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Comparative analgesic and anti-inflammatory properties of sodium salicylate and acetylsalicylic acid (aspirin) in rheumatoid arthritis

SALLY J. PRESTON, M. H. ARNOLD, ELAINE M. BELLER, P. M. BROOKS & W. WATSON BUCHANAN

Florance and Cope Professorial Department of Rheumatology and Sutton Rheumatism Research Laboratory, Department of Rheumatology, University of Sydney, Royal North Shore Hospital, St Leonards 2065, New South Wales, Australia

1 Enteric coated sodium salicylate 4.8 g daily was compared with the same dose of enteric coated aspirin in 18 patients with rheumatoid arthritis.

2 After an initial washout period lasting 3 days, patients were randomly allocated to treatment with sodium salicylate or aspirin. After 2 weeks the two treatments were crossed over.

3 Pain relief, reduction in articular index of joint tenderness, increase in grip strength, decrease in digital joint circumference and patients' assessment showed significant improvement with both treatments compared with the washout period. No significant differences were found between the two therapies.

4 No correlation was found in the degree of improvement in any of the clinical outcomes and the salicylate concentrations at steady state.

Keywords aspirin sodium salicylate non-acetylated salicylates clinical trial rheumatoid arthritis

> 'Sodium salicylate does not appear to be as potent as aspirin as an antipyretic or analgesic . . . but has not been compared under controlled conditions to aspirin in the management of inflammatory disorders'
>
> Stephen L. Dahl, 1987

Introduction

Salicylates have been widely employed to treat rheumatic diseases for over a century (Buss, 1875; Maclagen, 1876), and acetylsalicylic acid (aspirin) from the turn of the century (Witthauer, 1899). There is a widespread belief that aspirin is a superior analgesic and anti-inflammatory agent to non-acetylated salicylate preparations, in particular sodium salicylate (Lasagna, 1960; Levy, 1965; Calabro & Paulus, 1970; Champion *et al.*, 1975). Sodium salicylate, however, has been shown in clinical therapeutic trials in rheumatoid arthritis to be as equally efficacious as other nonsteroidal anti-inflammatory agents (Deodhar *et al.*, 1973). Surprisingly, there is, to our knowledge, no study comparing sodium salicylate with aspirin in rheumatoid arthritis. Bleckman & Lechner (1979) compared choline magnesium trisalicylate with aspirin in patients with rheumatoid arthritis and found both equally effective in reducing severity of symptoms. Liyanage & Tambar (1978) found salsalate and aspirin equally effective in controlling pain and stiffness in patients with osteoarthritis. We considered it of interest to compare sodium salicylate and aspirin in patients with rheuma-

Correspondence: Professor Peter M. Brooks, Royal North Shore Hospital, St Leonards 2065, New South Wales, Australia

toid arthritis and to determine whether the clinical response correlated with the serum salicylate concentration at steady state.

Methods

Eighteen patients with 'definite' or 'classical' rheumatoid arthritis, as defined by the diagnostic criteria of the American Rheumatism Association (Ropes *et al.*, 1958), participated in the study. Their mean age was 48.7 years (range 30 to 64 years) and 14 of them were female. Their mean duration of disease was 3.1 years (range 1 to 6 years). All the patients were seropositive for rheumatoid factor and all had erosions on X-ray. Six patients had subcutaneous nodules.

All of the patients had previously been treated with salicylates without adverse effects. All had discontinued salicylate therapy at least 3 months prior to the study and all were receiving other nonsteroidal anti-inflammatory medications. The purpose of the study was explained to the patients, all of whom freely agreed to participate. All the patients had been involved in previous clinical trials of nonsteroidal anti-inflammatory agents and had been compliant with the protocols.

After an initial washout period lasting 3 days, patients who showed an exacerbation of their arthritis were assigned to receive either enteric coated aspirin 4.8 g day^{-1} in four equally divided doses, or enteric coated sodium salicylate in the same dose. Thus, nine patients first received aspirin and nine sodium salicylate. After 2 weeks, the patients were crossed over to the other treatment schedule. The tablets were approximately the same size and colour. The enteric coated aspirin were red and the sodium salicylate tablets were burgundy.

