with inflammation (where prostaglandins apparently sensitise the nerve endings) and are less effective against sharp, stabbing pain caused by direct stimulation of sensory nerves.

In addition to these peripheral actions, direct effects of salicylates within the central nervous system (CNS) have also been described (Dubas and Parker, 1971). The mechanisms involved in such central activity have not been clearly defined, although inhibition of prostaglandin production within the CNS remains a possibility. Since analgesic doses of aspirin do not cause mental disturbances, hypnosis, or striking changes of mood, relieve pain without affecting other sensory modalities, and do not modify arousal mechanisms involving the brain stem reticular formation, it seems likely that any central mechanism is probably subcortical, perhaps at the level of the hypothalamus. The paucity of such CNS effects also suggests that the analgesic activity of salicylates is mediated largely through their peripheral actions.

1.3 Anti-Inflammatory Effects

This review was intended to cover the analgesic characteristics of the salicylates, but in some ways it is not possible to divorce these actions from the anti-inflammatory effects and, consequently, a brief overview of the anti-inflammatory properties of aspirin is needed. (For reviews see Bowman and Rand, 1980; Flower et al., 1980.)

Aspirin has been used since about 1900 for the treatment of inflammatory diseases such as rheumatoid arthritis, and it was not until very recently that other NSAIDs challenged its pre-eminence as an antirheumatic drug. At present it does not seem that any of the newer non-steroidal drugs are more effective anti-inflammatory agents, but at therapeutic dosages many of them are generally better tolerated (see p. 27).

Inflammation is an extremely complex defensive reaction to injury, which is characterised by erythema, oedema, tenderness and pain. As a result of cell damage, chemical mediators such as histamine, bradykinin, 5-hydroxytryptamine, slow-reacting substance of anaphylaxis (SRS-A), chemotactic factors, prostaglandins, etc. are liberated locally. As the inflammatory response progresses, the vascular endothelium becomes swollen and eventually blood elements leak into the interstitial spaces. Phagocytic cells (including leucocytes) migrate to the damaged area and probably contribute to the defensive reaction by releasing lytic enzymes. Any pain associated with inflammation is probably due to stimulation of nerve endings by one or more of the chemical mediators released during the host's response to injury. This somewhat simplistic outline of the acute inflammatory response to tissue damage serves to highlight the difficulties involved in evaluating the mechanism of action of aspirin during such a complex series of events. Aspirin and other NSAIDs are effective in modifying the inflammatory response in a variety of rheumatic diseases, but they are not curative, in that they do not stop the degenerative process.

Prostaglandins are released during the inflammatory response and they seem to be important mediators of the defensive reaction. Hence, the ability of salicylates to inhibit prostaglandin synthesis could account for their anti-inflammatory properties. However, as noted by Sause et al. (1982), various other mechanisms have been proposed such as interference with cellular metabolism, interference with the release of inflammatory mediators from plasma proteins, interference of sodium and potassium ion transfer across cell membranes, inhibition of the actions of chemical mediators other than prostaglandins, and stabilisation of lysosomes. Furthermore, the discovery of the lipoxygenase pathway and the production of leukotrienes adds another avenue which may contribute to the underlying process of inflammation. It is generally agreed, however, that the anti-inflammatory effects of NSAIDs are positively correlated with their anticyclo-oxygenase activity (Vane, 1973). Further studies are clearly necessary to elucidate the exact mechanisms by which salicylates produce their anti-inflammatory effects.

2. *Pharmacokinetic Properties*

Aspirin and some other derivatives of salicylic acid (e.g. choline salicylate, choline magnesium trisalicylate, magnesium salicylate, salsalate) are hydrolysed in the body to salicylic acid. Irrespective of the parent source of salicylate, once it is absorbed and hydrolysed the pharmacokinetic characteristics are essentially those of salicylic acid. It follows that blood and urinary data for salicylate are more meaningful than blood or urine concentrations of the parent drug (Dromgoole et al., 1981). Only in the last two decades have the complex pharmacokinetic properties of the salicylates been fully appreciated, and some aspects are still unresolved (Levy, 1981). Other derivatives of salicylic acid (notably diflunisal) are not hydrolysed to salicylate and will be discussed briefly where appropriate.

There is growing evidence that the pharmacokinetic behaviour of NSAIDs has a major impact on their therapeutic efficacy and tolerability (for recent reviews see Brune and Lanz, 1984, 1985). Indeed, it has been shown that these drugs achieve particularly high concentrations in those compartments in which they have beneficial and/or adverse effects. Consequently, an understanding of the pharmacokinetic properties of aspirin and related salicylic acid derivatives is of prime importance to our interpretation of the clinical attributes of this class of drugs.

2.1 Absorption

Orally administered aspirin is rapidly and usually completely absorbed from the gastrointestinal tract (both as unchanged drug and hydrolysed salicylate) [Dromgoole et al, 1981]. Absorption occurs by passive diffusion of un-ionised lipophilic molecules, partly from the stomach but mainly from the upper small intestine. Many factors are known to affect the rate of absorption (table I) and, of these, drug formulation has the major influence since it

controls the dissolution of aspirin and this has been shown to be the rate-limiting step for the absorption of solid tablets (Levy and Hollister, 1965). Over all, effervescent and soluble tablet preparations are most rapidly absorbed (15 to 40 minutes), followed by uncoated or film-coated tablets (25 to 60 minutes), and finally by enteric-coated (240 to 360 minutes) and extended-release formulations (60 to 120 minutes). The times in parentheses represent the approximate times to achieve mean peak aspirin concentrations; however, plasma aspirin concentrations decline rapidly as plasma salicylic acid concentrations increase. Thus, the corresponding times to achieve peak salicylic acid concentrations are 30 to 60 minutes for soluble or effervescent tablets, 45 to 120 minutes for uncoated or film-coated tablets, 4 to 12 hours for extended-release tablets, and 8 to 14 hours for enteric-coated tablets.

