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Editorials

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Salsalate, a Nonacetylated Salicylate, is as Efficacious as Diclofenac in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the efficacy of salsalate, a nonacetylated salicylate, in the treatment of patients with rheumatoid arthritis (RA).

Methods. Three hundred and one patients meeting the ACR criteria for RA were drawn from 16 centers. After withdrawal of nonsteroidal antiinflammatory drugs (NSAID) and subsequent flare, patients were randomized to receive either salsalate or diclofenac for 8 weeks, according to a double blind, double dummy protocol. Initial doses of salsalate 3.0 g/day and diclofenac 75 mg/day were titrated for the first 5 weeks. The primary outcome measure was a multivariate analysis at 8 weeks of tender joint count, pain, visual analog scale score, and physician's global assessment.

Results. One hundred and ninety patients completed the study. The mean stabilized dose of salsalate was 3.55 g/day, and that of diclofenac 112 mg/day. Discontinuations were due to lack of efficacy (17 salsalate vs 15 diclofenac); adverse events [19 salsalate (mainly tinnitus and hearing loss; $p = 0.0001$ and $p = 0.04$, respectively) vs 9 diclofenac]; laboratory abnormalities (3 salsalate vs 1 diclofenac); and other reasons, including protocol violations, intercurrent illness, and personal factors (24 salsalate vs 23 diclofenac). Both treatments produced significant improvement from flare ($p < 0.0001$). *Post hoc* power analysis showed that the study had sufficient power (0.60 to 0.90) to detect clinically important differences between the 2 drugs in the primary outcome measures; however, no statistically significant ($p = 0.29$) or clinically important treatment differences were recorded. Other than a difference in erythrocyte sedimentation rate that favored salsalate, there were no significant differences in secondary outcome measures between the 2 groups. All outcomes showed a tendency for more improvement with salsalate.

Conclusion. Salsalate is as efficacious as diclofenac. Salsalate may be considered an alternative to other NSAID in the first line treatment of patients with RA. (*J Rheumatol 1995;***22:617–24**)

Key Indexing Terms:
RANDOMIZED CLINICAL TRIAL
SALSALATE
RHEUMATOID ARTHRITIS
DICLOFENAC Na

Nonsteroidal antiinflammatory drugs (NSAID) are the first line of therapy for patients with rheumatoid arthritis (RA). Although many patients require additional second or third line agents to control their disease, NSAID are almost invariably continued as basic therapy. However, despite the proven efficacy of NSAID as a class, more than 50% of patients with RA who receive one discontinue it within 2 years, many because of toxicity[1]. Major adverse effects reported to be associated with NSAID include gastrointestinal (GI) events varying from mild dyspepsia to bleeding, perforation, and death. A recent metaanalysis[2] and several subsequent large scale studies[3,4] have confirmed that the risk of a serious GI event in an NSAID user is about 3 times that in a nonuser. The risk is even higher in patients who are aged,

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have a previous history of GI events, are taking concomitant steroids, or are in the early phase of NSAID therapy. Renal abnormalities have also been associated with NSAID administration.

As weaker inhibitors of prostaglandin (PG) synthesis, nonacetylated salicylates such as salsalate might be expected to produce less prostaglandin mediated gastric and renal damage than other NSAID, making them particularly advantageous in high risk patients. In support of that hypothesis, 5 endoscopy studies involving salsalate suggest that it does indeed lead to fewer erosions and ulcers than other NSAID[5-9]. However, nonacetylated salicylates have generally been perceived to be less efficacious than other NSAID, simply because they are weaker PG synthesis inhibitors. To test that anecdotal perception, it is of interest to compare the efficacies of nonacetylated salicylates with those of other NSAID in well controlled randomized clinical studies. Our investigation compares the efficacy of salsalate, a dimer of salicylic acid with salicylic acid as its major metabolite, with that of a widely used NSAID, diclofenac sodium, in patients with RA.

MATERIALS AND METHODS

Study design. This was a randomized, double blind, multicenter, parallel group study involving patients with active RA known to be responsive to NSAID therapy. The investigators met as a group to jointly develop the study design. Thereafter, progress at each center and data collection were monitored by Innovus, Inc., Hamilton, Ontario.

Patients. Patients were drawn from each of 16 participating study centers. Eligible patients were men and women aged 18 years or older who were being treated with salicylates or other NSAID for RA, meeting the American Rheumatism Association[10] criteria and of at least 6 months' duration. Women of childbearing potential were required to have a negative pregnancy test and to be using an approved method of contraception. Patients treated with non NSAID antirheumatics (penicillamine, gold complexes, methotrexate, antimalarials) and low-dose systemic corticosteroids ($\leq$7.5 mg/day of prednisone or equivalent) in a stable regimen for at least 3 months before study entry were eligible, providing the regimen remained stable throughout the study. Similarly, prestudy physical therapy could be continued if the regimen remained unchanged throughout.

