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Clinical Pharmacokinetics of the Salicylates

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Summary

The use of salicylates in rheumatic diseases has been established for over 100 years. The more recent recognition of their modification of platelet and endothelial cell function has lead to their use in other areas of medicine.

Aspirin (acetylsalicylic acid) is still the most commonly used salicylate. After oral administration as an aqueous solution aspirin is rapidly absorbed at the low pH of the stomach millieu. Less rapid absorption is observed with other formulations due to the rate limiting step of tablet disintegration - this latter factor being maximal in alkaline pH. The rate of aspirin absorption is dependent not only on the formulation but also on the rate of gastric emptying.

Aspirin absorption follows first-order kinetics with an absorption half-life ranging from 5 to 16 minutes. Hydrolysis of aspirin to salicylic acid by nonspecific esterases occurs in the liver and, to a lesser extent, the stomach so that only 68% of the dose reaches the systemic circulation as aspirin. Both aspirin and salicylic acid are bound to serum albumin (aspirin being capable of irreversibly acetylating many proteins), and both are distributed in the synovial cavity, central nervous system, and saliva.

The serum half-life of aspirin is approximately 20 minutes. The fall in aspirin concentration is associated with a rapid rise in salicylic acid concentration. Salicylic acid is renally excreted in part unchanged and the rate of elimination is influenced by urinary pH, the presence of organic acids, and the urinary flow rate. Metabolism of salicylic acid occurs through glucuronide formation (to produce salicyl acyl glucuronide and salicyl phenolic glucuronide), conjugation with glycine (to produce salicyluric acid), and oxidation to gentisic acid. The rate of formation of salicyl phenolic glucuronide and salicyluric acid are easily saturated at low salicylic acid concentrations and their formation is described by Michaelis-Menten kinetics. The other metabolic products follow first-order kinetics. The serum half-life of salicylic acid is dose-dependent; thus, the larger the dose employed, the longer it will take to reach steady-state. There is also evidence that enzyme induction of salicyluric acid formation occurs.

No significant differences exist between the pharmacokinetics of the salicylates in the elderly or in children when compared with young adults. Apart from differences in free versus *albumin-bound salicylate in various disease states and physiological conditions associated with low serum albumin, pharmacokinetic parameters in patients with rheumatoid arthritis, osteoarthritis, chronic renal failure or liver disease are essentially the same. Pharmacokinetic interactions with various non-steroidal anti-inflammatory drugs do occur, but the clinical relevance of these is uncertain. Clinically important interactions may occur with heparin or oral anticoagulants, but these are due mainly to an effect on platelet function rather than on pharmacokinetic parameters.*

The salicylates are found in many plants and have been used for over 2000 years in the treatment of a variety of conditions. Hippocrates, Galen and many medieval herbalists recorded their use (Gross and Greenberg, 1948), and in 1763, the Reverend Edward Stone reported to the Royal Society on the use of a powdered preparation of willow bark as an antipyretic. In 1826, salicylin was isolated from the willow bark and salicylic acid (SA) was first synthesised in 1852. Aspirin (acetylsalicylic acid; ASA) was synthesised in 1853, but it was not until 1893 that Felix Hoffman, a chemist with the Bayer Pharmaceutical Company, developed a commercial method for synthesising aspirin thus bringing it into widespread use.

Today the salicylates are available in hundreds of different forms (Buchanan et al., 1979) and the annual consumption of tablets can be measured in billions. Although over the last 25 years their place as drugs of first choice for the treatment of rheumatic diseases has been challenged by a variety of new non-steroidal anti-inflammatory agents, they still play a major role in the treatment of rheumatic diseases. Since the demonstration by Smith and Willis (1971) and Vane (1971) that aspirin prevented prostaglandin formation by inhibition of cyclo-oxygenase, it has been widely used as a pharmacological tool, not only in modifying inflammation (Moncada and Vane, 1979; Patrono et al., 1979) but also in the prophylaxis of cerebrovascular disease (Canadian Co-operative Study Group, 1978), coronary artery disease (Mustard, 1982), and arterial thrombosis (Genton, 1982). In many of these conditions the most appropriate dose of aspirin has not yet been determined and it is amazing that only in the last decade have the complex pharmacokinetics of aspirin been appreciated, with some aspects still unresolved (Levy, 1981). In this article we review the current state of knowledge of the clinical pharmacokinetics of the salicylates.