After oral administration of an aqueous solution, the absorption of aspirin was found to follow first-order kinetics (Rowland et al., 1972). In this study there was a wide variation in absorption half-life (4.5 to 16 minutes) and approximately 70% of the administered dose reached the systemic circulation unchanged. The remaining 30% was thought to be hydrolysed during absorption by esterases within the gut wall, plasma or liver.

Gastrointestinal pH has a major influence on the rate of absorption of aspirin by two different mechanisms. Firstly, low pH in the stomach provides optimum conditions for the absorption of undissociated aspirin molecules, although this is probably not important for drug preparations which are given in solution (effervescent and soluble tablets). Secondly, as pH rises (in the small intestine) the dissolution rate for aspirin tablets increases, and is maximal at pH 8 (for a recent review see Needs and Brooks, 1985). Some formulations of aspirin contain various buffers, but the effects of these on drug absorption are both variable and conflicting. Certainly, it now seems unlikely that buffered aspirin tablets cause less gastric irritation than uncoated plain aspirin tablets, as was previously thought (see Ivey, this issue).

Table I. Some important factors affecting the rate of salicylate absorption (after Needs and Brooks, 1985)

Drug formulation
pH of stomach contents
Rate of gastric emptying
Volume of food
Concurrent administration of other drugs
Nervous state
Posture
Exercise
Disease states associated with altered gastrointestinal transit time

Salsalate is completely absorbed from the gastrointestinal tract, although the relative amount reaching the circulation as unchanged drug has not been reported. Mean peak salsalate concentrations have been noted after approximately 1.5 hours; mean peak salicylic acid concentrations occurred within 2 to 4 hours. As for most derivatives of salicylic acid, food delays the absorption of salsalate and also reduces the mean peak plasma concentration.

Diflunisal is rapidly and completely absorbed after oral administration, generally achieving peak plasma concentrations within 2 to 3 hours. In fasted subjects the bioavailability of diflunisal is significantly decreased by concomitant administration of antacids containing aluminium hydroxide (Brogden et al., 1980). Because diflunisal has a long half-life, steady-state plasma concentrations are not attained for 3 to 4 days with low doses (125mg) and for 7 to 9 days with higher doses (500mg) administered twice daily.

2.2 Distribution

Once absorbed, aspirin is rapidly hydrolysed to salicylic acid with a half-life of only 15 to 20 minutes (Rowland and Riegelman, 1968). Thus, from this stage onwards the pharmacokinetics of aspirin, and other salicylates hydrolysed to salicylic acid, are predominantly dependent upon the salicylate moiety (Needs and Brooks, 1985) [see fig. 3].

Salicylic acid is normally highly protein bound (80 to 90%) at therapeutic plasma concentrations and this probably accounts for the low reported values for the apparent volume of distribution, which range between 9.6 and 12.7L in adults and between 0.12 and 0.14 L/kg in children (Graham et al., 1977; Wilson et al., 1982). Despite such low values for the apparent volume of distribution, salicylic acid rapidly distributes throughout extracellular fluid and into most tissues. Distribution appears to increase with increasing doses and this may be due, at least in part, to decreased protein binding at higher plasma salicylate concentrations. Salicylic acid protein binding is closely dependent upon serum albumin concentrations; if these decrease (e.g. during pregnancy and in patients with renal disease), the bound salicylate fraction decreases and the amount of free drug increases proportionally. It has been suggested that the binding of salicylic acid to the albumin molecule occurs at 2 primary and a number of secondary binding sites (Borgå et al., 1976).

Whereas salicylic acid is largely bound to plasma albumin, aspirin itself binds only poorly to plasma proteins, although it has been shown to acetylate plasma albumin as well as some enzymes such as cyclo-oxygenase. This latter effect is probably a major mechanism by which aspirin produces its analgesic and anti-inflammatory actions (see sections 1.1, 1.2 and 1.3).

After absorption, salicylate penetrates into synovial fluid, peritoneal fluid, saliva and milk, but not into gastric juice and only slightly into bile, sweat and inflammatory exudates. It readily crosses the placental barrier. Distribution of salicylate occurs by pH-dependent passive diffusion, which