Assessments were made at the end of the 3 day wash-out period and at 2 and 4 weeks. Patients were seen at the same time of day and by the same observer throughout the study. Blood was withdrawn at the 2 and 4 week visits for estimation of trough serum salicylate concentration. Compliance was confirmed by a tablet count.

It would have been desirable to have had a washout or placebo treatment period between the two active drug periods. However, this was decided against as previous experience had shown that this resulted in a high drop-out rate. The fact that the treatment periods with aspirin and sodium salicylate each lasted 2 weeks should have avoided a carry-over effect.

Pain was measured on a five point Likert scale (Likert, 1932) where: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain and 4 = very severe pain. The articular index of joint tenderness was assessed by the method of Ritchie and her colleagues (Ritchie *et al.*, 1987). Grip strength was measured by the method described by Lee *et al.* (1974) and digital joint circumference was measured by a spring gauge as described by Webb *et al.* (1973). Only those joints which had soft tissue swelling and which showed an increase in circumference at the end of the three day washout period were measured by the latter method. A total of 29 joints were assessed in 15 patients. Patients' assessment of treatment efficacy was recorded on a Likert scale similar to that used for pain, where: 0 = ineffective, 1 = slightly effective, 2 = moderately effective, 3 = very effective and 4 = extremely effective.

Serum salicylate concentrations were estimated by Trinders' method (1954) which is accurate to within 0.145 mmol l^{-1}.

Statistical analysis was performed by analysis of variance with multiple comparison and Pearsons' correlation method where appropriate.

Results

The results are summarised in Table 1. All of the clinical outcome measures were significantly different from baseline at the 0.01% level both with the sodium salicylate and aspirin. There were no significant differences between the outcomes with sodium salicylate and aspirin. Of particular interest, is the fact that reduction in joint circumference was the same with both drugs i.e. both had similar anti-inflammatory effect.

There was a wide range in the steady state serum salicylate concentrations from 1.09 mmol l^{-1} to 2.24 mmol l^{-1}. There was, however, no significant difference between serum salicylate concentrations achieved with sodium salicylate (1.79 ± s.e. mean 0.32 mmol l^{-1}) and aspirin (1.76 ± s.e. mean 0.24 mmol l^{-1}). No correlation was found between the degree of improvement in any of the outcome measures and the serum salicylate concentrations at steady state.

Discussion

Despite the widespread use of salicylate therapy, it is surprising how much we still have to learn. In particular, there is scant data regarding the comparable effects of aspirin and non-acetylated salicylates. In animal models, aspirin has generally been found to be a more effective analgesic and anti-inflammatory agent than non-acetylated

Table 1 Clinical and laboratory data on outcome measures comparing sodium salicylate and acetylsalicylic acid in 18 patients with rheumatoid arthritis (mean ± s.d.)

Outcome measures[1]	*Washout*	*Sodium salicylate*	*Acetylsalicylic acid*	*Mean difference between treatments*[2]
Pain	3.06 ± 0.54	1.89 ± 0.76*	1.94 ± 0.80*	−0.06 (−0.45, 0.34)
Articular index of joint tenderness	20.22 ± 4.1	12.94 ± 4.58*	13.00 ± 0.80*	−0.06 (−1.30, 1.19)
Grip strength (mm Hg)				
Right hand	94.28 ± 14.49	100.33 ± 17.12*	100.67 ± 16.85*	−0.33 (−2.59, 1.92)
Left hand	90.78 ± 12.76	95.17 ± 13.29*	94.94 ± 13.62*	0.22 (−2.03, 2.47)
Joint circumference (mm)	119.6 ± 60.09	113.87 ± 56.33*	114.07 ± 56.58*	−0.20 (−0.86, 0.46)
Patients' assessment	3.56 ± 0.86	2.11 ± 0.9*	2.06 ± 0.80*	0.06 (−0.26, 0.37)

[1] See text for explanation.
[2]Figures expressed represent mean of paired difference between sodium salicylate and acetylsalicylic acid. Bracketed figures represent 95% confidence intervals.
* Significantly different at 0.01% from washout period.

salicylates (Adams & Cobb, 1963; Collier, 1969), although Brogden *et al.* (1980) on the basis of a critical review of the literature, concluded that diflunisal, a difluorophenyl derivative of salicylic acid, was a more potent analgesic, anti-inflammatory agent and antipyretic than aspirin.