Patients were excluded if they had (1) signs of other rheumatic diseases (systemic lupus erythematosus, scleroderma, Reiter's syndrome); (2) RA onset before age 16 years; (3) a condition that might affect the absorption, distribution, biotransformation, or excretion of either drug; (4) a condition that might interfere with evaluation of the disease or obscure the evaluation of adverse experiences; (5) evidence of bleeding disorders or active peptic ulcer disease during the preceding 3 months; (6) used intraarticular corticosteroids, or anticoagulant medication within 2 weeks of entry or during the study; or nonstudy salicylates or NSAID as single entity or combination products during the study; (7) been treated within 3 months of study entry with cytotoxic drugs not approved for RA (e.g., cyclophosphamide, sulfasalazine); (8) used topical medication containing NSAID, salicylates, or derivatives within 48 hours of entry or during the study; (9) a history of hypersensitivity to any NSAID; (10) unexplained abnormal laboratory results; (11) 2 or more liver function tests >30% above the normal range; (12) chemical dependency; or (13) a history of noncompliance with therapy.

Patients were informed of the risks involved and the alternative therapies available. Informed consent was obtained from each patient before withdrawal of the previous NSAID. An institutional review board at each center approved the study protocol and informed consent form.

Methods. Disease status was assessed at study entry, when NSAID therapy was withdrawn. Patients who demonstrated both active RA and disease flare between 48 h and 2 weeks after withdrawal were randomized to one of the 2 study treatments.

Active RA was defined as the presence of at least three of[11]: 6 or more joints that were painful or tender upon motion; 3 or more swollen joints; morning stiffness with a duration of 45 min or more; Westergren erythrocyte sedimentation rate (ESR) of 28 mm/h or more (or appropriate method back calculated to the Westergren value)[12].

Disease flare was defined as the presence of at least 2 of: 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; at least a 20% increase in the pain visual analog scale (VAS) score.

Eligible patients were randomized in a balanced fashion at each center to receive either salsalate or diclofenac. Those in the salsalate group received the agent orally twice a day (morning and evening). Diclofenac was given 3 times daily. A double dummy technique was used to maintain the double blind throughout the dosage adjustments. The starting doses of salsalate and diclofenac, of 3.0 and 75 mg/day, respectively, were selected on the basis of prescribing information and described clinical equivalence to 3.6 g/day acetylsalicylic acid (ASA)[13]. A total of 3 dosage adjustments between the inclusive limits of salsalate 2.0-4.5 g/day and diclofenac 50-150 mg/day were allowed during the first 5 weeks to maximize therapeutic response and minimize adverse experiences. However, no dosage adjustment was allowed thereafter, leaving all patients on stable regimens from the Week 6 assessment onwards. Blood levels of salicylic acid were not obtained for logistical reasons.

Matching capsules prepared by 3M Pharmaceuticals contained either salsalate (Disalcid™), a whole enteric coated, 25 mg, diclofenac tablet (Voltaren®, Geigy) hidden inside a capsule, or placebo. All unused study medication was returned at each visit and counted. Compliance was defined as being within 20% of the prescribed dose. Noncompliant patients were either discontinued or not included in the efficacy analysis for particular visits. Acetaminophen (325 mg Tylenol® caplets, McNeil) was provided as an analgesic to be taken as needed, to a maximum 2600 mg/day, except during the 8 h immediately preceding efficacy assessments. Use of nonstudy NSAID and analgesics was not permitted.

Clinical assessments. The principal evaluation of improvement was based on 3 primary disease outcomes[14,15]: the number of tender joints, a VAS assessment of pain, and the physician's global assessment. The joint count consisted of an assessment of clinically active joints, determined by pain on passive motion or tenderness on pressure of 68 joints. The pain scale consisted of a 10 cm horizontal line labelled "none" at the left end and "severe" at the right, along which movement was tracked in mm. The physician's global assessment was a judgment of change from flare using a scale from "much worse" (0), through "slightly worse" (1), "no change" (2), "slight improvement" (3), and "good improvement" (4) to "very good improvement" (5).

Secondary outcomes included swollen joint count of 66 joints, joint tenderness score (modified after Ritchie, *et al*[16]), duration of morning stiffness, grip strength, patient global assessment, ESR, acetaminophen use, and the findings of a modification of the Problem Elicitation Technique (PET), a priority function questionnaire designed to identify individual disabilities due to arthritis and their relative importance to the patient[17]. Patients were questioned, in a standardized manner by a trained interviewer, about physical, social, emotional, occupational, and communication problems, and about difficulty with sleep. The level of difficulty that patients experienced with each problem area was assessed on a 7 point category rating scale from "without any difficulty" to "unable to do." Patients also ranked the problems in order of importance. The patient's global impression was recorded in terms of his/her responses when asked, "Think about how your rheumatoid arthritis affects your general overall activities. Over the last week, rate your ability to perform your usual daily activities." Possible responses were: " very poorly" (0), "poorly" (1), "fair" (2), "good" (3), "very good" (4), and "performance not affected by my arthritis" (5).