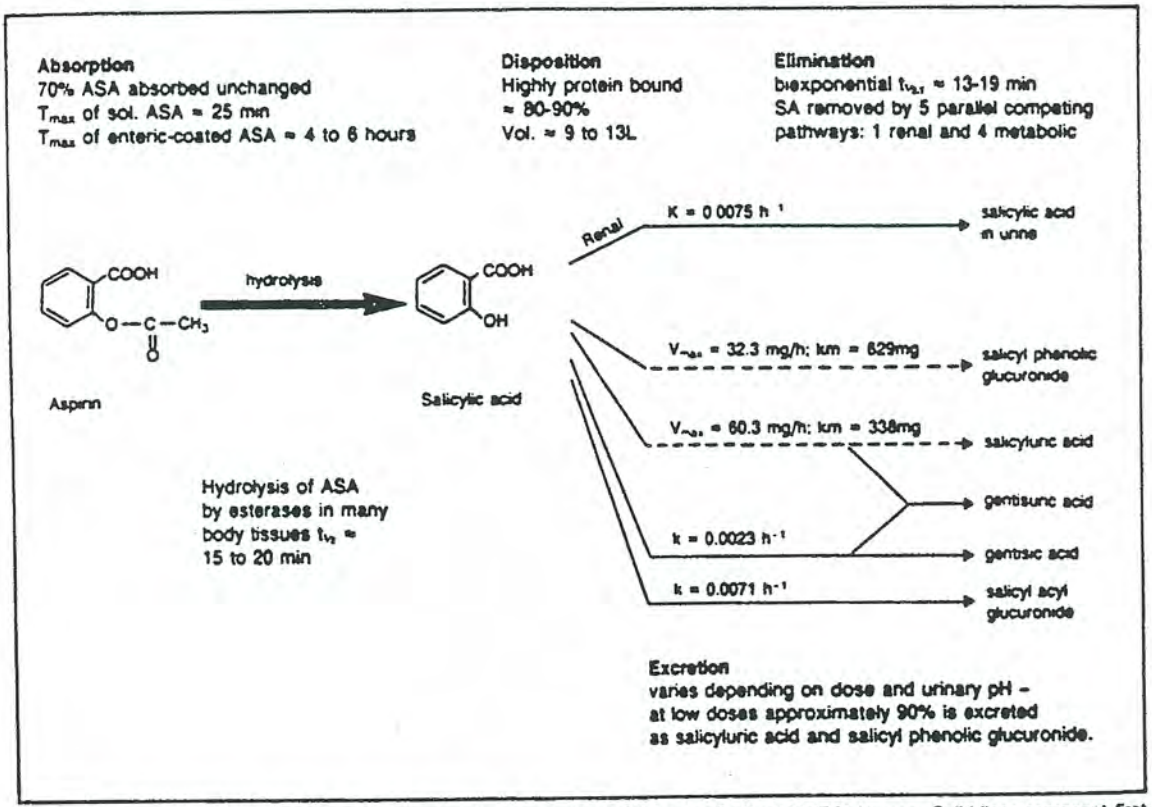

Fig. 3. Some important pharmacokinetic characteristics of aspirin (ASA) and salicylic acid (SA) in man. Solid lines represent first-order processes and Michaelis-Menten pathways (after Levy and Tsuchiya, 1972; Needs and Brooks, 1985).

limits its ability to cross the blood-brain barrier (Flower et al., 1980).

Diflunisal is 98 to 99% plasma protein bound and has a relatively low apparent volume of distribution of about 8L in patients with normal renal function (Brogden et al., 1980). The volume of distribution is significantly increased to almost 17L in patients with terminal renal insufficiency. In lactating women, the milk diflunisal concentration is 2 to 7% of that in plasma.

2.3 Elimination

As emphasised earlier, aspirin is rapidly metabolised to salicylic acid; the acetyl component is generally found in the gastric mucosa or is excreted as carbon dioxide after passing through the Krebs cycle (Rainsford et al., 1983). Following intravenous administration, the elimination kinetics of aspirin are best described by a biexponential equation with a terminal half-life of 13 to 19 minutes (Rowland and Riegelman, 1968).

The elimination of salicylic acid is far more complex and it is removed from the body by 5 parallel and competing pathways; 1 renal and 4 metabolic (fig. 3). The 3 main metabolites are salicyluric acid (glycine conjugate), salicyl phenolic glucuronide and salicyl acyl glucuronide. Small amounts of salicylate undergo oxidation to gentisic acid; gentisuric acid may be formed from it by glycine conjugation or from salicyluric acid by microsomal oxidation (Wilson et al., 1978). Because the 2 major metabolites of salicylic acid (salicyluric acid and salicyl phenolic glucuronide) are produced via saturable Michaelis-Menten pathways, the elimination kinetics are highly dose dependent. The other routes of elimination exhibit linear first-order kinetics (Levy, 1965, 1971, 1979) [fig. 3].

Biotransformation of salicylate occurs in many tissues but particularly in the endoplasmic reticulum and mitochondria of the liver (Flower et al., 1980). Some salicylic acid is excreted unchanged via the kidney and the various metabolites are also eliminated renally. The relative amounts of salicylic acid and its conjugates excreted in the urine vary widely, being dependent upon the dose administered and urinary pH. Notably, at high dosages the excretion of unchanged salicylic acid, salicyl acyl glucuronide and gentisic acid generally increases as a result of the saturable nature of the pathways forming salicyluric acid and salicyl phenolic glucuronide (at small doses of aspirin, 300mg or less, about 90% is excreted via these saturable routes). As urinary pH is increased from acidic to alkaline, the urinary excretion rate for free salicylic acid is markedly elevated, and the fraction of a single dose eliminated in the urine as unchanged drug may increase from as low as 5% to as high as 85%.

Reported values for the plasma half-life of salicylic acid are also dose dependent. It has been shown that at low doses (e.g. 325mg aspirin) salicylate elimination is first order with a half-life of about 2 to 3 hours. At higher doses, elimination of salicylate is limited by the ability of the liver to form salicyluric acid and salicyl phenolic glucuronide, and plasma half-life may increase up to 30 hours or more.

Salsalate is rapidly and extensively hydrolysed to 2 molecules of salicylate in the body (about 7 to 13% of a single oral dose is conjugated with glucuronide before hydrolysis). The drug is primarily excreted as salicylate metabolites by the kidneys: small amounts are eliminated as unchanged salsalate, some as a glucuronide metabolite, and most via the salicylic acid pathway. The plasma elimination half-life of salsalate is about 1 hour.

Unlike the drugs mentioned so far, diflunisal is not metabolised to salicylic acid and its elimination is almost entirely dependent on glucuronidation. About 80 to 95% of an oral dose of diflunisal is excreted in the urine in 72 to 96 hours with a terminal elimination half-life of about 10 hours. The half-life is considerably increased in patients with renal insufficiency (up to 115 hours when creatinine clearance is less than 0.12 L/hour) [Brogden et al., 1980].