In humans, aspirin has also been reported to be somewhat more effective than non-acetylated salicylates as both an analgesic and anti-inflammatory agent (Levy, 1965; Lim, 1966; Collier, 1969; Calabro & Paulus, 1970), although Seed (1965) found aspirin and sodium salicylate to be equipotent as antipyretics. However, comparison of choline magnesium trisalicylate in rheumatoid arthritis (Bleckman & Lechner, 1979) and salsalate in osteoarthritis (Liyanage & Tambar, 1978) with aspirin showed no clinical differences. Diflunisal has been found to be as, or more effective as an analgesic than aspirin in clinical therapeutic trials in osteoarthritis (Caruso *et al.*, 1978; Dieppe & Huskisson, 1978; Essigman *et al.*, 1979). However, diflunisal is not biotransformed to salicylate and so it is difficult to define comparable doses based on serum salicylate concentrations. Aspirin is certainly a more potent inhibitor of prostaglandins (Ferreira & Vane, 1974; Crook *et al.*, 1976; Brune, 1987) and also irreversibly acetylates many proteins (Pinckard *et al.*, 1968, 1970).

In the present study, sodium salicylate and aspirin in the same daily dose, were equally effective in patients with rheumatoid arthritis in terms of both analgesic and anti-inflammatory activity. There was no significant difference in the serum salicylate concentrations between groups at steady state, confirming that the two dosage regimens were equivalent.

Considerable differences were noted in the steady state plasma salicylate concentrations among the patients within each group which has been observed by other workers (Paulus *et al.*, 1971). Gurwich *et al.* (1984) found an inverse relationship between clinical effect and both total and free salicylate concentrations in rheumatoid arthritis, but no correlation was found in the present study between response and the serum salicylate at steady state. Many workers feel that monitoring serum salicylate concentrations is a poor guide in predicting clinical outcome and toxicity (Rainsford, 1984) and on the basis of our study we would support this view. Others, however, would refute this (Graham *et al.*, 1977). Some trials of other non-steroidal anti-inflammatory drugs have shown a correlation between clinical effect and plasma level (Day *et al.*, 1982; Dunagan *et al.*, 1986), whereas others have found this difficult to demonstrate (Brooks *et al.*, 1975; Orme *et al.*, 1976; Ekstrand *et al.*, 1980).

If, as suggested by the present study, sodium salicylate is equipotent with aspirin, then it can be argued that non-acetylated salicylates should be prescribed in preference to acetylated salicylates. There is considerable evidence, with few exceptions (Mitchell *et al.*, 1984), that gastro-intestinal mucosal damage in both animals and

humans is less with non-acetylated salicylates in comparison with aspirin (Pierson *et al.*, 1961; Leonards & Levy, 1973; de Schepper *et al.*, 1978). It is still uncertain whether dyspepsia is less frequent with non-acetylated preparations (Buchanan *et al.*, 1979).

Asthma, allergic rhinitis and angioedema may be precipitated by aspirin in sensitive individuals. Challenge with non-acetylated salicylates has failed to produce symptoms in known aspirin sensitive individuals (Samter & Beers, 1968; Scezeklik, 1987; Szczeklik *et al.*, 1975).

Sodium salicylate has been reported to cause hepatotoxity (Rich & Johnson, 1973), but no comparable data are available to determine whether the incidence and severity of this complication is less than with aspirin.

Although a number of clinical studies document the renal side effects of aspirin, only oedema has been reported with diflunisal among the non-acetylated salicylates in the review by Clive & Stoff (1984). The toxic effect of aspirin in the kidney is thought to be largely related to prostaglandin inhibition, and it is therefore likely that non-acetylated salicylates will prove to be less toxic. This, however, remains to be confirmed.

In conclusion, sodium salicylate and aspirin in the same dose were equipotent in analgesic and anti-inflammatory effect in a controlled clinical trial in rheumatoid arthritis. The improvement in pain, joint tenderness, grip strength and soft tissue swelling did not correlate with steady state serum salicylate concentrations. In view of the greater toxicity of aspirin, especially in relation to the gastrointestinal tract, a case can be made for prescribing sodium salicylate in preference to aspirin in rheumatoid arthritis.

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