1. Physicochemical Properties

Salicylic acid (2-hydroxybenzoic acid) and aspirin (the salicylate ester of acetic acid) are both relatively insoluble in aqueous solution. A number of physicochemical properties including ionisation play a role in determining solubility. These are discussed in section 3.1. Care must be taken in the preparation and use of aspirin solutions; for example, a freshly prepared solution at pH 7.4 stored at 17°C can be expected to exhibit 10% hydrolysis to salicylic acid after 1 day but less than 2% hydrolysis if stored for only 4 hours (Thiessen, 1982).

In view of the labile nature of aspirin, great care must also be taken in collecting and processing biological fluids. Blood samples should be collected with fluoride and the plasma taken off immediately and frozen (Rowland and Riegelman, 1967). Even in dry ice, aspirin has a hydrolysis half-life of 24 days (Walter et al., 1974) and therefore analysis should be completed as rapidly as possible.

2. Analytical Methods

As can be seen from figure 1, the total plasma salicylate includes the sum of all the metabolites plus the parent compound. (These compounds will also be seen in the urine.) A variety of methods for measuring plasma, serum or urinary salicylate have been developed. The early methods were spectrophotometric using either Trinder's (1954) original method or a modification of this (Schachter and Manis, 1958). This employs the chelation of iron by salicylic acid or its analogues to yield a coloured complex whose absorbence is then measured photometrically. However, there are a number of errors in this method as the reagent shows poor specificity for salicylate and depends on the differential hydrolysis of aspirin to salicylic acid. To measure total salicylates in biological fluids they must be hydrolysed to convert all the salicylate to salicylic acid prior to the reaction with Trinder's reagent.

Chromatographic methods using gas-liquid chromatography have also been developed (Rowland and Riegelman, 1967; Walter et al., 1974), and a number of high-performance chromatographic (HPLC) methods have recently been described (Cham et al., 1980, 1982; Day et al., 1981; Peng et al., 1978; Rumble et al., 1981). These methods allow for rapid quantification of aspirin as well as

salicylic acid and the major metabolites (without the use of hydrolysis or derivitisation procedures) and have greatly enhanced our understanding of aspirin pharmacokinetics in body tissues.

3. Fundamental Pharmacokinetic Properties

3.1 Absorption

After oral administration, absorption of salicylate occurs rapidly by passive diffusion of unionised lipophilic molecules from the stomach (Hogden et al., 1957; Rowland et al., 1972). Extensive salicylate absorption also occurs in the jejunum and small bowel by virtue of its surface area. A passive process again appears responsible for small bowel salicylate absorption (Hogden et al., 1959; Schanker et al., 1958). Although aspirin can spontaneously hydrolyse, this is slow so that there is little or no free salicylate in the intestine and it is absorbed as aspirin rather than salicylic acid (Leonards, 1962). Rectal absorption of salicylate is also possible and cutaneous absorption may occur from salicylate-containing rubefacients (Davison, 1971).

Following oral administration of an aqueous solution, the absorption kinetics of aspirin in man were found to follow a first-order process (Rowland et al., 1972). In this study, 68% of the aspirin dose reached the systemic circulation unhydrolysed, although there was wide variation in the absorption half-life (from 4.5 to 16 minutes). The remainder of the dose was considered to have been metabolised during passage from gastrointestinal fluids to the systemic circulation by esterases within the gut wall, plasma or liver.

Plasma concentrations of aspirin rise rapidly following absorption, with peak concentrations occurring approximately 25 minutes after ingestion of soluble aspirin preparations (Morgan and Truitt, 1965; Rowland et al., 1972) or 4 to 6 hours after ingestion of enteric-coated aspirin (Ross-Lee et al., 1982). Plasma aspirin concentrations decline rap-

