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Does the Acetyl Group of Aspirin Contribute to the Antiinflammatory Efficacy of Salicylic Acid in the Treatment of Rheumatoid Arthritis?

THE MULTICENTER SALSALATE/ASPIRIN COMPARISON STUDY GROUP

Abstract. **In a multicenter, double blind, parallel group study, 233 patients with classical or definite rheumatoid arthritis (RA) were randomized to 12 weeks of either salsalate (salicylsalicylic acid, nonacetylated salicylate) or aspirin following disease flare. One hundred-fifty patients completed, 83 taking salsalate and 67 taking aspirin. Patients received initial doses of 3 g/day of salsalate or 3.6 g/day of aspirin. Doses were adjusted during the first 5 weeks for efficacy and tolerance. Both treatments were equally effective as measured by all the usual variables, but there was a higher incidence of severe gastrointestinal problems among patients taking aspirin. Thus, this study demonstrated that the acetyl group of aspirin does not enhance the antiinflammatory efficacy of salicylic acid in RA.** (*J Rheumatol 1989;***16:321–327**)

Key Indexing Terms:
SALSALATE NONACETYLATED SALICYLATE ACETYLSALICYLIC ACID
RHEUMATOID ARTHRITIS DOUBLE BLIND CLINICAL TRIAL

Aspirin has long been considered to be the prototype nonsteroidal antiinflammatory drug (NSAID), the standard against which all newer NSAID have been compared. Its antiinflammatory effects in rheumatoid arthritis (RA) are generally accepted and have been documented[1,2].

The active acetyl group is known to endow aspirin with certain properties that are lacking in nonacetylated salicylate. *In vitro*, aspirin is a much more potent cyclooxygenase inhibitor than nonacetylated salicylate[3]. *In vivo,* irreversible acetylation of platelet cyclooxygenase inhibits thromboxane initiated platelet aggregation, whereas nonacetylated salicylate has little or no effect on platelet function or on platelet derived serum concentrations of prostaglandins (PG)[4,5]. Similarly, it has been suggested that nonacetylated salicylate has less effect than aspirin on PG dependent renal function[6], and causes significantly less occult gastrointestinal (GI) blood loss than aspirin[7]. Several clinical studies suggest that nonacetylated salicylate and aspirin produce comparable therapeutic responses in patients with RA[8,9].

The purpose of our study was to determine whether the antiinflammatory effects of acetylsalicylic acid in patients with RA were greater than those of nonacetylated salicylate. Salsalate (salicylsalicylic acid) was used as the nonacetylated salicylate. We used a carefully designed, multicenter, prospective study that compared doses of nonacetylated salicylate and aspirin that were calculated to provide equal amounts of bioavailable salicylate[10,11].

From the Multicenter Salsalate/Aspirin Comparison Study Group and 3M Riker, 3M Health Care Group, St. Paul, MN, USA.

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The Multicenter Salsalate/Aspirin Comparison Study Group: P.A. April, MD, 6465 South Yale, Tulsa, OK; M. Abeles, MD, Associate Professor, Department of Medicine (Division of Rheumatology), University of Connecticut Health Center, Farmington, CT; H.S.B. Baraf, MD, 10313 Georgia Ave., Silver Spring, MD; S.A. Cohen, MD, Internal Medicine Specialty Associates, Stratford, CT; N.J. Curran, BA; M.L. Doucette, BS; B.P. Ekholm, MS; M.B. Goldlust, PhD, 3M Riker; C.M. Knee, MD, 110 Warren Ave., Hohokus, NJ; E.A. Lee, 3M Riker; R.E. Marcus, MD, 185 Cedar St., Teaneck, NJ; G.R. Parrino, MD, 200 South Broadway, Tarrytown, NY; R.W. Reese, MD, 420 North Duke St., Lancaster, PA; W.G. Riskin, MD, 4700-C Sheridan St., Hollywood, FL; B.S. Samuels, MD, 3 Madbury Rd., Durham, NH; P.D. Utsinger, MD, 8815 Germantown Ave., Chestnut Hill, PA; A.M. Virshup, MD, 1500 North Dixie Highway, West Palm Beach, FL; M.E. Wenger, MD, 420 North Duke St., Lancaster, PA; J.C. Whelton, MD, 1665 Palm Beach Lakes Blvd., West Palm Beach, FL; R.R. Wilson, MD, Director, Medical Affairs, 3M Riker.