3. Analgesic Efficacy

Aspirin and other salicylates are weaker analgesics than most narcotic drugs and they are most effective in relieving mild to moderate pain such

as toothache, headache, arthralgia, dysmenorrhoea, discomfort (and fever) associated with common colds, and a wide range of muscular aches and pains. Salicylates are also useful in suppressing other forms of mild to moderate pain, such as postsurgical pain (dental, orthopaedic, general), postpartum/episiotomy pain and chronic pain of visceral origin in cancer patients. When used to treat pain associated with inflammatory disorders (e.g. rheumatoid arthritis, osteoarthritis and other rheumatic conditions) appropriately employed dosages of salicylates, particularly aspirin, compare favourably with other NSAIDs. This action of salicylates is dependent on their anti-inflammatory properties and will not be considered in any detail in this review. The aim is to evaluate the analgesic efficacy of this class of drugs and this has been most extensively studied in acute pain conditions, generally of a self-limiting nature (postsurgical pain, episiotomy pain, dental pain, etc.), in single-dose comparative clinical trials.

3.1 Acute Pain

Aspirin has been compared with placebo, many other non-narcotic analgesics (including other salicylates) and some centrally acting analgesics in a variety of acute pain conditions (for detailed reviews see Cooper, 1981, 1983; Seymour, 1983).

3.1.1 Comparisons with Placebo

In a recent review, Seymour (1983) reported that in almost all clinical trials in patients with dental pain following third molar surgery, aspirin, as might be expected, was significantly superior to placebo. In an extensive study, von Graffenried et al. (1980) found that in 5 separate placebo-controlled clinical trials aspirin 1g produced significantly ($p < 0.01$) better pain relief than placebo in 326 subjects after removal of impacted lower molars. Using 2 different doses of aspirin, Seymour and Rawlins (1982) demonstrated that a 600mg dose was only significantly superior to placebo in relieving postsurgical dental pain 45 minutes after administration. Aspirin 1200mg, on the other hand, produced significantly better pain relief at all time points between 45 and 240 minutes. Only isolated trials have failed to identify a significant advantage for aspirin compared with placebo, and these may not have employed methods sufficiently sensitive to record pain differences. In many other clinical studies in which a placebo period has been included, aspirin nearly always produced significantly greater pain relief than placebo (Cooper, 1983).

The analgesic efficacy of salsalate in acute pain conditions has not been extensively evaluated, although it is generally considered to be as effective as aspirin in chronic pain conditions associated with rheumatic diseases. In a placebo-controlled dose-comparative study, Forbes et al. (1982b) demonstrated that diflunisal at doses between 250 and 1000mg produced pain relief significantly superior to that provided by placebo and aspirin 650mg in 201 patients with postoperative pain after oral surgery (see fig. 4). The same group found that fendosal, a recently developed salicylic acid derivative, was also significantly better than placebo in providing pain relief after dental surgery (Forbes et al., 1984).

3.1.2 Comparative Efficacy of Some Derivatives of Salicylic Acid

Aspirin appears to be a better analgesic than sodium salicylate (Mehlisch, 1983; see section 1.1). A double-blind crossover trial in patients with pain resulting from dental surgery reported no difference in analgesic efficacy between sodium salicylate 537 and 1074mg and placebo (Seymour et al., 1984). However, the number of trials comparing aspirin and sodium salicylate are very few, and additional supporting data for this statement are still needed. Indeed, there is limited information regarding the comparative analgesic efficacy of most salicylates, although 'newer' derivatives have usually been compared with aspirin.

Diflunisal has been evaluated in a number of pain states and has been compared with a number of non-narcotic analgesics, particularly aspirin (for detailed reviews see Brogden et al., 1980; Cooper, 1983). In postoperative dental pain patients, diflunisal 250 to 1000mg was found to have a higher peak effect and a substantially longer duration of

action than aspirin 650mg (Forbes et al., 1982b) [fig. 4]. Comparisons between diflunisal and aspirin in patients with other forms of postoperative pain (orthopaedic, episiotomy, meniscectomy, general) have generally shown that the 2 drugs have similar peak effects but that diflunisal 500 to 1000mg has an 8 to 12 hour duration of action. This reflects the relatively long plasma half-life for diflunisal (about 10 hours; see section 2.3), which permits twice daily administration.

A similar analgesic profile has recently been reported for fendosal. Compared with aspirin 650mg, fendosal 200mg produced a slower onset of action (3 hours *vs* 1 hour), had a comparable peak analgesic effect, and had a significantly longer duration of analgesia (8 hours *vs* 2 hours) in 109 patients with pain after dental surgery (Forbes et al., 1984).

3.1.3 Comparisons with Paracetamol (Acetaminophen)

Aspirin and paracetamol have been compared in a variety of painful conditions such as postoperative pain resulting from oral surgery and dental extractions, episiotomy pain and pain associated with malignancy. In reviewing clinical trials up to 1981, Cooper (1981) concluded that aspirin and paracetamol are equianalgesic and, on a weight for weight basis, equipotent in most types of pain. A similar conclusion was reached by Mehlisch (1983). The 2 drugs have similar dose-response and time-effect curves (Cooper, 1983) [fig. 5].