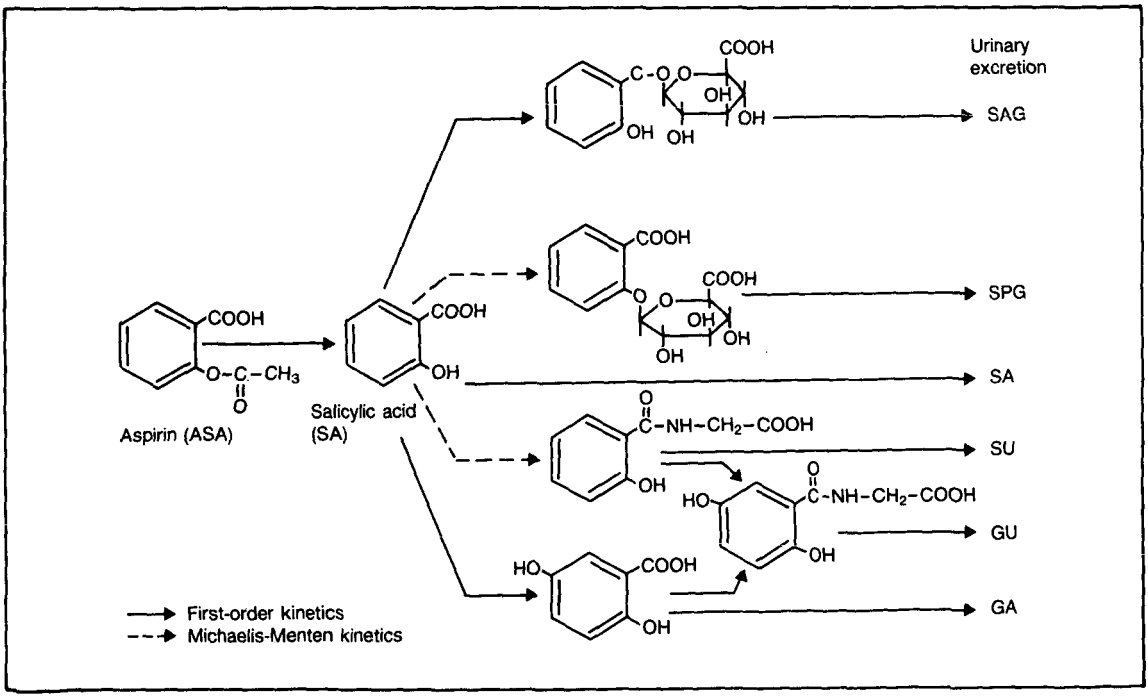

Fig. 1. Salicylate metabolism. [SAG = salicyl acyl glucuronide; SPG = salicyl phenolic glucuronide; SU = salicyluric acid; GA = gentisic acid; GU = gentisuric acid].

idly after achieving peak values as plasma salicylic acid concentrations increase.

The factors affecting absorption of salicylate are shown in table I. Although gastric absorption of aspirin is increased at low pH, the time to reach peak salicylate concentrations is not significantly different between pH 5 and pH 3 (Dotevall and Ekenved, 1976) due to increased gastric emptying at the higher pH. Food has been shown to significantly reduce the rate of absorption of effervescent aspirin (Volans, 1974), enteric-coated aspirin (Paull et al., 1976), and sustained-release forms (Brooks et al., 1978), while posture and activity may also affect gastric emptying at the time of drug ingestion. A number of studies (Castleden et al., 1977; Cuny et al., 1979; Salem and Stevenson, 1977) have failed to demonstrate significant differences in the absorption of salicylate between young and elderly subjects.

Aspirin (pK_a 3.5) and salicylic acid (pK_a 3.0) are weak acids, being 99% unionised at pH 1 and able to diffuse through lipid membranes. Schachter and Manis (1958) have shown that as the pH rises, the amount of salicylate absorbed from the stomach decreases. When salicylate is ingested in tablet form, it is the dissolution rate of the tablet that influences the rate of absorption (Levy and Hollister, 1965). The dissolution rate increases as the pH rises, and is maximal at pH 8 (Gibaldi, 1977). Salicylate salts are generally more soluble than the parent compounds (Leonards, 1963), with the exception of aluminium salts which are poorly absorbed (Levy and Sahli, 1962). Buffered aspirin preparations form salts as the tablets disintegrate giving enhanced dissolution and absorption (Levy and Hayes, 1960). Thus, the major factor affecting the absorption rate of aspirin or salicylic acid is the drug formulation itself (Martin, 1971).

The formulation of salicylate should, however, only influence the rate of absorption, such that the areas under the plasma concentration-time curves (AUCs) with each formulation will be similar. The most rapid absorption is obtained with effervescent tablets (Volans, 1974); buffered preparations containing 16 mmol of buffer are absorbed more rapidly than those containing 32 mmol (Mason and Winer, 1981). Aspirin from enteric-coated tablets is completely absorbed but absorption is often delayed due to prolonged gastric emptying (Leonards and Levy, 1965; Siebert et al., 1983); concurrent use of metoclopramide will enhance the rate of absorption from enteric-coated tablets (Paull et al., 1976).