To ensure uniformity of outcome measurement, each center was given onsite training by the same physician (PMJP) in the collection of the PET, joint examination, and other outcomes. A written and photographic description of the joint assessments was used by each center[18]. Grip strength was assessed uniformly using the same type of modified sphygmomanometer cuff[19] inflated to 20 mm Hg. To minimize observer variation, every patient in a particular center was asessed throughout the study by the same trained, blinded assessor.

Efficacy and safety assessments were made at study entry, flare, and every 2 weeks throughout the investigation, with the exceptions of ESR, which was assessed at entry and Weeks 4 and 8, and the PET, which was performed at flare and at the end of study.

Safety and laboratory assessments. Safety was evaluated by physical examination at the beginning and end of the study, by laboratory testing, by evaluation of changes in concomitant medication, and by the incidence and severity of adverse experiences. Hematology, blood chemistry, and urinalysis were performed at entry, Week 4, and at the end of study. To avoid unblinding by laboratory findings (for example, salicylates are known to reduce plasma uric acid), the results were evaluated by a designated individual other than the physician evaluating efficacy. Adverse experiences were elicited by indirect questioning at each visit and were followed to resolution. All randomized patients are included in the safety analysis (Table 1).

Data collection and statistical analysis. Consistency of the data generated and recorded at each center was ensured by frequent study site visits by an independent monitor (Innovus, Inc.). Sample size was based upon the painful/tender joint count observed in a previous trial[20], in which the standard deviations varied from 6.3 to 12.0 joints, with the most likely value about 9. Change in joint count standard deviations (SD) varied from 4.9 to 16.2, with the most likely value about 8. A clinically important difference was considered to be 3 joints, with alpha = 0.05, beta = 0.2 (or power = 80%), and the change effect size = 0.38, using the size[21] program, there needed to be 120 patients per group or 240 in total. Allowing for a 20% dropout rate expanded this requirement to 150 patients per group, for a total of 300 patients. Descriptive statistics were computed by tabulation procedures in a Scientific Information Retrieval database (SIR)[22]. For continuous variables, the mean and SD were presented. For categorical variables, cell frequencies and percentages were reported. Analyses of both efficacy (study completers) and intent to treat (all eligible enrolled patients) were performed to assess treatment effectiveness and potential bias due to discontinuations. Safety analyses were based on all patients who had received at least one dose of study medication.

Table 1. *Exclusions and withdrawals from safety and efficacy analyses*

Patient Groups*	Salsalate	Diclofenac
	No. Patients (%)	
Randomized and included in the safety analyses	149 (100)	152 (100)
Randomized not meeting eligibility criteria	6 (4)	1 (1)
Included in the intent to treat analyses for efficacy	143 (96)	151 (99)
Withdrawn from study for:		
Lack of efficacy	17 (11)	15 (10)
Adverse experience (Table 6)	19 (13)	9 (6)
Laboratory abnormality	3 (2)	1 (1)
Other (e.g., protocol violations, intercurrent disease, personal)	18 (12)	22 (15)
Total withdrawn	57 (38)	47 (31)
Included in the primary efficacy analysis (completers at Week 8)	86 (58)	104 (68)**

* There were no significant differences between treatment groups.
** Some secondary analyses include one patient (n = 105) who completed the study but had taken acetaminophen within 8 h of his final visit and was therefore excluded, as a protocol violation, from pain related outcomes.

The primary efficacy analysis consisted of a multivariate analysis of total painful joint count, pain VAS score, and the physician's global assessment on the efficacy dataset at Week 8 for completing patients. These primary outcomes were analyzed simultaneously using multivariate analysis of variance (MANOVA). Other disease outcomes were analyzed using univariate analysis of variance (ANOVA). Assessments of principal outcomes were performed for completers (i.e., randomized patients who met eligibility criteria and who successfully completed the double blind phase through Week 8) and on an intent to treat basis (i.e., all randomized patients who met the eligibility criteria; the end of study assessment is at Week 8 for completers and at their last visit for noncompleters). Treatment effect was assessed in statistical models containing: treatment, center, and treatment by center interaction. As treatment by center interactions were not significant, treatment difference was estimated (i.e., point estimate and confidence intervals) in models containing treatment and center effects[23,24].

