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Salsalate for Arthritis: A Clinical Evaluation

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ABSTRACT

In an open-label trial, 182 patients with common forms of arthritis were treated with 3 gm of salsalate daily (two 750-mg tablets twice daily) for 15 days. Before entering the study, these patients had received a wide variety of antarthritic medications. Five indices of disease severity (pain, stiffness, joint swelling, limitation of motion, and disability) were evaluated before and after salsalate therapy, the incidence of side effects was tabulated before and after treatment, and patient compliance with the salsalate regimen was assessed. A reduction in disease symptoms was noted in 79% of the treated patients. Median improvement, measured on a summary index, was 47%. The incidence of side effects experienced with previous therapy was reduced by 65% during salsalate administration. Patient compliance with the regimen was greater than 95%. The findings show salsalate to be effective and safe in ameliorating the symptoms of arthritic disease. The convenient twice-daily dosage regimen makes this drug particularly suitable for chronic use.

INTRODUCTION

Aspirin is the standard analgesic/anti-inflammatory used in the treatment of arthritis. As many as 40% of patients, however, cannot tolerate this drug.[1] Patients treated with aspirin often experience gastrointestinal (GI) side effects severe enough to preclude its long-term use.[2–4] The degree of GI irritation, erosion, and bleeding is directly related to the aspirin dosage and the duration of treatment.[3] For this reason, the search for aspirin substitutes continues. In recent years, more than 50 anti-inflammatory compounds have been investigated.[5]

The motivation behind the continuing search for new nonsteroidal anti-inflammatory drugs (NSAIDs) is acknowledged in the FDA *Guidelines for Clinical Evaluation of Anti-Inflammatory Drugs:* "Greater effectiveness than aspirin should not be required, since anti-inflammatory drugs with less frequent or serious side effects than aspirin are needed clinically."[6] Thus the goal of this search is a compound with anti-inflammatory activity equivalent to that of aspirin but

devoid of its undesirable pharmacological effects. The newer NSAIDs have been shown to approach this ideal drug profile in varying degrees.[7]

Dimeric salicylic acid (disalicyclic acid, salicylsalicylic acid, *salsalate*) is chemically more closely related to aspirin than any of the newer NSAIDs. However, the anti-inflammatory activity of salsalate, equivalent to that of aspirin,[8] is not accompanied by the ulcerogenic, hemorrhagic, and anaphylactic potential of the acetylated compound. The in vivo acetylating activity of aspirin has important and widespread effects, only some of which have been well-characterized. The profound suppression of prostaglandin E_2 synthesis that results from the acetylation of cyclo-oxygenase by aspirin[9] plays a major role in ulcerogenesis.[10] Suppression of thromboxane synthesis, another consequence of cyclo-oxygenase acetylation,[9] severely impairs platelet aggregation.[11] The inhibition of cyclo-oxygenase activity by acetylation also results in the shunting of substrate (arachidonic acid) to the lipoxygenase pathway,[12] which is not affected by aspirin. The consequent increase in leukotriene synthesis has been proposed as the pathogenetic mechanism of aspirin-induced anaphylaxis.[12,13]

The study reported here was undertaken to evaluate the therapeutic benefit of a standardized twice-daily salsalate* regimen in a geographically dispersed population of patients with a variety of inflammatory arthritides. The regimen was also assessed for safety and for patient acceptance, tolerance, and compliance.

*Trademark: Disalcid® (Riker Laboratories, Inc., Northridge, California).

METHODS AND MATERIALS

Methods

The investigators participating in this multicenter study followed a uniform protocol. To be eligible for admission to the study, patients were required to be at least 16 years of age and to have at least a six-month history of arthritis consistent with the diagnostic criteria of one or more of the three major categories—inflammatory polyarthritis, osteoarthritis, and nonarticular rheumatism. Patients who were receiving anticoagulants or who had been treated with corticosteroids during the month preceding the study were excluded. A need for anti-inflammatory therapy was required, but patients using disease-modifying drugs, such as gold salts and penicillamine, were excluded. Patients had to be able to discontinue any current therapy with NSAIDs when salsalate treatment was initiated.

A history of previous antarthritic therapy was obtained, and patients were questioned regarding its adequacy. To evaluate the current status of the disease, the investigator rated five indices of arthritis—pain, stiffness, joint swelling, limitation of motion, and disability—as mild (1), moderate (2), or severe (3). These indices were reevaluated after 15 days of treatment, and changes from baseline were determined. A summary index was calculated by combining the scores on the five primary indices. At both the beginning and the end of the study, the patient and the physician independently estimated the global degree of rheumatic disease as mild, moderate, or severe. Side effects present at the time of entry into the study and

those occurring during salsalate treatment were recorded and compared. Coexisting nonarthritic disorders and concomitant use of nonarthritis-related drugs were recorded for each patient.

Medication

Each patient was given one bottle containing 60 salsalate 750-mg tablets and was instructed to take two tablets twice daily (3 gm/day) for 15 days. If a patient was unable to tolerate the drug or if excessive tinnitus developed, reduction of the dosage was allowed. The investigator assessed patient compliance by counting the salsalate tablets remaining at the end of the 15-day treatment period.