Table I. Factors affecting salicylate absorption

Rate of gastric emptying
volume of food
pH of stomach contents
nervous state
concurrent drugs
exercise
posture
Formulation
Disease states associated with altered gastrointestinal transit time

Although early enteric-coated preparations were associated with poor bioavailability, recent enteric-coated and sustained-release preparations demonstrate salicylate bioavailability in excess of 90% (Brooks et al., 1978; Day et al., 1976).

When given in suppository form rectal absorption kinetics are similar to those of oral gelatin capsules containing sodium salicylate, providing the pharmaceutical formulation of the suppository base allows complete aspirin release (Parrott, 1971).

3.2 Distribution

Once absorbed, salicylates are distributed extensively through body fluids. Reported values for the apparent volume of distribution (Vd) of salicylate range from 9.6 to 12.7L in adults (Graham et al., 1977), with similar values (0.12 to 0.14 L/kg) in children (Wilson et al., 1982).

3.2.1 Plasma Protein Binding

Both aspirin and salicylic acid are partially bound to serum proteins, primarily albumin (Reynolds and Cluff, 1960). It has been suggested that the binding of salicylic acid to albumin occurs mainly at 2 primary, and a number of secondary

binding sites (Borgå et al., 1976). At therapeutic concentrations (1.1-2.2 mmol/L), salicylic acid is in molar excess compared with albumin such that binding is strongly dependent on both the salicylic acid and the albumin concentrations. The normal protein binding value of salicylic acid at therapeutic concentrations is 80 to 90% (Wanwimolruk et al., 1982). As the plasma concentration increases, the non-protein bound (free) fraction increases. Aspirin has been shown to acetylate the minor group of the 199 lysine residue in the human serum albumin primary sequence (Pinckard et al., 1968) and there is some evidence that this site is also shared by salicylic acid leading to a binding interaction between the two compounds (Ali and Routh, 1969; Pinckard et al., 1968). There is some evidence that salicylic acid binds to erythrocytes as well as to serum proteins (McArthur et al., 1971), but aspirin does not bind to proteins in the same reversible manner as it permanently acetylates the protein molecule (Hawkins et al., 1968). Protein acetylation is considered to be a major mechanism of action of aspirin leading to inactivation of enzymes such as prostaglandin synthetase (Hawkins et al., 1968; Pinckard et al., 1968; Roth and Chester, 1978).

Using a fluorescent probe analysis, Wanwimolruk et al. (1982) have recently failed to demonstrate any differences in the binding of salicylic acid to serum albumin in patients with rheumatoid arthritis or osteoarthritis.

3.2.2 Synovial Fluid Distribution

It has been shown that the protein binding of salicylic acid in synovial fluid is considerably lower than in plasma (Rosenthal et al., 1964; Soren, 1979; Trnavska and Trnavska, 1980; Wanwimolruk et al., 1983). Although the total salicylic acid concentration in synovial fluid is lower than that in plasma, this is likely to be explained by the lower albumin concentrations found in synovial fluid. Aspirin concentrations in synovial fluid are also significantly lower, but peak much later, than those concentrations seen in plasma, and aspirin remains in the synovial fluid long after it has disappeared from the plasma (Soren, 1979).

3.2.3 Cerebrospinal Fluid Penetration

Both salicylic acid and aspirin have been found to diffuse slowly into the cerebrospinal fluid (CSF) due to the high degree of ionisation of salicylic acid at the pH (7.4) of plasma (Brodie et al., 1960). The ratio of CSF to plasma salicylic acid is often less than would be predicted on the basis of pH changes alone, and the possibility of an active transport mechanism into the CSF of cats was suggested by Lorenzo and Spector (1973). These data have not been confirmed in other *in vivo* studies (Spector and Lorenzo, 1973), but only low salicylate concentrations were studied. A recently developed pharmacokinetic model has been used successfully to study salicylate kinetics in the CSF (Chen et al., 1978). Plasma pH is the major factor determining salicylic acid concentrations in the CSF: the lower the plasma pH, the more salicylic acid enters (Goldberg et al., 1961).

3.2.4 Distribution in Saliva

In saliva, the concentration of salicylic acid has been found to be proportional to the plasma concentration (Brooks et al., 1978; Graham and Rowland, 1972; Roberts et al., 1978). However, the concentration may vary with salivary pH at the site of production and it has been suggested that this method is unsuitable for routine salicylate concentration monitoring (Levy et al., 1980).

