Leading Article

Drugs 36: 1-6 (1988)
0012-6667/88/0007-0001/$03.00/0

Salicylates Revisited
Are They Still the Hallmark of Anti-Inflammatory Therapy?

Sanford H. Roth
Arthritis Center Ltd, Phoenix, Arizona, USA

Salicylates have enjoyed a curious, convoluted role in the management of pain and various diseases, which have been mainly rheumatic. Originally a herbal remedy, numerous cation-salicylate molecular modifications were synthesised before the current acetylated derivative emerged and predominated. So overwhelming was the popularity of acetylsalicylic acid that its original trade name, aspirin, ultimately became the generic name and by all accounts it is now the most widely used drug in the world.

For rapid pain relief, no non-narcotic analgesic has surpassed aspirin, and it is also an effective antipyretic. Of central interest to this review, however, is the peculiar place of favour and disfavour of aspirin in the treatment of various rheumatic diseases. With aspirin included within the greater body of salicylate molecular modifications, formulations, and applications, this article aims to provide a perspective on the commanding presence and continually evolving impact of the salicylates on what is now over a $US2 billion anti-inflammatory therapy market that dwarfs most other important arenas of pharmacotherapy by comparison. Central to this theme is the role of anti-inflammatory therapy in rheumatic disorders and, in particular, the role of the salicylates in relation to the many other non-salicylate anti-inflammatory drugs now available.

1. Anti-Inflammatory Therapy: Recognition and Ramifications

Rheumatoid arthritis has long been used as the prototype for systemic inflammatory joint disease. Historically, it was also the motivating factor for the original synthesis of aspirin in 1899 by the chemist Hoffman in order to relieve the suffering of his father. Yet, in the first half of this century, it is remarkable how few reports suggested that high doses of aspirin were necessary to achieve what we now recognise to be systemic anti-inflammatory concentrations. In fact, medical giants ranging from Sir William Osler to Russell L. Cecil did not recommend high doses for this disorder, and it was not until corticosteroids were discovered in the late 1940s, and a double-blind trial with high-dose aspirin as the control was undertaken, that the medical literature first documented the importance of anti-inflammatory therapy. This situation may have arisen in part due to the significant analgesic efficacy of aspirin [and all subsequent non-steroidal anti-inflammatory drugs (NSAIDs) for that matter] at doses far below the level necessary for systemic anti-inflammatory activity. Additionally, in view of the considerable intolerance to high doses of aspirin (gastric upset, tinnitus, CNS symptomatology, etc.), the attraction of low doses for simple

symptomatic pain relief with fewer side effects appears obvious.

The introduction of corticosteroids at the higher dosages first employed (out of ignorance of endocrine toxicities) resulted in complete ablation of overt inflammatory activity. This underlined the role of inflammation in the fibrositic and musculoskeletal events that devolve into significant loss of function, strength, and ultimately disability and and debility. From this point, the search for effective anti-inflammatory drugs was on. With aspirin, the consensus was that serum salicylate concentrations of 200 to 300 mg/L were desirable and achievable in the treatment of rheumatic diseases such as rheumatoid arthritis and related disorders (Roth 1980a). Similarly, Gurwich et al. (1984) noted that the therapeutic concentration range for salicylate anti-inflammatory action was generally accepted to be 150 to 300 mg/L. Concern about the drug's considerable toxicities was mainly confined to obvious acute events. However, the significant problems of compliance brought about by the frequent short term intolerance to high-dose aspirin led to the proliferation of numerous NSAID alternatives. It was several decades before the long term consequences of all forms of such non-steroidal anti-inflammatory drug therapy became a major focus of concern.

Laboratory models for inflammation proliferated, from seaweed carageenin granulomas induced in guinea-pigs to ultraviolet burns of shaved rat paws, and to the ultimate benchmark, measures of inhibition of prostaglandin (PG) synthetase activity. However, with regard to the prostaglandin pathway, recent research has indicated that prostaglandins may be either pro- or anti-inflammatory and therefore do not fully satisfy the criteria necessary to judge acute and chronic inflammation (Vane 1987). The spectrum of inflammation actually implicates a cascade of mediators including kinins, biogenic amines (autacoids), and intracellular events such as calcium flux, and cyclic adenosine monophosphate (cAMP) activity. This further leads to inhibition of activation of neutrophils and complement activation with a potential for parallel propagation of the immune cycle (Weissmann 1987). Furthermore, the differential role of the lipoxygenase pathway as linked to NSAID attenuation of rheumatic disease activity continues to be re-evaluated (Weissmann 1987).