RESULTS

Demographic Characteristics

The 87 participating investigators submitted data forms for 182 patients who completed the full 15-day treatment course. Women outnumbered men by more than 2:1 (Table I). The mean ages of the men and the women were nearly the same, but more of the women were older than 70 years of age.

Slightly more than two thirds of the women and nearly three fourths of the men had osteoarthritis (Table II). Inflammatory polyarthritis was diagnosed twice as often in women as in men, whereas nonarticular forms of rheumatic disease were found more frequently in men. This diagnostic distribution conforms to that of the general population of arthritis patients.[14–16] The duration of the disease was similar in the two sexes (Table III). The mean duration of disease (and, in parentheses, the range) was 80.6 (six to 730) months in the 51 men for whom the information was available, 79.8 (six to 480) months in the 105 women for whom the information was available, and 80.1 (six to 730) months in these men and women combined.

Table I. Age distribution of patients, by sex, and mean and median ages (years) and range of ages (years) in men, women, and all patients.

	Men (n = 57)		Women* (n = 124)		All Patients (N = 181)	
Age (Years)	No.	%	No.	%	No.	%
28–30	1	1.8	2	1.6	3	1.7
31–55	11	19.3	25	20.2	36	19.9
56–70	29	50.9	48	38.7	77	42.5
71–90	16	28.1	49	39.5	65	35.9
Mean	63.3		65.5		64.8	
Median	64.8		66.5		65.0	
Range	28–88		29–90		28–90	

*Age of one woman not stated.

Table II. Diagnostic categories of patients, by age and sex.

	Men (n = 56)*						Women (n = 121)*					
					Total						Total	
	28–30	31–55	56–70	71–90	No.	%	28–30	31–55	56–70	71–90	No.	%
Inflammatory polyarthritis	0	0	2	4	6	11	0	8	6	12	26	21
Osteoarthritis	0	7	24	10	41	73	2	12	35	33	82	68
Nonarticular rheumatism	1	4	3	1	9	16	0	4	5	4	13	11

*Diagnostic category not stated for one man and for four women.

Table III. Distribution of patients by duration of disease, and mean and median duration and range of duration of disease (months) in men, women, and all patients.

	Men		Women		All Patients	
Months	No.	%	No.	%	No.	%
6–12	6	10.5	12	9.6	18	9.9
13–24	9	15.8	19	15.2	28	15.4
25–60	19	33.3	33	26.4	52	28.6
61–120	13	22.8	27	21.6	40	22.0
121–240	2	3.5	8	6.4	10	5.5
241–360	1	1.8	5	4.0	6	3.3
361–730	1	1.8	1	0.8	2	1.1
Not stated	6	10.5	20	16.0	26	14.3
Total	57		125		182	
Mean	80.6		79.8		80.1	
Median	59.6		59.6		59.6	
Range	6–730		6–480		6–730	

Previous Antarthritic Treatment

Nearly all (96%) of the patients reported previous use of antarthritics, chiefly aspirin and the newer NSAIDs, including benoxaprofen, fenoprofen, ibuprofen, indomethacin, meclofenamate, naproxen, piroxicam, sulindac, tolmetin, and zomepirac sodium (Table IV). Patient evaluations were recorded for 94% of the drugs previously used for the relief of arthritis. Overall, only 28% were rated as satisfactory. Of the 86 patients previously treated with aspirin, 59 (69%) rated the drug as unsatisfactory. The newer NSAIDs were rated as unsatisfactory in 68% of the instances in which such drugs were administered.

Nonarthritic Conditions and Concomitant Drug Use

Coexisting disease was recorded in 77% of the men and 65% of the women. Cardiovascular disease, with or without hypertension, occurred frequently in men (60%) but was much less common in women (23%). A similar pattern was noted for diabetes, which was present in 16% of the men and 8% of the women. Anxiety/depression states were noted in 34% of the women but in only 3% of the men.

Concomitant medication consisted of antihypertensive drugs and diuretics in 43% of the patients, antiarrhythmic and cardiotonic drugs in 18%, specific anti-

Table IV. Patient evaluation of previous antarthritic medication.*

Drug	Satisfactory		Unsatisfactory		Not Rated		Total
	No.	%	No.	%	No.	%	
Aspirin	22	26	59	69	5	6	86
Other salicylates†	3	50	2	33	1	17	6
NSAIDs	53	25	142	68	14	7	209
Corticosteroids	5	56	4	44	0	0	9
Phenylbutazone	3	43	4	57	0	0	7
Hydroxychloroquine	1	100	0	0	0	0	1
Gold	3	75	1	25	0	0	4
All drugs	90	28	212	66	20	6	322

* Number of patients reporting previous use of antarthritic medication was 175 (96%); many patients had used more than one drug.
† Excluding salsalate.

gout medication in 4%, and miscellaneous analgesics in 19%. A variety of other drugs unrelated to arthritis were used, each by fewer than 5% of the patients. Two men and eight women were allowed to continue use of an NSAID other than salsalate during part or all of the course of salsalate therapy.