Address requests for reprints to Dr. P.A. April, Warren Professional Building, 6465 South Yale, Suite 516, Tulsa, OK 74136.

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MATERIALS AND METHODS

Study design. This was a randomized, double blind, multicenter, parallel group study in patients with active RA known to be responsive to NSAID therapy. Disease status was assessed at study entrance. Prestudy NSAID therapy was then withdrawn and patients were given placebo 4 times a day under single blind conditions. To qualify for randomization to the 12-week study drug treatment, patients were required to demonstrate active RA plus flare of their disease at some time from 48 h to 2 weeks after NSAID withdrawal.

Active RA was defined as at least 3 of the following: 6 or more joints painful or tender on motion; 3 or more swollen joints; morning stiffness with duration of 45 min or more; Westergren erythrocyte sedimentation rate (ESR) of 28 mm/h or more[12]. Flare was defined as at least 2 of the following: an increase of 2 or more painful joints; an increase of 2 or more swollen joints; an increase in duration of morning stiffness by at least 30 min.

The randomization schedule assigned patients to one of the 2 study drugs after they flared. Salsalate was given orally twice a day at a starting dose of 3000 mg/day and was alternated with matching placebo to simulate a 4 times/day regimen. Aspirin was given orally 4 times a day at a starting dose of 3600 mg/day. These starting doses were selected on the basis of previous data[10,11] to provide equal amounts of bioavailable salicylic acid from each of the drugs. Identically appearing capsules prepared by Riker Labora-

tories, containing either salsalate or acetylsalicylic acid (Monsanto), were used to maintain blinding. The salsalate formulation was identical to the currently marketed formulation.

Up to 3 dosage adjustments (of 2 tablet/day increments) were allowed during the first 5 weeks to maximize therapeutic response and minimize adverse effects. Plasma salicylic acid levels were not used to guide dosage adjustments (i.e., there was no target salicylic acid level). Dosages were then not allowed to change for the remainder of the 12-week study participation. Thus all patients were on stable regimens beginning at Week 6 assessments. Doses could range from 1500–4500 mg/day of salsalate and from 1800–5400 mg/day of aspirin.

Patients were allowed to take acetaminophen (325 mg capsules) as needed as an analgesic up to a maximum of 2600 mg/day, except during the 8 hours immediately preceding efficacy assessments. Use of nonstudy NSAID and analgesics was prohibited.

Patients. Participants were male and nonpregnant, nonlactating female patients at least 18 years of age. No upper age limit was set. Patients were required to meet the criteria for classical or definite RA[13] and to have had the disease for at least 6 months with onset after age 16. Patients were receiving NSAID therapy immediately before entering the study and were responsive to that therapy as shown by active disease plus flare after therapy withdrawal.

Patients receiving gold salts, antimalarial drugs, and/or penicillamine in a stable regimen for at least 6 months preceding study entry, or low dose corticosteroids ($\leq$ 7.5 mg/day of prednisone or equivalent) in a stable regimen for at least 3 months preceding entry were allowed to enroll providing regimens could remain stable throughout the study. Prestudy physical therapy could be continued if that therapy regimen remained unchanged during study participation.

Patients were excluded if they presented signs of other rheumatic diseases[13]; conditions that might affect the absorption, distribution, biotransformation, or excretion of salicylic acid; conditions that might interfere with evaluation of the disease or obscure the evaluation of adverse experiences; evidence of bleeding disorders or active peptic ulcer disease during the preceding 3 months; history of hypersensitivity to any NSAID; unexplained abnormal laboratory test results; 2 or more liver function tests greater than 30% above the normal range; chemical dependency; or a history of noncompliance with therapy.