3.2.5 Placental Transfer and Secretion into Breast Milk

Salicylic acid readily crosses the placenta, fetal plasma concentrations being higher at birth than concurrent maternal concentrations (Garrettson et al., 1975; Levy and Garrettson, 1973; Levy et al., 1975). Salicylate distributes readily into breast milk, and although after a single dose the amount ingested by a nursing infant is small, considerable exposure to salicylate is possible if the mother regularly ingests large doses (Findlay et al., 1981).

3.3 Metabolism and Excretion

Aspirin is rapidly converted to salicylic acid with a half-life of only 15 to 20 minutes (Rowland and

Riegelman, 1968). This hydrolysis is due to non-specific esterases found in many body tissues (Harris and Riegelman, 1967). The acetyl component of aspirin after oral and intravenous dosing is found in gastric mucosal cells or is excreted as carbon dioxide after passing through the Krebs cycle (Rainsford et al., 1983).

During absorption, aspirin esterase activity in the gastrointestinal mucosal membranes contributes 28 to 35% of the hydrolysis of aspirin (Rowland et al., 1972). This esterase activity is highest in the mucosal cells of the gastric fundus (Dawson and Pryse-Davies, 1963), though considerable age, sex and disease differences may exist in tissue esterase activities (Gupta and Gupta, 1977; Menguy et al., 1972; Rainsford et al., 1980; Windorfer et al., 1974); for example, aspirin esterase activity is reduced in patients with alcoholic liver disease (Rainsford et al., 1980). Aspirin is the dominant form of the drug in the plasma during the first 20 minutes after ingestion and can be detected for several minutes before there is any measurable salicylic acid. However, it then disappears from the blood rapidly and hence the aspirin concentration is remarkably dependent on the rate of absorption. Diurnal variations in aspirin pharmacokinetics have also been demonstrated (Markiewicz and Semenowiczk, 1979).

Salicylic acid is partly excreted unchanged and partly metabolised (see fig. 1 and section 3.4 below). Free salicylic acid diffuses readily across the glomerulus and is also actively secreted by the proximal tubule. The conjugates of salicylic acid are also renally excreted, being dependent on glomerular filtration and tubular secretion. The hydroxylated metabolite gentisic acid is excreted in the same way as free salicylic acid.

3.4 Elimination Kinetics

After intravenous administration of aspirin, its elimination kinetics are described by a biexponential equation, the half-life of the second component being 13 to 19 minutes (Rowland and Riegelman, 1968). *In vitro* hydrolysis of aspirin to salicylic acid by esterase in the plasma is rapid, with a half-life of 15 to 20 minutes (Rowland et al., 1972).

Salicylic acid is removed from the body by 5 parallel and competing pathways, namely, renal elimination and formation of 4 metabolites (fig. 1). Salicylic acid is conjugated with glycine to form salicyluric acid (SU), conjugated with glucuronic acid to form salicyl phenolic glucuronide (SPG) and salicyl acyl glucuronide (SAG), and oxidised to gentisic acid (GA) [Levy and Tuschiya, 1972]. Gentisuric acid (GU) may be formed from SU via microsomal oxidation or from GA via glycine conjugation (Wilson et al., 1978). The elimination pathways of salicylic acid to SU and SPG are saturable and follow Michaelis-Menten kinetics, whereas the other pathways exhibit linear (first-order) kinetics (Levy, 1965, 1971, 1979; Levy and

Table II. First-order rate constants and Michaelis constants reported in various studies of salicylate elimination kinetics

Reference	No. of patients	SA k_e (h^{-1})	SA→SAG k (h^{-1})	SA→GA k (h^{-1})	SA→SU		SA→SPG	
					V_{max} (mg/h)	Km	V_{max} (mg/h)	Km
Levy and Tsuchiya (1972)	4	0.0075	0.0071	0.0023	60.3	338 (mg)	32.3	629 (mg)
Bochner et al. (1981)	5				43.4 ± 10	14.3 ± 3.4 (mg/L)		
Boreham and Martin (1969)	6			0.006				

Abbreviations: k = first-order rate constant; k_e = elimination rate constant; K_m = Michaelis-Menten constant; V_{max} = theoretical maximum velocity of metabolism.

Leonards, 1966; Levy et al., 1972; Tsuchiya and Levy, 1972b). The rate constants applying to these processes are shown in table II.