A further consideration in relation to blockade of prostaglandin synthetase activity by aspirin and most NSAIDs is that in addition to their beneficial effects some of the serious common toxicities of these agents can also be linked to this action. Prostaglandins are organ specific. Gastric PGE_2 and PGI_2 (prostacyclin) are now recognised as important in the mucosal cytoprotective events that are critical to the defence of the gastric mucosa (Isselbacher 1987). In addition, renal PGE_2 appears central to the renin/angiotensin/aldosterone interaction that is necessary for sustaining renal function and also impacts upon fluid retention mechanisms (Dunn 1987). The anti-inflammatory effects of the salicylates and related NSAIDs are dose dependent and can be expressed across a gradient of activity. Anti-inflammatory doses of these drugs may require up to 2 weeks for maximum effect to occur. Consequently, the potential for toxicity with this form of therapy can be readily appreciated.

2. *Salicylates* vs *NSAIDs in Rheumatic Disorders*

Although the salicylates are effective anti-inflammatory agents, they were initially studied as analgesic/antipyretic drugs. All currently available non-salicylate NSAIDs share these analgesic and antipyretic actions, even at low dosages. At present, however, no non-salicylate NSAID has clearly surpassed the range of anti-inflammatory activity demonstrated by the salicylates: rather, the NSAIDs appear to be characterised by a variable range of anti-inflammatory activity. Furthermore, a range of clinical responses is found in patients on any particular NSAID, so that clinical studies to date cannot validate why one particular subset of patients respond to one non-salicylate NSAID better than to another (Roth 1980b). Indeed, in double-blind studies comparing salicylates with NSAIDs, it is usual to see the broadest range of clinical responsiveness with the salicylates, which appear to

Table I. Historical evolution of the salicylates

1.	**Ancient extracts** Willow bark (*Salix*)
2.	**Age of aspirin** Acetylsalicylic acid. 1853 (identified by Gerhardt)
3.	**Salicylate-NSAID era** Cationic salicylates (magnesium, choline, calcium, combinations)
4.	**Disalicylates** Salsalate

exert the most consistent dose-dependent anti-inflammatory effects.

Thus, after decades of investigation and clinical use of scores of NSAID alternatives, the salicylates have remained as the benchmark of anti-inflammatory therapy. But within the salicylate group, there are now a variety of safer alternatives to aspirin, which are also simpler to use, as well as newer delivery systems. The basis for seeking newer salicylate alternatives is the same as for the search for NSAID alternatives: the toxicity inherent in the sustained use of high-dose aspirin therapy.

Aspirin is rapidly absorbed from the gastrointestinal tract and hydrolysed by esterases to salicylic acid (Roth 1985). Hydrolysis to salicylic acid also occurs with the non-acetylated salicylate derivatives listed in table I. The cationic non-acetylated salicylates include: magnesium salicylate, which is potentially troublesome for patients with compromised renal function due to its magnesium content; sodium salicylate, which is no longer used because of intolerance and its sodium content; choline salicylate, which is too hygroscopic for solid form; and choline magnesium trisalicylate (which is available in a tablet form). Benorylate is an irrational combination of aspirin with paracetamol (acetaminophen) which has the same potential for toxicity as the 2 drugs taken together.

Salsalate (salicylsalicylic acid) is a non-acetylated salicylate without a cationic residue. This 'disalicylate' is insoluble in gastric acid, but dissolves in the alkaline contents of the bowel. Following absorption, it is rapidly hydrolysed to 2 molecules of salicylic acid (Roth 1985). This drug is the first of the group of non-acetylated salicylates to convincingly show equivalent efficacy to therapeutic doses of aspirin in a recently reported large US multicentre study involving a double-blind long term controlled trial in rheumatoid arthritis (April et al. 1987). Previous studies comparing non-acetylated salicylate with aspirin have often been flawed in design, tending to bias against salicylate by using unduly high doses of aspirin in a 3 times daily regimen to emphasise aspirin toxicity and intolerance (Blechman & Lechner 1979).

Because 2 of the major metabolites of salicylic acid (salicyluric acid and salicyl phenolic glucuronide) are produced via saturable Michaelis-Menten pathways, the elimination kinetics of salicylates are highly dose dependent. At low doses elimination is linear (first-order) and the serum half-life is about 2 to 3 hours, but at higher doses elimination is limited by the ability of the liver to form salicyluric acid and salicyl phenolic glucuronide and the serum half-life may increase up to 30 hours or more (Roth 1985). Bolus salicylate dosing to achieve this with regular aspirin is impractical due to the expected gastric irritation. However, salsalate, which causes less gastric side effects (McPherson 1984), can safely be given in doses of 1500mg or more twice daily and monitored by serum salicylate concentrations. Serum salicylate concentrations reach steady-state levels within 7 days, but should be measured again after 30 days since salicylate may induce its own metabolism, resulting in lower serum concentrations (Roth 1986b). At this stage, the salicylate dosage needs to be 'tailored' to fit the particular metabolic handling of the drug in the individual patient. The widespread availability and use of therapeutic drug monitoring methods further commends salicylates for long term anti-inflammatory therapy.