To reduce variation between patients, and due to dose titration, the change from flare was considered the response outcome in all analyses, except for ESR, where only change from baseline was available. The independence of treatment and safety variables was tested using the χ^2 statistic and the Mantel-Haenszel statistic[25]. For laboratory variables, changes from normal values at baselines to abnormal values at final visit, within treatment group, were tested using the McNemar test[23,25]. An additional analysis was performed to determine the number of patients who had what was considered a clinically meaningful improvement from flare. The definition of such improvement consisted of at least 20% reduction in both painful/tender and swollen joint counts, plus at least 20% improvement in any 3 of the following 5 outcomes: patient's global score; physican's global score; pain VAS score; disability (PET); and acute phase reactant (ESR). These 5 are part of the 7 outcomes recommended core set for RA trials[14].

Adverse events were coded using the World Health Organization[26] dictionary and grouped into preferred terms and body systems. Incidents of adverse events were compared between the 2 treatment groups using the χ^2 statistic. A 2 tailed significance level of 0.05 was used in all analyses without adjustments for multiple comparisons.

RESULTS

Patient group and baseline characteristics. Of the 301 patients randomized (Table 1), 7 were found not to have met eligibility criteria; the remaining 294 patients were included in the intent to treat efficacy analysis (salsalate n = 143; diclofenac n = 151). A total of 57 patients (38%) in the salsalate group and 47 patients (31%) in the diclofenac group were withdrawn from the study due to lack of efficacy, adverse events, laboratory abnormality, protocol violation, intercurrent illness, etc. The primary efficacy analysis was based on the patients who completed the 8 week treatment period and assessment (salsalate n = 86; diclofenac n = 104).

Demographic and disease history data were not different between the 2 groups at baseline (Table 2). Most patients had received at least one second line drug, and about 20 to 30% had received 3 or more. The most commonly prescribed second line agents were antimalarials, methotrexate, and gold. About one-third of patients were also maintained on a constant low dose (≤7.5 mg/day) of prednisone or equivalent.

Clinical characteristics at baseline (flare) are shown in Table 3.

Table 2. *Characteristics of patients completing 8 weeks*

Characteristics*	Salsalate (n = 86)	Diclofenac (n = 104)
Demographics		
Age (y)	53.9; 12.2	53.5; 12.1
Age at RA onset (y)	49.1; 12.5	47.8; 12.2
Female (%)	58 (67)	83 (80)
White (%)	82 (95)	97 (93)
Disease history		
Duration of RA (m)	62.2; 52.9	72.5; 68.3
Positive rheumatoid factor	68 (83)	78 (77)
Number of antirheumatics (AR)**		
NSAID only	7 (8)	11 (10)
NSAID + 1 AR	30 (35)	33 (31)
NSAID + 2 AR	32 (37)	29 (28)
NSAID + 3 or more AR	17 (20)	32 (31)
Types of AR:		
Antimalarial	41 (48)	46 (44)
Gold	36 (42)	57 (54)
Methotrexate	34 (40)	48 (46)
Corticosteroid	32 (37)	33 (31)
Penicillamine	5 (6)	12 (11)
Sulfasalazine	3 (3)	2 (2)
Azathioprine	2 (2)	5 (5)
Cyclosporine	1 (1)	1 (1)

* For continuous variables: mean; SD. For categorical variables: the number of patients (%) are indicated.

** Includes one patient taking Voltaren (n = 105) not included in primary analysis (excluded pain medication), but included in analysis of secondary outcomes.

Dosage. The starting doses at study entry were 3.0 g/day (bid) of salsalate and 75 mg/day (tid) of diclofenac (Table 4). During the first 5 weeks, the dose was titrated to a mean at Week 8 of salsalate 3.55 g/day and diclofenac 112 mg/day.

Table 4. *Prescribed dosage levels at Week 8*

Salsalate (n = 86)		Diclofenac (n = 105)	
Dosage (g/day)	% Patients*	Dosage (mg/day)	% Patients
2.5	9	50	0
3.0**	28	75**	28
3.5	24	100	24
4.0	25	125	19
4.5	15	150	28
Mean; SD			
3.55; 0.61		111.9; 29.0	

* $p = 0.01$ (4 DF, $\chi^2 = 12.86$) for comparison of dose distributions between groups.

** Starting dosage at study entry.

There were slightly more patients in the higher dose range in the diclofenac group than in the salsalate group.

Response to therapy. The primary efficacy analysis of completers at 8 weeks is summarized in Table 3. With the exception of ESR in the diclofenac group ($p = 0.78$), both groups improved significantly from baseline (flare) to Week 8 in all outcome measures ($p < 0.0001$). For example, the total painful joint count improved by 10.7 active joints in the salsalate group and by 9.5 in the diclofenac group; the pain VAS score improved by 29.2 mm in the salsalate group and by 22.4 mm in the diclofenac group; and the physician's global assessment improved by 3.3 points in both groups.