After a small dose of aspirin (300mg or less), about 90% is excreted as SU or SPG (Levy and Leonards, 1966). Levy and co-workers have demonstrated that while steady-state plasma salicylic acid concentrations increase with increasing doses, steady-state concentrations of SU do not. After a 3g dose of aspirin, 50% of the dose was excreted as SU, 20% as SPG, 14% as salicylic acid, 11.0% as SAG, and 3.1% as GU (Levy et al., 1972; Tsuchiya and Levy, 1972a). The saturable nature of the SU pathway, and the V_{max} and Km values have been elegantly defined by utilising the inhibitory effect of benzoic acid on SU formation. The conversion of benzoate to hippurate uses the same enzyme system as the conversion of salicylic acid to SU (Levy and Amsel, 1966). Recently, it has been suggested that with long term use, salicylate may induce its own metabolism by increasing the production of SU (Day et al., 1983a; Furst et al., 1977; Rumble et al., 1980). Steady-state salicylic acid concentrations in patients on day 20 of treatment were found to be 48% of those found in the same patients on day 7 (Muller et al., 1975).

Peak concentrations of SAG occur at the same time as peak concentrations of free salicylic acid, but the SPG peak is delayed for 8 hours. After investigating the excretion rate of salicylic acid and the 4 salicylate metabolites, deriving their pharmacokinetic parameters and using computer simulations, the capacity-limited formation of SPG was determined (Tsuchiya and Levy, 1972b) – confirmed by utilising the salicylamide interaction with glucuronide formation (Levy and Procknall, 1968).

GA is formed by the hydroxylation of salicylic acid and is produced in small quantities along with a number of other minor metabolites such as GU and other oxidation products (Wilson et al., 1978). The possibility that GA formation followed Michaelis-Menten kinetics was explored by Boreham and Martin (1969) but this has not been confirmed. Renal excretion of salicylic acid occurs by first-order kinetics and is extremely sensitive to urinary pH (Levy and Leonards, 1971; Smith et al., 1946), urinary organic acids (Liegler et al., 1969) and urinary flow rate (Milne, 1963). The effect of urinary pH on salicylate clearance is most marked at high salicylate concentrations but is still observable at low dosage (Levy and Leonards, 1971). Antacid-induced changes in urinary pH (Gibaldi et al., 1974; Hansten and Hayton, 1980) will cause decreases in steady-state plasma salicylate concentration to occur. The renal excretion of SA is also reduced by probenecid, which competes for secretion in the proximal tubule (Schachter and Manis, 1958) [see also section 6.5].

4. Pharmacokinetics in Various Age Groups and Disease States

4.1 Children

As well as a reduced albumin concentration, neonates have impaired conjugating mechanisms and thus eliminate maternally-ingested salicylate more slowly than adults (Wolff et al., 1982). Studies in children who had accidently ingested excessive amounts of salicylates have shown that the Vd varies with the dose; the higher the initial dose, the higher the Vd. This can be explained on the basis of saturation of protein binding sites and changes in plasma pH. This highlights the importance of not using the serum salicylic acid concentration alone in estimating the risk of toxicity from salicylate overdose in children (Done, 1974; Levy, 1978; Levy and Yaffe, 1974). Pharmacokinetic parameters of salicylate are not influenced by febrile states in children (Wilson et al., 1982).

4.2 Elderly

No significant differences exist in the absorption of aspirin in the elderly compared with younger adults. Although one report showed an increased Vd and a slower rate of elimination of salicylic acid in the elderly (Cuny et al., 1979), a more recent single-dose study was unable to demonstrate any significant pharmacokinetic differences between the elderly and younger adults (Roberts et al., 1983). Salicylate toxicity may present a spectrum of clinical features in the elderly, ranging from con-

fusion and encephalopathy through to hyperventilation, highlighting the importance of careful monitoring in this age group (Vivian and Goldberg, 1982).

4.3 Rheumatoid Arthritis

Serum albumin concentrations are often diminished in patients with rheumatoid arthritis, and hence alterations in free salicylate fraction may occur. There is, however, no evidence that protein binding of salicylate *per se* is altered in patients with rheumatoid arthritis (Wanwimolruk et al., 1982).

4.4 Renal and Liver Disease

The free fraction of salicylic acid has been shown to be increased in patients with renal failure; however other pharmacokinetic features are unchanged. The higher salicylic acid concentrations in this group are related to displacement from protein binding sites (Lowenthal et al., 1974). These authors used a single dose of salicylic acid (500mg/1.73m^2) and one would expect that at higher doses of salicylate, toxicity may occur due to impaired elimination of SU and free salicylic acid.