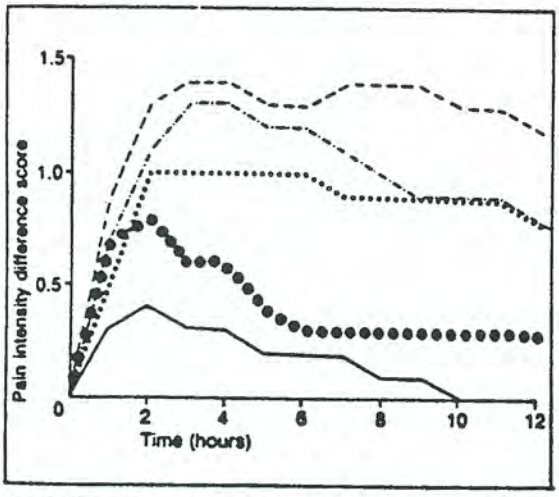

Fig. 4. Change in mean pain intensity difference score with time following administration of placebo (——, n = 38), aspirin 650mg (•••, n = 42), diflunisal 250mg (—•—, n = 39), diflunisal 500mg (•••, n = 41), and diflunisal 1000mg (——, n = 41) in 201 patients with postoperative pain following oral surgery (adapted from Forbes et al., 1982b).

Peak analgesic effects of diflunisal 500 and 1000mg were found to be significantly greater than that of paracetamol 600mg and comparable with that of a combination of paracetamol 600mg and codeine 60mg (Forbes et al., 1982a). Similarly, Melzack et al. (1983) demonstrated that diflunisal 1000mg produced a significantly greater reduction in pain than paracetamol 650mg from hours 5 to 12. Other studies have found that diflunisal 500mg is a superior analgesic to paracetamol 500 or 1000mg (Quiding et al., 1985); diflunisal 250mg and a combination of paracetamol 500mg, codeine phosphate 8mg and caffeine 30mg were equally efficacious (White and Strunin, 1982); and diflunisal 500mg twice daily produced better relief from night pain and pain associated with passive movement and tenderness than a combination of paracetamol and dextropropoxyphene (Rao and Sharma, 1982). In these studies diflunisal had a significantly more prolonged duration of action, although its onset may be slightly slower.

3.1.4 Comparisons with Other NSAIDs

Cooper (1983) has recently reviewed the available data concerning the analgesic efficacy of NSAIDs including the salicylates and paracetamol. This extensive review focused on the use of these drugs in acute pain conditions, but mainly pain associated with oral surgery. In general terms the results clearly demonstrated the greater analgesic effects of newer NSAIDs such as ibuprofen, indoprofen, suprofen, ketoprofen, flurbiprofen, zomepirac, etc. Advantages such as quicker onset of action or a more sustained duration of action have also been reported for some of these drugs. The author suggests that the newer non-steroidal drugs appear to fill a void between mild non-narcotic analgesics and potent injectable narcotic analgesics. An additional advantage of the newer NSAIDs

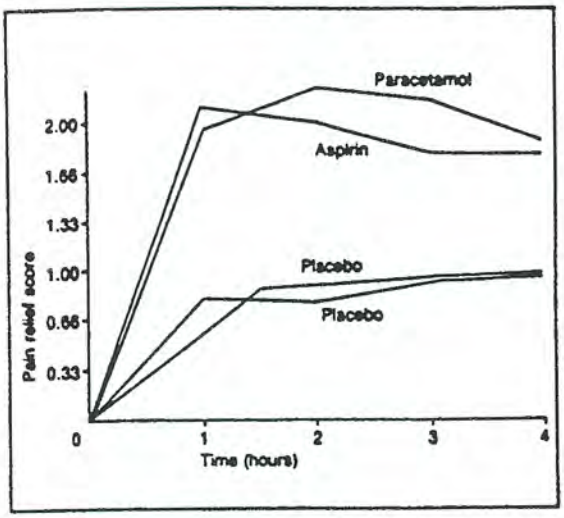

Fig. 5. Composite time-effect curve from 2 separate clinical studies comparing aspirin 650mg with placebo, and paracetamol 650mg with placebo in patients with pain following oral surgery (from Cooper, 1981, with permission).

is that they almost all have more favourable side effect profiles than aspirin. However, when aspirin has been contraindicated these newer drugs are also contraindicated, or they should be used with extreme caution (see Szczeklik, this issue). The analgesic properties of NSAIDs are discussed more fully by Brogden (this issue, p. 27).

Ibuprofen was the first propionic acid derivative with analgesic properties to be marketed and it has only recently received approval for over-the-counter supply. It will be of great interest to see the extent to which it makes in-roads into the tight hold that paracetamol and aspirin have had on the mild to moderate analgesic market.

3.1.5 Comparisons with Centrally Acting Mild to Moderate Analgesics

Aspirin has been compared with a small number of narcotic analgesics such as codeine, pentazocine and dextropropoxyphene, which are generally used to treat mild to moderate pain (for a recent review see Seymour, 1983). Single dose studies in patients with postoperative dental pain demonstrated that aspirin is a superior analgesic to these 3 drugs. Cooper and Beaver (1976) showed that aspirin 650mg gave considerably better pain relief than codeine 60mg and the combination of these 2 drugs was even more effective.

Diflunisal 500mg was found to be superior to low doses of codeine in patients with pain resulting from the removal of impacted mandibular wisdom teeth and as effective as pentazocine 50mg in patients with mild to moderate pain resulting from cancer.

3.2 Visceral Pain Associated with Cancer

Malignant diseases may cause pain in a variety of ways. Usually direct local pressure from a tumour on a nerve, sensitive tissues, viscera or bone is the main mechanism; indirect effects may also be responsible (Woods, 1983). Salicylates provide relief from mild forms of pain, but usually the pain is severe and stronger analgesics are required. In a double-blind crossover study, various analgesics were compared in 57 patients with mild to moderate pain resulting from an unresectable malignancy (Moertel et al., 1972). Aspirin 650mg produced better pain relief in a greater number of patients than most of the other mild to moderate analgesics tested.

4. Side Effects

Occasional use of usual dosages of aspirin for analgesic or antipyretic purposes generally causes few adverse effects. However, when large doses are administered or when it is given for sustained periods, the incidence of side effects increases; these reactions are probably related to the limited capacity of the metabolic pathways responsible for the elimination of aspirin (see section 2.3).