The changes in these primary outcomes were neither clinically important nor statistically significant ($p = 0.29$) between the 2 groups. Similarly, there were no significant differences between the 2 drugs in terms of their effects on secondary outcome measures (other than a change in ESR favoring salsalate; $p = 0.004$). All outcome measures

Table 3. *Response to therapy for primary efficacy analysis (completers) at Week 8. All data shown as change in salsalate minus diclofenac; a negative number indicates improvement*

Outcome Measure	Flare		Change at Week 8		Estimated Treatment Difference (95% CI)	p
	Salsalate (Mean; SD)	Diclofenac (Mean; SD)	Salsalate (Mean; SD)	Diclofenac (Mean; SD)		
Primary: Multivariate analysis						
Total painful joint count	23.3; 12.5	22.6; 11.2	−10.7; 11.8	−9.5; 9.8	−1.7 (−6.0, 2.7)	
Pain VAS score	56.4; 22.6	59.3; 21.9	29.2; 25.4	−22.4; 24.5	−7.3 (−17.9, 3.3)	0.29†
Physician's global score	—*	—*	3.3; 1.4	3.3; 1.2	−0.1 (−0.6, 0.4)	
Secondary: Univariate analysis						
Swollen joint count	11.5; 7.6	12.3; 6.9	−4.8; 6.6	4.6; 6.1	−0.7 (−2.3, 1.0)	0.29††
Painful joint score	32.7; 22.4	32.7; 21.1	−16.1; 20.9	−15.4; 18.1	−1.6 (−7.0, 3.8)	0.77
Grip strength (mm Hg)	159.6; 75.0	149.5; 81.8	−29.4; 55.5	−21.1; 45.7	−6.6 (−21.7, 8.4)	0.58
Morning stiffness (min)	172.0; 205.5	172.9; 188.3	−124.3; 228.5	−111.3; 198.0	−9.0 (−72.5, 54.4)	0.90
Patient global score	1.6; 0.9	1.7; 1.1	−1.2; 1.2	−1.0; 1.2	−0.3 (−0.6, 0.1)	0.29
PET global assessment	5.3; 1.8	5.4; 1.9	1.4; 2.0	−1.0; 1.4	−0.4 (−0.9, 0.1)	0.14
PET overall score**	110.8; 43.9	114.0; 49.7	−30.3; 35.8	−23.9; 38.7	−5.4 (−16.3, 5.5)	0.50
ESR (mm/h)***	31.2; 22.7	30.1; 21.2	−6.9; 15.7	−0.4; 14.1	−6.3 (−10.8, −1.8)	0.004
Acetaminophen usage (mg/day)	912.0; 755.0	1014.0; 1004.0	−686.0; 822.0	−549.0; 880.0	−117.4 (−252.3, 17.5)	0.13

* No baseline measure. Evaluation is itself a change versus flare.

** Weighted sum of the 5 most important problems by the Problem Elicitation Technique (PET).

*** Erythrocyte sedimentation rate (Westergren). Baseline was preflare value.

† 3 primary outcome measures here analyzed simultaneously using MANOVA.

†† Secondary outcome measures here analyzed using univariate ANOVA.

returned to prestudy values in all patients completing 8 weeks of treatment.

Results of the intent to treat analysis for effectiveness are comparable to those of the efficacy analysis and are not presented here.

Changes over time in the mean number of painful joints, the pain VAS score, and the physician's global assessment are presented in Figure 1. The time courses of improvement were similar in both groups, with no statistically significant differences at any point.