The experienced clinician will recognise that salicylate disposition is dependent on a variety of different factors that influence the drug's absorption, distribution, and elimination characteristics. Accordingly, the initial dosage should be adjusted on the basis of the clinical response and tolerance of such common minor side effects as tinnitus. In

this way, the almost exponential rise in salicylate concentrations that may occur if the metabolic capacity is too rapidly exceeded can be moderated in careful steps towards the recommended anti-inflammatory level of 200 to 300 mg/L.

Various coated and matrix-release forms of aspirin are now available to modify the drug's gastric toxicity. However, these preparations may be characterised by a variable absorption problem that appears to be quite unpredictable (Bland 1983; McCarty & Csuka 1987). The slow release of aspirin from matrix-release preparations means that absorption continues for up to 12 hours in contrast to the rapid absorption seen with regular aspirin tablets. The clinical significance of this sustained exposure of the bowel mucosa to aspirin with delayed-response formulations requires further investigation.

The non-salicylate NSAIDs exhibit significant differences in pharmacokinetics, with half-lives ranging from a few hours to up to 50 or 60 hours. Unlike the salicylates, no convincing correlations between serum concentrations and efficacy have been demonstrated with any of these agents. Since serum concentrations of the salicylates can be readily monitored and their pharmacokinetic properties permit simple twice daily dosing (thereby maximising compliance), and the cost of salicylates is significantly less than that of existing NSAIDs, the salicylates have re-emerged as the anti-inflammatory hallmark. Pivotal to this emergence has been a re-evaluation of the safety of salicylates and alternative NSAIDs.

3. Safety as the Cornerstone of Long Term Anti-Inflammatory Therapy

In 1985, the US Food and Drug Administration (FDA) began a series of safety reviews of existing NSAIDs (Harter 1985). Of concern in some of these reviews has been the problem of evaluating raw data from various sources and methodologies. Epidemiologically, it is hazardous to assign a basis for cause and prevalence rates of observed adverse reactions to a particular NSAID. While it is beyond the scope of this review to appropriately evaluate these issues, it is generally agreed that various 'signals' are evident from the great mass of worldwide data so obtained. If the raison d'ètre for the NSAIDs is the major gastropathy toxicity problems of aspirin, the data reviewed have demonstrated that this is in fact the major toxicity of *all* NSAIDs (Roth & Bennett 1987). This problem has been ubiquitous; not only associated with symptoms but also with important pathology, serious bleeding and deaths. In fact, the data have suggested that NSAID toxicities are not dissimilar to those of aspirin (Roth & Bennett 1987). The basis for this toxicity, as discussed earlier, is the inhibition of prostaglandin synthetase by all these agents. However, the non-acetylated salicylates are weak prostaglandin E_2 and thromboxane inhibitors (Morris et al. 1985; Needs & Brooks 1985) and do not appear to cause gastropathy (Fassett 1984; Roth 1986b; Voltin 1984), renal complications (Dunn 1987; Ryan et al. 1985) or hypersensitivity reactions (Chudwin et al. 1986; Pleskow et al. 1983; Samter 1973; Samter & Beers 1967) to the same extent as aspirin and alternative NSAIDs (Roth 1985). On the other hand, this dangerous hypersensitivity to the triad of asthma, nasal polyps and eosinophilia is commonly shared by all other NSAIDs (Szczeklik et al. 1977). Hence, it is important to distinguish these salicylates from aspirin, the most toxic of them.

Gastropathy caused by aspirin preparations at sustained anti-inflammatory dose levels has been documented throughout the literature. Being an effective analgesic and commonly used in patients with high pain thresholds, at least half of the cases of gastropathy are asymptomatic (Roth et al. 1987). This same 'silent' gastropathy is now known to be associated with the NSAIDs as well (Roth 1986a). Thus, the FDA has had twice as many cases of bleeding as ulcers reported to it (Harter 1985). The fact that 10% of gastric bleeds prove fatal (Roth & Bennett 1987) is of particular concern in an increasingly elderly population, since the incidence of gastric bleeding is 7 times higher in those aged 75 years and older.