Patients were also excluded if treated with azathioprine, cyclophosphamide, or methotrexate during the preceding 6 months; high dose corticosteroids ($>$ 7.5 mg/day of prednisone or equivalent) during the preceding 3 months; intraarticular or topical corticosteroids or investigational drugs during the preceding month; or anticoagulants during the preceding 2 weeks.

All patients were informed of the risks involved and alternative therapies available and each gave written consent before entering the study. The study was reviewed and approved by institutional review committees.

Clinical assessments. Disease activity was evaluated just before discontinuation of prestudy NSAID, at a minimun of weekly intervals during the washout of NSAID therapy, and at biweekly intervals during the 12 weeks of treatment with study drug. Assessments included (1) number of painful joints out of 68 assessed; (2) degree of pain in each of the 68 joints (modified from the Ritchie index[14]); (3) number of swollen joints out of 66 assessed; (4) duration of morning stiffness; (5) Westergren ESR; (6) mean bilateral grip strength; (7) time to walk 50′; (8) ARA functional classification[15]; (9) physician's global impression; (10) patient's global impression; and (11) use of acetaminophen.

Physician's global impression was scored relative to the patient's condition at flare using the following scale: 0 = worse than; 1 = no change; 2 = slight improvement; 3 = moderate improvement; 4 = much improvement. Patient's global impression was scored on how the patient felt at the time of the visit using the following scale: 0 = uncomfortable; 1 = reasonably comfortable; 2 = comfortable. Physician's global impression was scored at each visit before the patient gave his/her global score.

Safety and laboratory assessments. Safety was evaluated by examination at the beginning and completion of the study, by laboratory testing, by evaluation of concomitant medication requirements, and by the incidence and severity of adverse experiences. Hematologic, blood chemisty, and fecal occult blood tests (Hemoccult®, SmithKline Diagnostics), and urinalyses were performed at study entrance and after 4, 8, and 12 weeks taking study drug. All laboratory tests, except prothrombin time, partial thromboplastin times, and fecal occult blood tests, were performed at a central laboratory (MetPath, Teterboro, NJ). Information regarding adverse experiences was elicited at each visit and all adverse experiences were followed to resolution. Samples for plasma salicylic acid levels were collected at each visit to document that both treatment regimens maintained similar compliance and plasma levels but not to document the steady state levels attained or to correlate plasma levels to efficacy. Analysis of these samples was blinded and performed after the completion of the study. Blood sampling times were based on patient and investigator convenience and were generally 5 to 6 h longer than the usual dosing intervals. (By design the next dose was withheld until the blood sample was collected.)

Compliance. Compliance was determined by capsule count plus patient interview. Noncompliance was defined as self-administration of less than 80% of the prescribed number of capsules during the intervals between visits or omission of any doses during the 3 days immediately preceding each visit. Special instruction cards for self-administration of study drug were provided to enhance compliance; an objective of plasma drug monitoring was also to enforce compliance.

Statistical analysis. Joint assessments, duration of morning stiffness, time to walk 50′, grip strength, and the amount of acetaminophen used were compared between treatment groups using an analysis of covariance. This analysis modeled improvement from flare on center, treatment group, center by treatment group interaction, and flare response. Because the center by treatment group interaction was not significant, the data from the 13 centers were pooled. From this covariance model, least squared estimates of the mean and standard error for improvement from flare were obtained for both treatment groups. For each treatment group, a t test of the estimated mean improvement from flare over the standard error as derived from the analysis of covariance was used to determine if there was a significant treatment effect.

Global impressions and ARA functional class were analyzed using linear model methods[16]. The response was modeled on center, treatment group, and center by treatment group interaction, and the treatment effect was tested for significance.