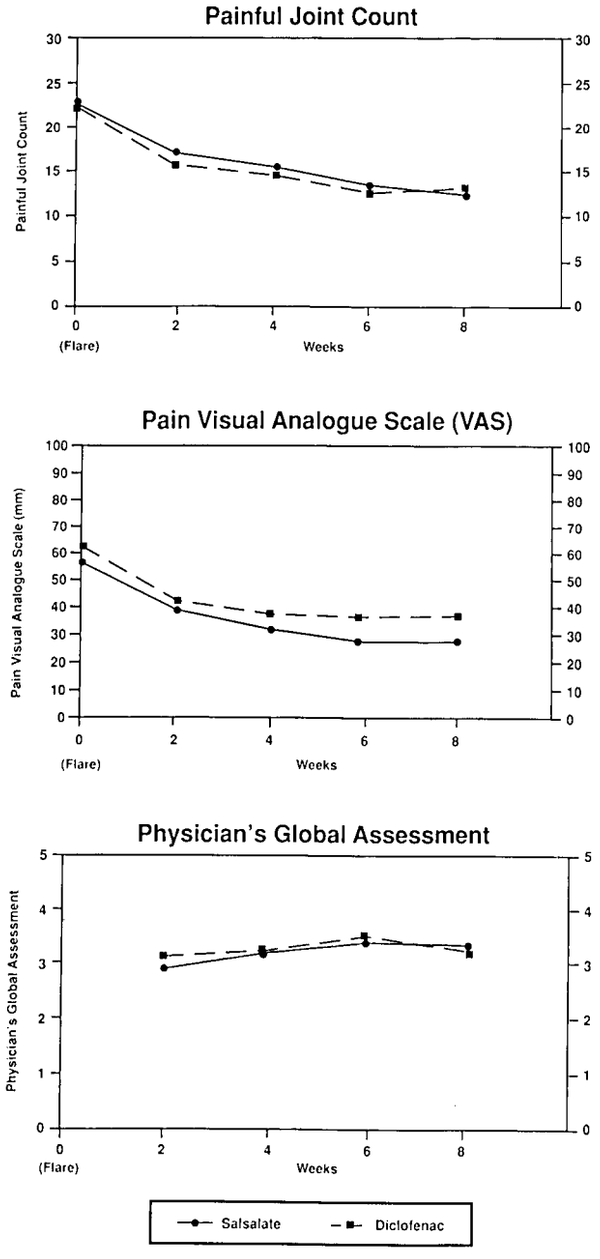

Fig. 1. Primary outcome measures by treatment group at each assessment point. Each point represents the mean at a specific time. Solid line indicates mean values for salsalate and broken line, means values for diclofenac.

In the efficacy analysis, the proportion of patients showing improvement was 47.7% in the salsalate group and 35.6% in the diclofenac group (Figure 2) ($p = 0.092$). For comparison, the proportion of patients who improved in the intent to treat analysis is also presented; again there was no significant difference between the 2 groups ($p = 0.673$).

Safety and withdrawal analysis. All adverse events with an 8 week incidence of 5% or more, as well as those that caused withdrawal from the study in either treatment group are presented in Table 5. There was a higher incidence in the salsalate group than the diclofenac group ($p = 0.002$).

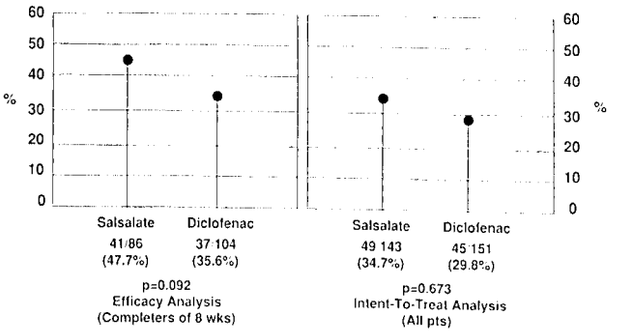

Fig. 2. Percentage of patients having clinically important improvement by treatment group analysis. Important improvement is ≥20% reduction in both painful/tender and swollen joint counts, and ≥20% improvement vs flare in any 3 of the following 5 outcomes: patient's global score, physician's global score, pain score, disability, or ESR (vs prestudy value).

Table 5. *Adverse events by treatment group*

Preferred Term*	Salsalate (n = 149) No. Patients (%)	Diclofenac (n = 152) No. Patients (%)	p
Tinnitus	56 (38)	10 (7)	<0.001
Headache	31 (21)	27 (18)	0.60
Hearing loss	28 (19)	2 (1)	<0.001
Nausea	23 (15)	23 (15)	0.93
Abdominal pain	18 (12)	13 (9)	0.41
Dyspepsia	17 (11)	12 (8)	0.40
Fatigue	15 (10)	5 (3)	0.03
Diarrhea	11 (7)	16 (11)	0.45
Upper RTI	11 (7)	8 (5)	0.60
Arthralgia	9 (6)	10 (7)	0.96
Dizziness	8 (5)	11 (7)	0.67
Edema	8 (5)	2 (1)	0.10
Infection	8 (5)	6 (4)	0.76
Constipation	7 (5)	2 (1)	0.17
Flatulence	7 (5)	6 (4)	0.97
Pain	7 (5)	6 (4)	0.97
Somnolence	6 (4)	4 (3)	0.72
Depression	5 (3)	1 (1)	0.21
Rash	4 (3)	8 (5)	0.40
Vomiting	4 (3)	8 (5)	0.40
Patients reporting ≥ 1 event	125 (84)	99 (65)	0.002

* WHO classification. Terms with 8 week incidences under 5% for both treatments are not indicated, except when the term was also associated with a premature withdrawal from study (see Table 6).

However, this difference relates mostly to the incidence of tinnitus and hearing loss, and 20 of the 84 patients who reported these experiences withdrew from medication as a result (Table 6). None of the 12 patients in the diclofenac group withdrew because of tinnitus or hearing loss. About 55% of reported disturbances to the hearing and vestibular systems were recorded within the first 2 weeks of salsalate treatment, and 79% were reported through Week 4 of treatment. Only 32% of the reports of hearing disturbances that led to discontinuation were rated as severe by the study personnel. There was no obvious relationship between age and reports of tinnitus.