In recent years, salicylates (particularly aspirin) have been the subject of a great deal of attention with regard to their side effect profiles. Considering aspirin's wide usage, it is perhaps not surprising that it has been reported to cause a multiplicity of adverse reactions and to affect many of the organs of the body. However, as noted by Jick (1981), even without collecting formal data, it does seem as

though serious side effects with aspirin are rare; if this were not the case, the extensive use of the drug would result in a continuous epidemic of severe adverse toxic reactions.

Some of the more recently developed salicylates such as diflunisal and salsalate seem to have improved side effect profiles compared with aspirin; these drugs may be more reasonable choices for the longer term treatment of chronic diseases such as rheumatoid arthritis. However, if aspirin is contraindicated these drugs are probably also contraindicated or, at best, they should be introduced with caution.

4.1 Gastrointestinal Effects

Gastrointestinal complaints are the most frequently reported side effects associated with the administration of NSAIDs, especially aspirin (see Ivey, this issue). Symptoms include dyspepsia, heartburn, epigastric pain, nausea and vomiting; objective signs of gastrointestinal irritation reported most often are gastric erythema, pinpoint haemorrhages, mucosal erosions, occult blood loss, exacerbation of gastric ulceration and, more seriously, severe gastric ulceration and frank haemorrhage (for reviews see Ivey, 1983; Piper, 1983).

The relative incidence of gastrointestinal side effects caused by aspirin is low; it has been estimated that between 2 and 6% of patients will develop dyspepsia, nausea and vomiting (Editorial, British Medical Journal, 1981). Additionally, epidemiological surveys have demonstrated an increased risk of severe haemorrhage or gastric ulceration only in persons taking aspirin in large doses (more than 15 tablets per week) or regularly (4 or more days per week). Such adverse consequences are rare: their respective incidences have been calculated as 10 and 15 per 100,000 habitual aspirin users (see Editorial, British Medical Journal, 1981; Levy, 1974; Rees and Turnberg, 1980). For a discussion of the gastrointestinal toxicity of aspirin and salicylates see Ivey, this issue.

The mechanisms by which NSAIDs cause gastrointestinal disturbances are complex and are discussed by Ivey in this issue. At the present time, inhibition of prostaglandin synthesis seems fundamental to the changes that occur, and such a mechanism would explain why all the acidic NSAIDs share gastrointestinal irritancy as their most frequent adverse effect.

In various animal species, including man, prostaglandins (particularly of the E series) have been demonstrated to inhibit gastric acid secretion, increase mucosal blood flow, and have a cytoprotective role (Hanks, 1982; Vane, 1975). It follows that peripheral cyclo-oxygenase inhibitors, which reduce the biosynthesis of prostaglandins (see section 1.1), probably increase the risk of gastric mucosal damage. Other mechanisms which may contribute to the adverse effects of aspirin in the stomach include a direct irritant action and its ability to interfere with platelet function (see section 4.4). The relative importance of the local and systemic effects of aspirin in the pathogenesis of gastrointestinal injury remains debatable, and further research is needed to clarify the exact mechanisms involved.

Numerous formulations of aspirin and many new derivatives of salicylic acid have been evaluated to try and reduce gastrointestinal complaints while maintaining analgesic efficacy. From studies published to date, a number of conclusions can be reached:

1. Plain unbuffered formulations of aspirin cause the greatest amount of gastrointestinal damage.

2. Other formulations of aspirin, such as soluble, adequately buffered, enteric-coated and extended-release, reduce the incidence of gastrointestinal effects but not to an extent that they can be recommended without reservation for use in patients with upper gastrointestinal problems such as dyspepsia.

3. Newer non-narcotic analgesics related to salicylic acid, like choline magnesium trisalicylate, salsalate, fendosal, fosfosal and diflunisal, also appear to have significantly less effect on the gastrointestinal tract. However, although such drugs produce a lower overall incidence of adverse gastric reactions, gastrointestinal toxicity seems inevitable owing to their actions on cyclo-oxygenase,

and they should be used with extreme caution in patients with suspected gastrointestinal disease.

4.2 Renal Effects

Generally, renal function is not adversely affected by intermittent administration of usual dosages of aspirin and related salicylates. However, there is extensive clinical evidence linking analgesic abuse with chronic renal disease (see Kincaid-Smith, this issue). The characteristic lesion is renal papillary necrosis with secondary cortical damage leading to progressive renal failure (for an extensive review see Prescott, 1982). Analgesic nephropathy is, in the majority of instances, associated with chronic analgesic abuse, especially with combinations of various non-prescription drugs.

From the outset, phenacetin was considered the main instigator of analgesic-induced changes in kidney function, although the evidence implicating it as the sole nephrotoxic agent appears circumstantial. Indeed, removal of phenacetin from several of the world's markets has not been followed by the expected reductions in mortality from renal disease. As emphasised by Prescott (1982), serious doubt must be cast on the supposed role of phenacetin as the major aetiological agent associated with analgesic nephropathy. The part played by non-narcotic analgesics such as aspirin and other acidic anti-inflammatory drugs should also be considered fundamental to the development of renal injury. Animal studies have confirmed that chronic administration of aspirin produces renal damage and, in man, salicylates can produce a transient increase in the urinary excretion of renal tubular epithelial cells, increases in blood urea nitrogen, and proteinuria. Furthermore, more than 150 examples of analgesic nephropathy have been reported in patients taking aspirin without phenacetin. Putting the renal effects of aspirin and related salicylates into some perspective, their overall actions seem relatively minor; usual analgesic doses, even when administered for years, have rarely produced any serious effects on the kidney. However, chronic use of anti-inflammatory doses, or abuse, have produced a high incidence of renal papillary necrosis in patients with rheumatoid arthritis and in analgesic abusers. The precise mechanisms causing renal damage are not known, although inhibition of renal prostaglandin synthesis has been postulated and would explain why the acidic anti-inflammatory analgesics share the potential for nephrotoxicity. Since aspirin inhibits cyclo-oxygenase, it should be used with caution in patients with impaired renal function and those likely to have increased dependence upon renal prostaglandins for maintenance of renal blood flow (e.g. those with congestive heart failure, ascites, systemic lupus erythematosus).