Efficacy variables were analyzed at 6, 8, 10, and 12 weeks after flare. Only patients who were receiving study drug at those time points were included. When patients were noncompliant during an interval between visits, disease evaluations at the next visit were not analyzed. Because 2 patients taking aspirin and one patient taking salsalate had changes in concomitant antirheumatic therapy during the study, their disease evaluations for all subsequent visits were not considered acceptable. Eligibility determinations were made before breaking the code.

The study was designed to have at least 80% power to detect a difference between the 2 treatments of 20% in global scores, 2 to 4 swollen or painful joints, and 30 min of morning stiffness.

To test for bias due to dropouts, 2 intent-to-treat analyses, an endpoint analysis and a Gould analysis[17] were compared with the results of the analysis of 12-week completers.

The incidences of discontinuations and adverse experiences were compared between the 2 groups using a χ^2 test. For laboratory values and vital signs, changes from prestudy were calculated for each patient. A paired t test was used to test for significant changes from disease flare for each treatment group, and Student's t test was used to compare the changes between groups. Plasma drug levels were compared between the 2 groups by a Wilcoxon rank sum test. Patients were included in the comparison if they were compliant on drug therapy, were maintained on a constant dose during Weeks 8, 10, and 12, and had plasma salicylic acid levels at each of those weeks.

RESULTS

Patients. Two hundred thirty-three patients met the criteria for disease flare during washout and entered the study. One hundred twenty-five were randomized to salsalate and 108 were randomized to aspirin. The 2 groups were similar in both physical characteristics and in disease status at study entrance (Table 1). The mean age of all qualifying patients was 55.5 years and the mean duration of RA was 9.3 years. Seventy-nine percent of all qualifying patients were female and 21% were male. The large majority of patients were in ARA functional class II (85%) and at ARA anatomical stage II (78%). Sixty-seven percent of all patients were receiving concomitant antirheumatic drug therapy; 21% were receiving a corticosteroid, 30% were taking a single slow acting antirheumatic drug, 14% were taking a combination of a corticosteroid plus a slow acting antirheumatic drug, and 2% were taking a combination of slow acting antirheumatic drugs. There was no significant difference between the 2 treatment groups in use of concomitant antirheumatic drug therapy.

There was no significant difference between treatment groups in disease status at baseline. The mean number of days from withdrawal of prestudy NSAID therapy to flare was 6.8 days for the salsalate group and 6.6 days for the aspirin group. Patients in both groups averaged 3.1 capsules of acetaminophen/day during washout.

Of the 233 patients who qualified, 66% (83/125) of the patients taking salsalate and 62% (67/108) of the patients taking aspirin completed the study. The sample size was adequate to detect the specified differences between treatments in global scores, number of swollen or painful joints, and duration of morning stiffness.

Table 1. *Characteristics of qualifying patients**

	Salsalate	Aspirin
Number of patients	125	108
Male	32 (26%)	18 (17%)
Female	93 (74%)	90 (83%)
Mean ± SD age (years)	56.1 ± 12.2	54.8 ± 12.9
Mean ± SD duration of RA (years)	8.8 ± 7.7	9.8 ± 9.3
ARA functional class (%): I	10 (8)	6 (6)
II	105 (84)	93 (86)
III	10 (8)	9 (8)
ARA anatomical stage (%):		
I	2 (2)	2 (2)
II	100 (80)	83 (77)
III	23 (18)	23 (21)
Concomitant antiarthritic therapy (%)	90 (72)	66 (61)
Corticosteroid only	29 (23)	19 (18)
Single SAARD**	42 (34)	28 (26)
Corticosteroid plus SAARD	17 (14)	16 (15)
Combination SAARD	2 (2)	3 (3)

* No significant differences between treatments.
** SAARD: slow acting antirheumatic drug.

Response to therapy. Both treatment groups showed clinically and statistically significant improvement from flare at all visits. The rates of discontinuation due to inadequate therapeutic response alone were equivalent (12%) for both drugs. An additional 4% of patients taking salsalate and 6% of patients taking aspirin discontinued due to inadequate therapeutic response plus adverse experiences (Table 2).