Nine events (in 6 patients) were reported as serious by the investigators. Four serious events occurred in 3 diclofenac patients: a right sided cerebrovascular accident 15 days into study therapy; a septic middle finger 19 days into therapy; and a dilation and curettement after 11 days and a hysterectomy 52 days into therapy for the same patient. Five events occurred in 3 salsalate patients: left pleuritic chest pain 45 days into therapy; cardiac arrest 10 days into therapy; and a viral upper respiratory infection 26 days into therapy with granulocytopenia and thrombocytopenia 29 days into therapy. No serious event was judged to be due to the study medication according to the site investigator. No deaths occurred.

Statistically significant changes between treatments were observed in clinical laboratory tests. A higher incidence of hematologic abnormalities was observed in the diclofenac group for hemoglobin, hematocrit, and partial thromboplastin time (PTT) ($p \leq 0.01$). Thirteen percent diclofenac and 4% salsalate patients had hemoglobin decreases at the final visit. Hematocrit had decreased to abnormal levels at the final visit in 11% diclofenac and 5% salsalate patients. In addition, 1% salsalate patients and 7% diclofenac patients showed increased PTT.

There were no significant treatment differences in urinalysis characteristics. With regard to blood chemistry, statistically significant differences ($p \leq 0.02$) between treatment groups were observed for AST, alkaline phosphatase, albumin, and uric acid. Abnormal increases in AST were observed in 21% of salsalate patients and 7% of diclofenac patients. Abnormal alkaline phosphatase elevations were noted in 2% salsalate and 6% diclofenac patients. Abnormal decreases in albumin were observed in 17% salsalate and 9% diclofenac patients. Uric acid decreased abnormally in 47% salsalate patients (a known salicylate effect[27]) and no diclofenac patient. One percent diclofenac and 2% salsalate patients were discontinued from the study for laboratory abnormalities, specifically liver function tests.

Table 6. *Premature withdrawal associated with adverse events*

Preferred Term*	Salsalate (n = 149) No. Patients (%)	Diclofenac (n = 152) No. Patients (%)	p
Tinnitus	14 (9)	0 (0)	<0.0001
Hearing loss	6 (4)	0 (0)	0.04
Nausea	6 (4)	4 (3)	0.72
Headache	5 (3)	0 (0)	0.07
Depression	4 (3)	0 (0)	0.13
Dizziness	4 (3)	0 (0)	0.13
Fatigue	3 (2)	1 (1)	0.60
Somnolence	3 (2)	0 (0)	0.24
Abdominal pain	2 (1)	3 (2)	0.98
Dyspepsia	1 (1)	3 (2)	0.63
Withdrawn patients reporting ≥ 1 event	19 (13)	9 (6)	0.07

* WHO classification. Terms with 8 week incidence under 2% for both treatments are not reported.

DISCUSSION

In this randomized, double blind study, salsalate and diclofenac were similar with respect to a wide range of RA disease outcome measures. The primary analysis of completers showed salsalate to have comparable efficacy to diclofenac. Furthermore, the intent to treat analysis was consistent with these results, indicating that discontinued patients did not bias the primary analysis conclusions. Analysis of the primary and secondary disease outcome measures provided evidence supporting treatment comparability, although there was a tendency toward greater improvement in the salsalate group for all outcome measures.

Post hoc power analysis for the efficacy analysis (patients who completed all 8 weeks of treatment) showed that the study had sufficient power (0.60–0.90) to detect clinically important differences in the 3 primary outcome measures; for example, a difference in change between treatments of 3.5 painful joints had a power of 0.61. *Post hoc* power analysis for the intent to treat analysis (all randomized patients) varied from 0.84 to 0.96.

The effectiveness of salsalate in our study supports the results of a 12 week study that demonstrated the comparability of salsalate and ASA in patients with RA[20].

After our study had been designed and initiated, a meeting was convened by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Committee[15] to develop a set of outcome measures for use in RA clinical trials and to define criteria for clinically important changes in those measures. The American College of Rheumatology (ACR) subsequently published a proposed core set of outcome measures[14]. The primary outcomes in our study were painful/tender joint count, pain VAS score, and physician's global assessment. However, all 7 of the recommended core set of outcomes[14] were included in the present trial. Following the publications by the OMERACT and ACR committees, a retrospective analysis of the 7 proposed core outcome measures was performed, using the criterion of at least 20% improvement. This analysis (Figure 2) indicated that the 2 drugs in this trial were comparable, slightly favoring salsalate. About 30 to 48% of the patients improved using either analysis of efficacy.