In a single-dose study, aspirin and salicylic acid kinetics in patients suffering from alcoholic liver disease were not different from aged or young controls, but unbound salicylic acid concentrations were significantly higher in those with liver disease. This was due to a decrease in plasma protein binding and clearance of SA (Roberts et al., 1983).

5. Clinical Implications of Pharmacokinetic Properties

The optimal dose of aspirin required to reduce platelet adhesiveness and still maintain vascular prostacyclin production is not known. A dose as small as 160mg results in an 82% acetylation of platelet membrane cyclo-oxygenase at 24 hours (Burch et al., 1978). Recently, Ross-Lee et al. (1982) demonstrated a significant reduction in platelet aggregation following a 650mg dose of enteric-coated aspirin. Other studies have reported inhibition of platelet aggregation with enteric-coated and sustained-release preparations despite the absence of measurable plasma aspirin concentrations (Brantmark et al., 1982; Siebert et al., 1983).

Evidence suggests that aspirin is a better analgesic than salicylic acid (Lasagna, 1961; Lim, 1966). The analgesia produced by aspirin is dose-dependent, although the response does not parallel serum aspirin concentrations (Levy, 1981). The dose of aspirin required for its antipyretic action is less than that required for analgesia (Wilson et al., 1982).

The generally accepted therapeutic plasma concentration range of salicylate for the treatment of chronic inflammatory disease is 15 to 30mg/100ml (150-300 mg/L or 1-2 mmol/L), requiring daily doses in excess of 3g (Boardman and Hart, 1967; Graham et al., 1977; Multz et al., 1974; Vesell, 1974). However, this therapeutic plasma concentration range does not appear to have been confirmed with any degree of certainty (Orme, 1982; Smyth and Bravo, 1975).

Side effects of salicylate, in particular tinnitus, are related to the total salicylic acid concentration (Day et al., 1983b) but tinnitus has not been a practical measure of salicylate toxicity in patients with rheumatoid arthritis (Mongan et al., 1973). As the optimum plasma concentration is only slightly below toxic values, care must be taken in the clinical use of salicylates. The rate-limited kinetics of salicylic acid mean that its elimination half-life increases with dose so that a small increase in dose causes more than a proportional increase in the steady-state concentration (Tsuchiya and Levy, 1972a). Paulus et al. (1971) have shown that an increase in the daily salicylate dose from 65 mg/kg to 100 mg/kg results in a 3-fold increase in the plasma salicylic acid concentration. Tsuchiya and Levy (1972a) have shown by computer simulation that it takes only 2 days to reach steady-state salicylate concentrations if a dose of 0.5g is given at a dosing interval of 8 hours. Increasing the dose to 1g with the same dosing interval of 8 hours increases the time taken to reach steady-state concentrations to 7 days, and this doubling of the salicylate dose results in a more than 6-fold increase

in steady-state plasma concentrations.

Calabro et al. (1976) reported that a reduction in the fractional daily dose of aspirin (from 5 to 3 doses) increases the incidence of side effects such as tinnitus. However, Levy and Giacomini (1978) have clearly demonstrated by computer simulation that, providing the daily dose has been correctly chosen, differences in the size of the aspirin dose fraction or the time interval between doses have little effect on steady-state plasma concentrations. Individualisation of dose can be achieved by monitoring plasma concentrations of SA, but a number of other variables affecting salicylate elimination kinetics cannot be readily evaluated from plasma concentration data alone. Nomograms do not adequately take into consideration the pronounced interindividual differences in salicylate elimination, and dose-rate adjustments must therefore be empirically based on information obtained from plasma concentration monitoring and evaluation of the patient's clinical status (Levy and Giacomini, 1978). Therapeutic steady-state salicylic acid concentration during the total 24-hour period would seem to be required for the ideal management of rheumatic disease. There are theoretical reasons which would suggest that the use of enteric-coated or soluble formulations of aspirin given on a 12-hourly schedule, while capable of achieving these therapeutic concentrations, may be associated with toxicity immediately following ingestion. However, in practice this rarely occurs with enteric-coated tablets, and these or sustained-release preparations should be prescribed for long term antirheumatic therapy to reduce gastrointestinal blood loss. As an aid to predicting patient response to salicylates in rheumatoid arthritis, Graham et al. (1977) used a 1.2g test dose followed by a serum salicylate concentration measurement 12 hours later. Salicylic acid concentrations greater than 1mg/100ml after the test dose predicted therapeutic concentrations above 15mg/100ml during long term therapy.