The extent of improvement from flare at each biweekly visit was generally comparable for the 2 treatment groups. Figure 1 shows changes over time for 8 efficacy assessments. The only statistically significant differences between the treatment groups, by analysis of covariance, were as follows: the aspirin group had less improvement in ESR at Weeks 8 and 12, and less improvement in the number of swollen joints at Week 12; the salsalate group used about one more capsule of acetaminophen (325 mg)/day than did the aspirin group during the 2 week periods preceding Week 6, 8, and 10 assessments. Due to the large number of comparisons, these differences between treatments could have been due to chance alone. None of these differences were clinically significant.

The 2 intent-to-treat analyses of all qualifying patients and the analysis of Week 12 data on patients who completed the study provided similar results. In all 3 analyses, patients taking salsalate had significantly greater improvement from flare in ESR than did patients taking aspirin. In the analysis of patients who completed, but not in either of the intent-to-treat analyses, patients taking salsalate also showed a greater improvement from flare than patients taking aspirin in the number of swollen joints.

Patients in both treatment groups were similarly distributed across ARA functional classifications at Week 12 with 87–90% of patients in class II. Comparable numbers from each group, 11% (salsalate) and 15% (aspirin), had an improvement in classification from that at study entrance.

There was no significant difference between the groups

Table 2. *Discontinuations*

Reason for Discontinuation	No. of Patients: Salsalate (N=125) (%)	Aspirin (N=108) (%)
Lack of efficacy	15 (12)	13 (12)
Lack of efficacy and adverse experiences	5 (4)	6 (6)
Adverse experiences (includes laboratory abnormalities)	16 (13)	16 (15)
Other* (includes personal, intercurrent disease and lost to followup)	6 (5)	6 (6)
TOTAL	42 (34)	41 (38)

* One patient in each group completed the Week 12 visit but the visit did not qualify for efficacy analysis; these patients are considered discontinuations.