The starting dose of 75 mg/day of diclofenac in this trial was based upon the recommended dose in the prescribing information provided in the Compendium of Pharmaceuticals and Specialties (CPS)[13], where both 75 mg of diclofenac and 3.0 g of salsalate are described as having the same bioequivalency as 3.6 g of ASA. Because the initial dose of diclofenac used in current practice has been increasing since the introduction of the drug, we allowed for dose titration during the first 5 weeks of the trial. Indeed, at the 8 week visit, there were more patients in the higher dose range in the diclofenac group (150 mg/day) than in the higher dose range in the salsalate group (4.5 g/day), 28 versus 15%. Furthermore, the mean 8 week dose was close to current prescribing patterns in Canada: 112 mg/day (IMS, 92).

One outcome measure, ESR, showed a statistically significant and clinically important change (greater than 20%) from prestudy for both the completing patients and intent to treat analyses. For example, for completers, ESR was decreased by a mean of 6.9 mm/h in the salsalate group ($p < 0.0001$ vs prestudy, and $p = 0.004$ vs diclofenac) (Table 3). The previous trial comparing salsalate with ASA also showed a clinically important change in ESR from flare and versus ASA; ASA produced a significant but smaller decrease in ESR[20]. The mechanistic and clinical implications of these data remain unclear at present.

The most common symptomatic adverse experiences reported in the salsalate group in this trial were tinnitus or temporary hearing loss, headache, and GI disturbances such as nausea. The incidence of hearing related disturbances was the only clinically important difference between salsalate and diclofenac in adverse experience. Most complaints occurred within the first month of treatment. Such effects are generally rated by physicians as medically minor, easily recognized by the patient or physician, and usually resolve spontaneously with minor dosage adjustments or temporary discontinuation of the drug. Occasionally, however, some patients find them intolerable.

No unexpected symptomatic adverse experiences were reported for salsalate (other than those expected from spontaneous field reports and other clinical data[20]). However, it should be noted that the more important toxicities of NSAID, such as serious GI events, ulceration, and bleeding, are often asymptomatic, while our trial collected symptomatic experiences.

Because PG play a protective role in the gastric mucosa[28], salsalate with its weak inhibitory effect on PG synthesis, would be expected to be less toxic than other NSAID to the upper GI tract mucosa. This theoretical advantage is supported by the results of 5 endoscopy studies[5-9], of 1 week to 3 months' duration. Among both patients and control volunteers, there was a significantly lower incidence of upper GI erosions or ulcers with salsalate at antiinflammatory doses compared to other NSAID. One of these studies also demonstrated a lack of effect on PG synthesis in the gastric mucosa[9]. Furthermore, a ^{51}Cr red cell study indicated less GI toxicity, with bleeding rates for salsalate being comparable to placebo and less than ASA after 2 weeks of administration[29].

Although there is a need for longterm studies focussing on GI bleeds to confirm the safety of salsalate, additional data support the evidence from the endoscopy investigations that salsalate is safer than other NSAID. Fries, *et al*[30,31] reported data from their Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) database comparing the toxicities of several NSAID in patients with RA using a toxicity scoring system, with subanalyses including hospitalizations. Although differences in overall efficacy have not been demonstrated between NSAID in other studies, substantial differences in overall toxicity were reported by Singh, *et al*[32]; variations in toxicity are statistically significant and clinically important (some drugs being 2-3 times as toxic as others). Most toxic NSAID were indomethacin, tolmetin sodium, and meclofenamate sodium. The safest drugs were salsalate and ibuprofen, which could not be statistically differentiated.

In addition, a toxicity index for GI problems derived from the ARAMIS database has recently been reported by Singh, *et al*[33]. The GI index is a subset of the overall safety index; it reflects GI symptoms (nausea, vomiting, abdominal pain, heartburn, diarrhea, anorexia) and number of hospital days due to a GI problem divided by patient years of drug exposure. Salsalate ranked as the least toxic of the 12 NSAID studied, including diclofenac. This low GI toxicity ranking is consistent with findings from controlled endoscopy studies, and is reinforced by the data comprising the subscore for hospitalizations, which ranked salsalate as having the single lowest associated incidence score of the studied NSAID. The other drugs, including ASA, had hospitalization subscores 3 to 7 times greater than that of salsalate[32].

Consistent with salsalate being a weak inhibitor of PG synthesis, a controlled trial in normal volunteers indicated that renal PG synthesis is affected to a lesser extent by salsalate than by either ASA or naproxen[34].

In conclusion, the comparable efficacy of salsalate to other NSAID has now been demonstrated in a second multicenter trial in patients with RA. Coupled with supportive GI safety data, these results indicate that salsalate should be considered as an alternative to other NSAID as a first line drug in the treatment of patients with RA. In addition, the RA trial methodology in this study reflects current recommendations for outcome measures. This core set of outcomes should allow for more effective study designs and permit easier comparison of drug effects across studies.

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