A safe approach is to commence therapy with 60 mg/kg/day. Using a 8-hour dosing schedule for 1 week, a blood sample is obtained 1 to 3 hours after a dose and the daily dose is increased to 80 mg/kg/day if the plasma salicylic acid concentration is below 15mg/100ml. Upward dosage adjustment must be made cautiously in small increments and should only be carried out after a thorough clinical and pharmacokinetic assessment of the patient (Levy and Giacomini, 1978). Alternatively, a 12-hour dosage schedule may be employed using sustained-release formulations.

To achieve rapid absorption with early peak aspirin concentrations, effervescent formulations are appropriate. The addition of metoclopramide will further enhance the rate of absorption and this has been suggested for analgesia in migraine (Ross-Lee et al., 1983).

6. Pharmacokinetic Drug Interactions

6.1 Indomethacin

Since publication of the study by Jeremy and Towson (1970) suggesting that concurrent use of indomethacin and aspirin resulted in reduced indomethacin concentrations, conflicting reports have appeared in the literature. However, a clinical study has suggested that no additive therapeutic effect is achieved and there is an increase in side effects with this combination (Brooks et al., 1975).

6.2 Proprionic Acid Derivatives

Reductions in the AUC have been noted for fenoprofen (Rubin et al., 1973), naproxen (Serge et al., 1974), flurbiprofen (Brooks and Khong, 1977), and ibuprofen (Grennan et al., 1979) when given concurrently with aspirin. However, these interactions are probably not of clinical importance.

A more complex interaction exists between ketoprofen and aspirin. Increased plasma clearance of ketoprofen occurs as well as reduced renal elimination of conjugated metabolites and reduced formation of these conjugates (Williams et al., 1981).

6.3 Diflunisal

The interaction of diflunisal and aspirin is dose-dependent, as doses greater than 2.4g of aspirin per day cause significant reductions in diflunisal con-

centrations. However, at doses below 1.2g aspirin per day, no significant effect is seen (Schultz et al., 1976).

6.4 Diclofenac

Aspirin has been shown to reduce the peak concentrations and AUC of diclofenac after intravenous and orally administered doses. Diclofenac Vd and clearance were both increased with aspirin coadministration (Reiss et al., 1978; Willis et al., 1980). However, the clinical relevance of this interaction is not clear.

6.5 Phenylbutazone, Probenecid and Sulphinpyrazone

These drugs will abolish the uricosuria associated with aspirin doses greater than 2.5 g/day (Oyer, 1960; Pascale, 1955; Tu, 1963). Likewise, the uricosuric effect of probenecid is inhibited by simultaneous low dose aspirin use. A similar effect is also seen with sulphinpyrazone which appears more sensitive to the effect of aspirin than probenecid. Salicylates should be avoided in patients receiving these uricosuric drugs.

6.6 Methotrexate

Aspirin/methotrexate combinations may precipitate methotrexate toxicity (Mandel, 1976). The clearance of methotrexate is reduced 30% by aspirin due to competition between the two drugs for renal elimination (Leigler et al., 1969). Aspirin in therapeutic doses also produces a 20 to 60% decrease in methotrexate protein binding, although this was found to have little clinical significance (Taylor and Halprin, 1977).

6.7 Antacids

Aluminium hydroxide gel, magnesium hydroxide and sodium bicarbonate cause an increase in urinary pH and hence an increased rate of salicylic acid elimination. An increase in urine pH from 5 to 8 will increase the rate of salicylic acid elimination 20-fold (Smith et al., 1946). However, antacids have no affect on the bioavailability of aspirin (Gibaldi et al., 1974).

6.8 Other Drugs

Many theoretical interactions may occur through displacement of drugs from protein binding sites by aspirin and salicylic acid. Reports indicate that phenytoin (Leonard et al., 1981) and oral hypoglycaemics (Anderson, 1977) fall into this category, but the clinical relevance of these interactions is uncertain. Clinically important interactions may occur with heparin and oral anticoagulants (Hansten, 1975; Prescott, 1969), but these appear to be due mainly to an effect on platelet function rather than on pharmacokinetic parameters.

Drugs that acidify urine, such as ascorbic acid (which may be self-administered in large amounts), will reduce urinary salicylic acid excretion and raise the plasma concentration (Hansten and Hayton, 1980).

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