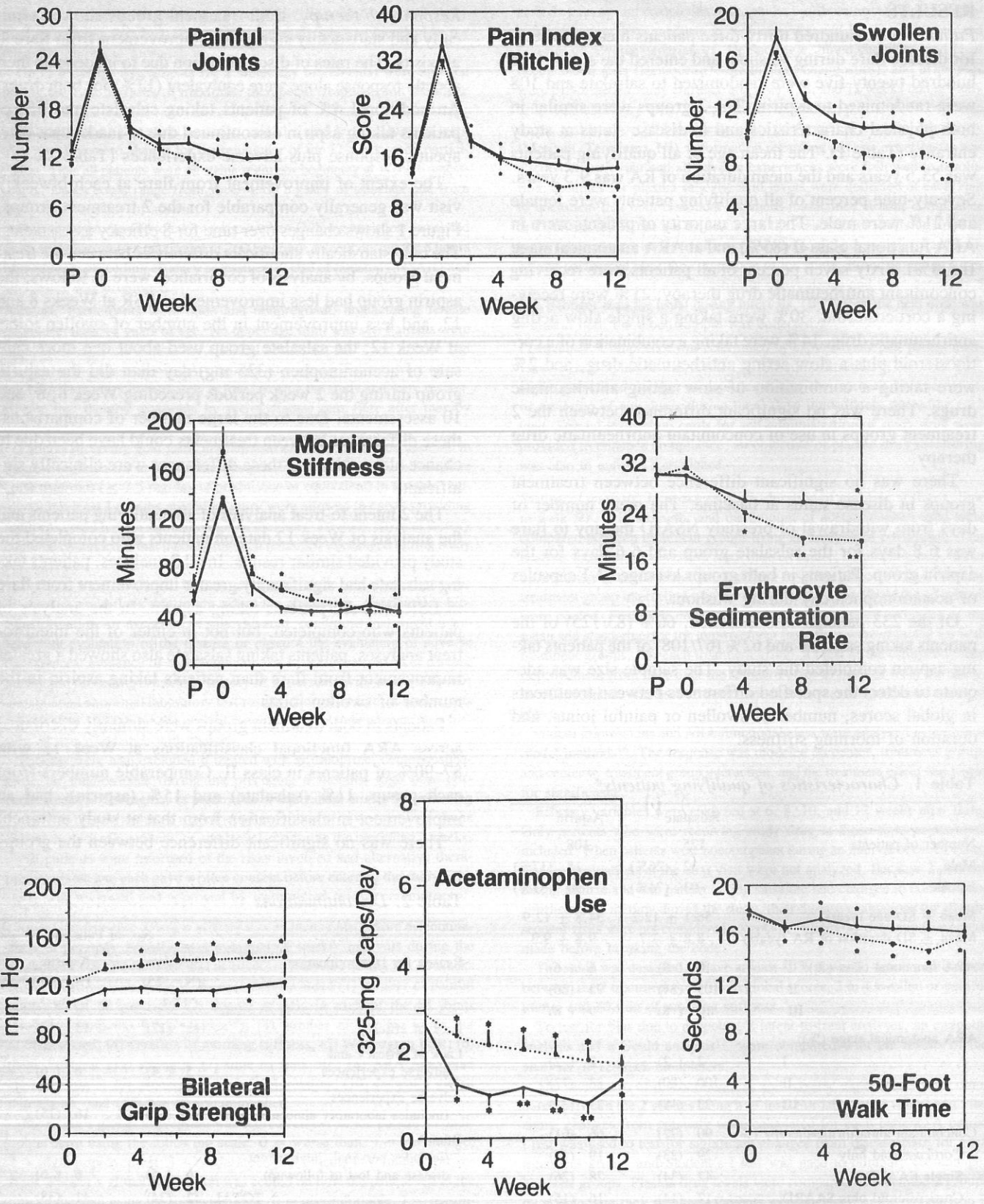

Fig. 1. Changes in mean efficacy values, with SE intervals, for patients who completed 12 weeks. .....salsalate; ——— aspirin. *Significant ($p<0.05$) change from flare. **Significant ($p<0.05$) difference between treatments plus significant change from flare. P = prestudy; O = flare.

in the physicians' global impressions of the patients' conditions at Week 12 relative to flare (Figure 2). Investigators described 96% of the patients taking salsalate and 94% of those taking aspirin as showing at least some improvement from flare. Patients' global impressions were also comparable between the 2 groups, with 93% of the patients taking salsalate and 88% of the patients taking aspirin rating themselves as either reasonably comfortable or comfortable at Week 12 (Figure 3).

The distributions of doses of study drug at Week 12 were comparable for the 2 treatments, taking into consideration the bioavailability of salicylic acid from each of the drugs[10,11]. The median and most frequently used doses at Week 12 were the initial doses, 3000 mg/day of salsalate and 3600 mg/day of aspirin. The range of doses used by patients was 2000 to 4500 mg/day of salsalate and 2400 to 5400 mg/day of aspirin.

Adverse experiences. Three patients were hospitalized during the study for reasons considered possibly or probably related to study drug. Two patients receiving aspirin were hospitalized for upper GI bleeding which was probably drug related. The first patient developed generalized weakness and severe anemia after 32 days of treatment at 3600 mg/day of aspirin. Concomitant therapy included intramuscular aurothioglucose at a stable dose for the preceding 9 months. Roentgenography revealed erosive duodenitis. Following treatment with transfusions, a histamine H_2 receptor antagonist, and antacids, the patient recovered and was subsequently treated with salsalate. After 40 weeks of salsalate at 4000 mg/day, there was no evidence of recurrence of the duodenitis. The second patient experienced severe hemorrhage secondary to a duodenal ulcer after 7 days at 3600 mg/day of aspirin. This patient was receiving no concomitant therapy. Treatment for this patient included transfusions, surgical repair of the ulcer, pyloroplasty, and vagotomy.