Aspirin does have a dual potential to cause gastropathy. With delayed absorption as salicylic acid it may be directly corrosive and create an 'in place'

ulcer. Furthermore, via its blockade of cytoprotective prostaglandins, aspirin may be directly associated with gastropathy (Roth et al. 1987). In contrast, enteric-coated aspirin spares direct topical toxicity but may still, through the usual blockade of cytoprotection, be associated with ulcer crater disease.

At the same time, reports in the literature have indicated that non-acetylated salicylates may actually have a gastric-sparing potential (Blechman & Lechner 1979). Aspirin, due to its inhibitory effect on platelet aggregation, may potentially increase the danger of bleeding from gastropathy, and the alternative NSAIDs appear to share this potential (Langman 1986; Mielants et al. 1979). However, unlike aspirin, salicylic acid only reversibly inhibits platelet aggregation and thus has a lesser impact on the coagulation mechanism (Estes & Kaplan 1980).

The known renal toxicity of aspirin and the NSAIDs has not been found to be shared by non-acetylated salicylates, possibly due to their weak PGE_2 inhibitory effect (Dunn 1987). This also appears to be the case with aspirin-induced hypersensitivity reactions (Roth 1985). The anaphylactoid reactions and deaths reported with aspirin and with other NSAIDs again appear to be related to prostaglandin synthetase inhibition. Patients at particular risk include those with the clinical triad of nasal polyposis, asthma, and eosinophilia. Up to 1% of the population can experience such anaphylactoid reactions with aspirin and the incidence is perhaps 10 times greater in the hypersensitivity triad group. Non-acetylated salicylates appear to be the *only* agents that can be given, cautiously, to such patients (Roth 1987).

Salicylate overdosage can give rise to metabolic problems, especially in the very young and the elderly. Such instances are best avoided by proper therapeutic drug monitoring. When they occur, they are treated by cessation of salicylates, alkalinisation, and hydration. As well as confusion, mental obfuscation, or other more serious consequences of metabolic acidosis, salicylate overdosage can also be associated with elevated transaminases – a reversible enzyme phenomenon not associated with known hepatic damage, in contrast to the cellular hepatic toxicity associated with some non-salicylate NSAIDs (Russell et al. 1971).

Finally, because of its effect on platelet aggregation, aspirin may enhance the effect of anticoagulant drugs, potentially increasing the risk of bleeding complications. This is generally less of a problem with the non-acetylated salicylates.

4. Conclusions

It is clear that aspirin differs from other salicylates and as far as its safety is concerned should be classified separately. The non-acetylated salicylates have been relatively under-utilised and unappreciated as anti-inflammatory agents. Due to their pharmacokinetic properties which permit simple twice daily dosing regimens, their low cost, superior safety and widespread availability of therapeutic drug monitoring methods, the non-acetylated salicylates clearly warrant re-evaluation. They are to be commended as worthy successors to the primacy aspirin has so long enjoyed in arthritis therapy.

References

April PA, Curran NJ, Ekholm BP, Doucette ML, Wilson RR, et al. Multicenter comparative study of salsalate (SSA) vs aspirin (ASA) in rheumatoid arthritis (RA). Abstract. Arthritis and Rheumatism 30: S93, 1987

Bland J. Absorption of enteric coated aspirin Correspondence. Journal of the American Medical Association 249: 59, 1983

Blechman WJ, Lechner DL. Clinical comparative evaluation of choline magnesium trisalicylate and aspirin in RA. Rheumatology and Rehabilitation 18: 119-124, 1979

Chudwin DS, Strub M, Golden HE, Frey C, Richmond GW, et al. Sensitivity to non-acetylated salicylates in a patient with asthma, nasal polyps and rheumatoid arthritis. Annals of Allergy 57: 133-134, 1986

Dunn M. The role of arachidonic acid metabolites in renal homeostasis: non-steroidal anti-inflammatory drugs, renal function, and biochemical histological and clinical effects and drug interactions. Drugs 33 (Suppl. 1): 56-66, 1987

Estes D, Kaplan K. Lack of platelet effect with aspirin analog, salsalate. Arthritis and Rheumatism 23: 1303-1307, 1980

Fassett WE. Gastrointestinal intolerance to anti-inflammatory drugs: is salsalate an exception? Practical Gastroenterology VIII (5), 1984

Gurwich EL, Raees SM, Skosey J, Niazi S. Unbound plasma salicylate concentration in rheumatoid arthritis patients. British Journal of Rheumatology 23: 66-73, 1984