Table II. Summary of reported incidence of salicylate-induced hepatic injury calculated by Zimmerman (1981) in healthy subjects and patients with various rheumatic and collagen diseases

Clinical diagnosis	Incidence of salicylate-induced hepatic injury (%)
Normal subjects and patients with non-rheumatic disease	0 to 30
Adult rheumatoid arthritis	20
Systemic lupus erythematosus[a]	47
Rheumatic fever	50 to 70
Juvenile rheumatoid arthritis[a]	25 to 70

a Active disease has higher incidence and greater severity of injury than 'inactive' disease.

4.3 Hepatic Effects

It was not until fairly recently that the hepatotoxic effects of aspirin were first suspected – after more than 50 years of clinical use. Generally, aspirin-induced liver injury develops after 1 to 4 weeks' treatment with relatively large doses of aspirin, and in most cases it is mild and reversible. Hepatotoxicity appears to be related to serum salicylate concentrations, usually occurring at levels in excess of 200 to 250 mg/L (Zimmerman, 1981; Prescott, this issue).

Plasma concentrations of aspartate and alanine aminotransferase are elevated and increases in al-

kaline phosphatase are occasionally found. Plasma bilirubin concentrations may be elevated - with jaundice in approximately 3% of patients. Blood prothrombin concentrations have infrequently been decreased to an extent that caused an increase in prothrombin time. Many patients are asymptomatic, although some develop nausea, vomiting, anorexia, abdominal pain, liver tenderness and/or hepatomegaly.

Although aspirin-induced hepatotoxicity has been reported in healthy subjects, it most frequently develops in patients with inflammatory diseases (table II). These patients usually receive high doses of aspirin and are more likely to have high salicylate plasma concentrations.

Diflunisal has been reported to cause occasional reversible elevations in liver function tests and very rarely cholestasis and/or jaundice.

4.4 Haematological Effects

Single oral doses of aspirin 300mg and greater have been demonstrated to inhibit platelet aggregation and prolong bleeding time in healthy individuals (Farah and Rosenberg, 1980; Flower et al., 1980; Mielke, 1981). These effects appear to be mediated through inhibition of cyclo-oxygenase and hence thromboxane A_2 production (Hanks, 1982). Aspirin irreversibly acetylates cyclo-oxygenase, but other salicylates (including diflunisal) act as competitive inhibitors and do not seem to produce such a marked and prolonged inhibition of platelet aggregation (Nitelius et al., 1984).

The above actions of aspirin on platelet function do not normally result in any morbidity in healthy subjects. However, they may be a problem in patients at risk of bleeding, such as those with haemophilia, vitamin K deficiency, hypoprothrombinaemia or hepatic damage and those taking anticoagulants or about to undergo surgery. In addition to these effects, salicylates may cause iron deficiency anaemia as a result of chronic gastrointestinal blood loss.

Serious blood dyscrasias induced by salicylates are extremely rare. Isolated reports have implicated aspirin as a cause of aplastic anaemia and thrombocytopenia. The first case of aspirin-induced haemolytic anaemia with thrombocytopenia was reported in 1984 (Hubert et al., 1984). Salicylates do not ordinarily alter leucocyte counts.

4.5 Hypersensitivity

Aspirin is one of the most common causes of 'allergic' drug reactions such as asthma, rhinitis, urticaria and angioedema. Systemic anaphylaxis occurs occasionally in patients with pseudo-allergic reactions to aspirin (see Szczeklik, this issue). Estimates of the incidence of aspirin hypersensitivity have been extremely varied, depending on the type of analysis and the type of patient. It is clear that the incidence in historical surveys is much lower than after provocative testing of patients at risk. Furthermore, certain patient groups appear to be much more susceptible (Settipane, 1983) [table III]. Recent studies have revealed that aspirin sensitivity may have different clinical manifestations with different underlying pathogeneses. Two major subtypes of patient have been identified: those who develop a respiratory reaction such as rhinitis and/or asthma, and those who react with the development of urticarial weals and angioneurotic oedema (Hanks, 1982; Settipane, 1983; Szczeklik, 1983).

The allergic response to aspirin usually occurs within minutes of ingestion and almost always

Table III. Approximate frequency of aspirin hypersensitivity in various groups of patients (adapted from Settipane, 1983)

Study group	Frequency of aspirin hypersensitivity (%)[a]
General population	≈ 0.3
Rhinitis	≈ 1.4
Asthma	4-19
Nasal polyps	14-23
Chronic urticaria	23-28

a Low frequencies are associated with studies based on historical data; higher frequencies are associated with aspirin challenge studies.

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given for analgesic/anti-inflammatory purposes during the first 6 months of pregnancy. In the last trimester aspirin must be avoided because it may prolong labour and/or lead to greater blood loss during delivery.

Salicylates are excreted to a minor extent in breast milk and should be administered with caution to nursing mothers. However, occasional single doses seem to present little risk.

The use of diflunisal in pregnant women and nursing mothers reflects the caution necessary for salicylates in general. Safety in pregnancy has not been established. Diflunisal is excreted in breast milk at about 2 to 7% of the plasma concentration.