A cachetic 67-year-old patient taking salsalate was hospitalized after 58 days at 3000 mg/day. On admission, the patient was confused, disoriented, and incontinent and showed possible left-sided weakness. The symptoms were suggestive of possible salicylism and salsalate was discontinued. However, plasma salicylic acid level measured at the time of hospitalization was well below the toxic range and less than levels obtained throughout study participation. Symptoms resolved following rehydration and improvement in nutritional status.

Thirteen percent of patients taking salsalate and 15% of patients taking aspirin discontinued the study due solely to adverse experiences. Five additional patients (4%) taking salsalate and 6 additional patients (6%) taking aspirin discontinued because of adverse experiences plus lack of therapeutic response. The 2 most common reasons for discontinuation are shown in Table 3.

Adverse experiences necessitated decreases in study drug doses for 21% of patients receiving salsalate and 29% of patients receiving aspirin. In addition, 10 patients (8%) taking salsalate and 8 patients (7%) taking aspirin omitted one or more doses of study drug as a result of adverse experiences.

Adverse experiences were grouped by body system and were further categorized by severity (mild, moderate or severe) based on the opinions of the investigators. The only significant differences between the 2 treatment groups were more mild (32% vs 21%, $p = 0.04$) and more severe (13% vs 5%, $p = 0.02$) GI problems among patients receiving aspirin.

A further indication of the difference between treatment groups in GI problems is reflected in the initiation of antacid therapy. Ongoing antacid therapy at the time patients entered the study was similar in the 2 treatment groups. However, initiation of antacid therapy during the study was significantly ($p = 0.022$) higher among patients who received aspirin (19%) compared with patients who received salsalate (9%). Even though antacid therapy use was initiated in more patients in the aspirin group, GI complaint was the leading cause of discontinuation among these patients. Eight patients (8%) taking aspirin and 3 patients (3%) taking salsalate also tested positive for fecal occult blood. Two of these

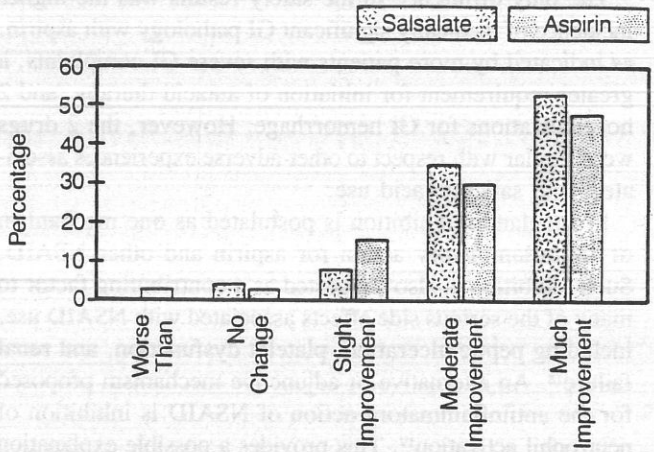

Fig. 2. Distribution of physicians' global impressions of patients' conditions at Week 12 relative to flare.

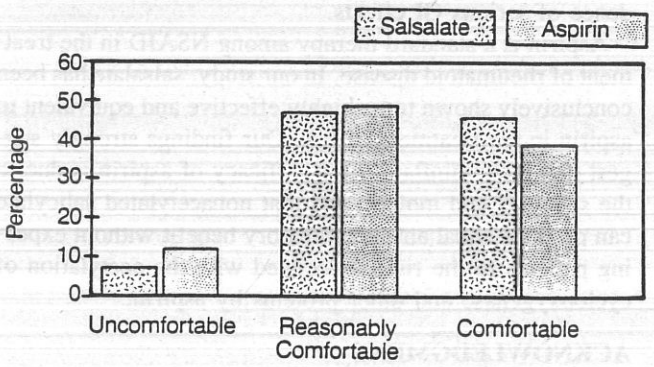

Fig. 3. Distribution of patients' global impressions of their conditions at Week 12.