Harter JG. FDA drug review perspective. Presented at 'The Terrible Twosome: NSAIDs & Ulcers' Symposium, 49th Annual American Rheumatism Association Meeting, Anaheim, USA, June, 1985

Isselbacher KJ. The role of arachidonic acid metabolites in gastrointestinal effects. Drugs 33 (Suppl. 1): 38-46. 1987

Langman MJS. Anti-inflammatory drug intake and the risk of ulcer complications. Medical Toxicology 1 (Suppl. 1): 34-38. 1986

McCarty DJ. Csuka ME. Aspirin in the treatment of chronic inflammatory arthritis. Correspondence. Journal of the American Medical Association 257: 1331. 1987

McPherson TC. Salsalate use for arthritis: a clinical evaluation. Clinical Therapeutics 6: 388-390. 1984

Mielants H. Veys EM. Verbruggen G. Schelstraet K. Salicylate-induced gastrointestinal bleeding: comparison between soluble. buffered enteric-coated. and intravenous administration. Journal of Rheumatology 6: 210-218. 1979

Morris HG. Sherman NA. McQuain C. Goldlust MB. Chang SF. et al. Effects of salsalate (non-acetylated salicylate) and aspirin on serum prostaglandins in humans. Therapeutic Drug Monitoring 7: 435-438. 1985

Needs CJ. Brooks PM. Clinical pharmacokinetics of the salicylates. Clinical Pharmacokinetics 10: 164-177. 1985

Pleskow WW. Stevenson DD. Mathison DA. Simon RA. Aspirin sensitivity in rhinosinusitis and asthma: spectrum of adverse reactions to aspirin. Journal of Allergy and Clinical Immunology 71: 574-579 1983

Roth SH. Salicylates: revolution versus evolution. In New directions in arthritis therapy. pp. 23-26. PSG Publishing. Littleton. 1980a

Roth SH. New directions via molecular modification in NSAIDs. In New directions in arthritis therapy. pp. 59-98. PSG Publishing. Littleton. 1980b

Roth SH. Salicylates. In Roth (Ed.) Rheumatic therapeutics. pp. 309-323. McGraw-Hill. New York. 1985

Roth SH. NSAID gastropathy. We started it - can we stop it? Editorial. Archives of Internal Medicine 146: 1075. 1986a

Roth SH. Treating arthritis and sparing the stomach: the NSAID gastropathy dilemma. Arthritis and Rheumatism 8: 78-83. 1986b

Roth SH. Salicylates. In Katz (Ed.) Management of rheumatic disease. 2nd ed.. Lippincott. Philadelphia. in press. 1987

Roth SH. Agrawal N. Mahowald M. Montoya H. Robbins D. Misoprostol heals aspirin-induced gastropathy in rheumatoid arthritis. Presented at the 51st Annual American Rheumatism Association meeting. Washington DC. June. 1987. Abstract. Arthritis and Rheumatism 30 (Suppl.). 1987

Roth SH. Bennett RE. Nonsteroidal anti-inflammatory drug gastropathy: recognition and response. Archives of Internal Medicine 147: 2093-2100. 1987

Russell AS. Sturge RA. Smith MA. Serum transaminases during salicylate therapy. British Medical Journal 2: 428. 1971

Ryan JR. McMahon FG. Vargas R. Differential influences of salsalate. aspirin and naproxen on plasma renin activity and platelet thromboxane synthesis. Abstract. 2nd International Meeting on Side Effects of Anti-Inflammatory Analgesic Drugs. Cambridge. England. July. 1985

Samter M. Intolerance to aspirin. Hospital Practice 50: 92-98. 1973

Samter M. Beers FR. Concerning the nature of intolerance to aspirin. Journal of Allergy 40: 218-293. 1967

Szczeklik A. Gryglewski RG. Czerniawska-Mysik G. Clinical patterns of hypersensitivity to non-steroidal anti-inflammatory drugs and their pathogenesis. Journal of Allergy and Clinical Immunology 60: 276-284. 1977

Vane J. The evolution of non-steroidal anti-inflammatory drugs and their mechanisms of action. Drugs 33 (Suppl. 1): 18-27. 1987

Voltin RF. NSAIDs from a GI point of view. Practical Gastroenterology VIII (4). 1984

Weissmann G. Pathogenesis of inflammation: effects of the pharmacological manipulation of arachidonic acid metabolism on the cytological response to inflammatory stimuli. Drugs 33 (Suppl. 1): 28-37. 1987

Author's address: Dr *Sanford H. Roth*. Medical Director. Arthritis Center Ltd. 3330 North 2nd Street. Phoenix. AZ 85012. (USA).