4.9 Other Adverse Effects – Toxicity

Usual doses of salicylates have minimal effects on the cardiovascular, central nervous or respiratory systems. However, acute overdosage can lead to gastrointestinal disturbances, tinnitus, deafness, hyperventilation and disturbed acid/base balance – respiratory alkalosis and eventually metabolic acidosis due to uncoupling of oxidative phosphorylation and accumulation of organic acids. More severe toxic effects such as severe hyperventilation, convulsions, cyanosis, coma, oliguria, uraemia, pulmonary oedema and respiratory or cardiovascular failure may occur as the plasma salicylate concentration increases.

Salicylism may also develop with high dose chronic salicylate therapy. Such intoxication is manifested initially as headache, tinnitus, deafness, vertigo, lassitude, sweating, thirst, hyperventilation, nausea, and vomiting. More severe CNS disturbances, marked alterations in acid/base balance, and fever may develop if salicylate is allowed to accumulate in the blood. Children and the elderly are particularly at risk of chronic salicylate intoxication, but rarely from intentional overdosage; it usually occurs accidentally from overuse of a drug which many people still consider to be completely safe. Mortality from chronic salicylate intoxication (about 25%) is considerably higher than that reported after acute overdose (1 to 2%) [Proudfoot, 1983].

5. Drug Interactions

A large number of drug interactions involving salicylates have been documented but relatively few seem to be clinically important. Drugs which are considered to produce the most significant interactions with salicylates include anticoagulants and thrombolytic agents, sulphonylurea hypoglycaemic agents, uricosuric agents, methotrexate, corticosteroids and some diuretics (Hull Hayes, 1981; Thomas, 1983b).

5.1 Anticoagulants and Thrombolytic Agents

Salicylates have the potential to affect the activity of oral anticoagulants by several mechanisms. Large doses (⩾ 3 g/day) occasionally result in a reduction of plasma prothrombin concentration (see section 4.3) and may enhance the hypoprothrombinaemic effects of oral anticoagulants. Salicylates can displace coumarin anticoagulants such as warfarin from their plasma protein binding sites, consequently producing a transient rise in free active anticoagulant.

Probably of greater clinical importance is that salicylates cause gastric erosions and increase gastrointestinal blood loss (see section 4.1). Aspirin, in particular, inhibits platelet aggregation and may cause prolongation of bleeding time (see section 4.4). These findings militate against the concomitant administration of salicylates with drugs such as anticoagulants, streptokinase, urokinase and heparin. Obviously, administration of salicylates in patients treated with anticoagulants or thrombolytic agents is contraindicated.

5.2 Oral Hypoglycaemic Agents

Salicylates may potentiate sulphonylurea-induced hypoglycaemia (e.g. with chlorpropamide, tolbutamide) and the combination is best avoided. The precise mechanisms involved are not known.

5.3 Uricosuric Agents

Aspirin and related salicylates antagonise the uricosuric effects of probenecid, sulphinpyrazone

and phenylbutazone. The most likely explanations for these interactions appear to involve changes in plasma protein binding and/or competition for renal routes of elimination. It seems clinically prudent to avoid the concomitant use of salicylates with these drugs.

5.4 Methotrexate

Salicylates increase the toxic effects of methotrexate when the 2 drugs are co-administered and, again, the mechanism appears to be related to direct competition of the drugs in question for plasma binding sites and/or active renal transport sites. Because methotrexate has a low therapeutic index, and consequently a narrow margin of safety, this combination of drugs must be avoided.

5.5 Corticosteroids

There is limited clinical evidence that administration of corticosteroids may decrease serum salicylate concentrations when given concomitantly. However, these drugs are frequently used together without deleterious consequences. Special care may be needed when corticosteroids are discontinued, since a rebound increase in plasma salicylate concentration may occur. An isolated case of salicylate toxicity following hydrocortisone withdrawal has been recorded (Klinenberg and Miller, 1965).

5.6 Diuretics

Aspirin has been shown to slightly reduce the natriuretic effects of spironolactone and to attenuate the diuretic effects of frusemide (furosemide) [American Hospital Formulary, 1985; Webster, 1985]. The principal adverse clinical effect of the attenuated natriuretic response to diuretics by NSAIDs is worsening of cardiac failure. Additionally, diflunisal causes a 25 to 30% increase in the plasma concentration of hydrochlorothiazide and a decrease in its urinary excretion. However, the clinical importance of these interactions is not certain (Brogden et al., 1980).

5.7 Other Interactions

Many of the interactions described above are pharmacokinetic interactions that relate to direct competition of salicylates and concomitantly administered drugs for the same plasma protein binding sites and/or for active transport mechanisms within the proximal tubule of the nephron. Other drugs which may interact with salicylates in this way include penicillins, phenytoin, valproic acid, other NSAIDs and some sulphonamides. Salicylates may also displace bilirubin from its albumin binding sites in neonates, with the risk of causing hyperbilirubinaemia.

Food delays the onset and reduces the extent of salicylate (including diflunisal) absorption; however, most aspirin formulations should be taken after food to minimise gastrointestinal toxicity. Concomitant administration of salicylates and ethanol should be avoided since salicylate-induced gastric disturbances may be accentuated by alcohol (see Ivey, this issue).

Because salicylate excretion is pH dependent (see section 2.3), any drug which affects urinary pH may substantially alter salicylate reabsorption/excretion. Thus, antacids, which increase urinary pH and decrease salicylate reabsorption, will lower plasma salicylate concentrations. Drugs which acidify the urine (e.g. ammonium chloride) have the converse effect.

Acetazolamide should be avoided in patients receiving salicylates, since it not only has the potential to increase urinary pH (thus decreasing salicylate reabsorption) but it also induces metabolic acidosis, which would enhance salicylate penetration into the central nervous system and other tissues.

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