Table 3. *Adverse experiences most commonly associated with study discontinuation*

Reason for Discontinuation	No. of Patients		p Value
	Salsalate* (N=131) (%)	Aspirin* (N=115) (%)	
GI system disorders	8 (6)	15 (13)	0.079
Hearing and vestibular disorders	13 (10)	6 (5)	0.23
Other disorders	11 (8)	7 (6)	0.49
Number of patients discontinuing for an adverse experience**	21† (16)	22† (19)	0.52

* Includes all qualified and nonqualified patients who received study drug.

** Includes 5 aspirin and 5 salsalate patients who discontinued for adverse experiences plus lack of efficacy.

† Sum of individually listed disorders exceeds number of patients discontinuing because some discontinuations were associated with more than one disorder.

patients taking aspirin were hospitalized for GI bleeding, as previously noted.

Although significant movement out of normal range occurred for some of the laboratory variables at some time points, all changes were either attributable to intercurrent disease, expected effects associated with the use of salicylic acid or were not of the magnitude or frequency to be considered clinically significant. Three patients, 2 (salsalate) and 1 (aspirin), were discontinued because of elevation in AST (SGOT) and ALT (SGPT). Values for all 3 patients returned to normal 2–3 weeks after discontinuing study drug. Similar mean levels and variabilities of plasma salicylic acid were maintained from week to week with each treatment and between treatments, indicating that the 2 treatment groups were similarly compliant.

There were no clinically significant changes in vital signs or body weight in either treatment group.

DISCUSSION

In our randomized, double blind, parallel group study, the nonacetylated salicylate, salsalate, was highly effective and equivalent to aspirin in the treatment of patients with RA. The patients in both treatment groups entered the study with similar progression of disease, responded similarly to withdrawal of prestudy NSAID therapy, and demonstrated equivalent mean improvement from flare while taking the study drug.

The study design included titration of study drug doses intended to achieve an optimal combination of efficacy and drug tolerance. Since patients showed significant improvement from flare at doses substantially less than the maximum allowed, and since most patients completed the study and reported themselves as feeling at least reasonably comfortable, the study provided a fair comparison of the study drugs.

It allowed a preselected dose range of salsalate based on results of previous studies[10,11]. The mean and median doses of salsalate at Week 12 were 3.3 and 3.0 g/day, respectively, which is consistent with current prescribing recommendations. The mean and median final doses of aspirin and salsalate used were bioequivalent as sources of salicylic acid. Our study also supports the effectiveness of twice daily dosing with salsalate and provides further efficacy and safety data on the acceptable use of doses other than 3.0 g/day.

The only difference in the safety results was the higher incidence of medically significant GI pathology with aspirin, as indicated by more patients with severe GI complaints, a greater requirement for initiation of antacid therapy, and 2 hospitalizations for GI hemorrhage. However, the 2 drugs were similar with respect to other adverse experiences associated with salicylic acid use.

Prostaglandin inhibition is postulated as one mechanism of antiinflammatory action for aspirin and other NSAID. Such inhibition is also suggested as a contributing factor to many of the serious side effects associated with NSAID use, including peptic ulceration, platelet dysfunction, and renal failure[18]. An alternative or adjunctive mechanism proposed for the antiinflammatory action of NSAID is inhibition of neutrophil activation[19]. This provides a possible explanation why an NSAID such as salsalate, a relatively poor PG synthetase inhibitor, might provide a therapeutic response equivalent to a strong PG inhibitor, but with a lower incidence of serious GI effects.

Aspirin is a standard therapy among NSAID in the treatment of rheumatoid disease. In our study, salsalate has been conclusively shown to be highly effective and equivalent to aspirin in the treatment of RA. Our findings strongly suggest that the antiinflammatory efficacy of aspirin is due to the salicylic acid moiety, and that nonacetylated salicylate can produce equal antiinflammatory benefit without exposing patients to the risks associated with the acetylation of cyclooxygenase and other proteins by aspirin.

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