Response to Salsalate Treatment

At the time of entry into the study, the patients' median scores on the summary index were 7.44 (of a possible maximum of 15) for men, 7.94 for women, and 7.74 for men and women combined (Table V). After two weeks of salsalate therapy, the combined score for men and women had decreased to 4.09, an improvement of 3.65 points, or 47%. The change from baseline was slightly more pronounced for men (47%) than women (43%).

Table VI displays changes in indices recorded during the course of salsalate treatment. For the total population the median scores for pain, stiffness, and limitation of motion decreased 44%; the median score for joint swelling declined 64%, and the median score for overall disability was 45% lower after treatment. With the exception of the score for joint swelling, which dropped 71% in men and 58% in women, there were only minor differences between men and women in the degree of relief in any of the symptoms evaluated.

The numbers of patients who experienced improvement according to each of the individual indices evaluated and the summary index are shown in Table VII. There were decreases in pain and stiffness in more than 60%, a decrease in joint swelling in 46%, less limitation of motion in 52%, and less disability in 43%. The summary index showed improvement in 79% of the patients. The redistribution of patients by disease status at the end of the two-week course of salsalate is depicted graphically in Figure 1.

The physicians recorded global evaluations of 141 patients, and 147 patients provided global assessments of themselves. The global evaluations made by the physicians and patients generally agreed, with the physicians' assessments being slightly more conservative (Table VIII). Improvement in disease status from "severe" to "moderate" or from "moderate" to "mild" was reported by 69 (47%) of the 147 patients. Physicians judged such improvement to have occurred in 59 (42%) of the 141 patients they assessed. The conditions of only 3% of the patients were judged by both the patients and their physicians to have become worse. This divergence of global impressions and scores on the summary index (improvement in 42% and 47% versus 79%), although not unusual, emphasizes the importance of using objective criteria when assessing changes in the status of arthritis.

Side Effects of Antarthritic Drug Therapy

Both the number of side effects and the number of patients reporting side effects possibly attributable to antarthritic therapy declined sharply during the course of salsalate treatment. With previous therapy, 47 side effects were reported in 27 men. During salsalate therapy, only 15 side effects were seen in ten men, a reduction of 68% in the number of side effects and of 63% in the

Table V. Median (±SE), minimum, maximum, and mean (±SE) summary index scores* before and after salsalate therapy for men, women, and all patients.

	Men (n = 57)				Women (n = 125)				All Patients (N = 182)			
			Change				Change				Change	
	Before	After	Points	%	Before	After	Points	%	Before	After	Points	%
Median	7.44±0.48	3.91±0.49	−3.53	−47	7.94±0.35	4.53±0.39	−3.41	−43	7.74±0.29	4.09±0.31	−3.65	−47
Minimum	2.00	0.00			2.00	0.00			2.00	0.00		
Maximum	14.00	11.00			15.00	15.00			15.00	15.00		
Mean	7.11±0.38	4.11±0.39	−3.00	−42	8.00±0.28	4.90±0.31	−3.10	−39	7.72±0.23	4.65±0.25	−3.07	−40

*Sum of the scores for pain, stiffness, joint swelling, limitation of motion, and disability.

Table VI. Median scores on indices of disease, before and after salsalate therapy, in men, women, and all patients.

	Men (n = 57)				Women (n = 125)				All Patients (N = 182)			
			Change				Change				Change	
Indices	Before	After	Points	%	Before	After	Points	%	Before	After	Points	%
Pain	1.883	1.034	−0.849	−45	2.008	1.136	−0.872	−43	1.970	1.102	−0.868	−44
Stiffness	1.800	0.963	−0.837	−46	1.904	1.079	−0.825	−43	1.870	1.044	−0.826	−44
Joint swelling	0.737	0.212	−0.525	−71	1.213	0.512	−0.701	−58	1.076	0.392	−0.684	−64
Limitation of motion	1.438	0.750	−0.688	−48	1.630	0.914	−0.716	−44	1.568	0.884	−0.684	−44
Disability	1.217	0.705	−0.512	−42	1.459	0.781	−0.678	−46	1.367	0.757	−0.610	−45

Table VII. Number and percentage of men, women, and all patients in whom individual indices of disease worsened, remained the same, or improved after salsalate treatment.

	Men (n = 57)						Women (n = 125)						All Patients (N = 182)					
	Worse		Same		Better		Worse		Same		Better		Worse		Same		Better	
Indices	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Pain	5	9	16	28	36	63	8	6	41	33	76	61	13	7	57	31	112	62
Stiffness	4	7	18	32	35	61	3	2	46	37	76	61	7	4	64	35	111	61
Joint swelling	5	9	29	51	23	40	3	2	62	50	60	48	8	4	91	50	83	46
Limitation of motion	3	5	22	39	32	56	3	2	60	48	62	50	6	3	82	45	94	52
Disability	2	4	30	53	25	44	3	2	69	55	53	42	5	3	99	54	78	43
Summary index	7	12	6	11	44	77	8	6	18	14	99	79	15	8	24	13	143	79

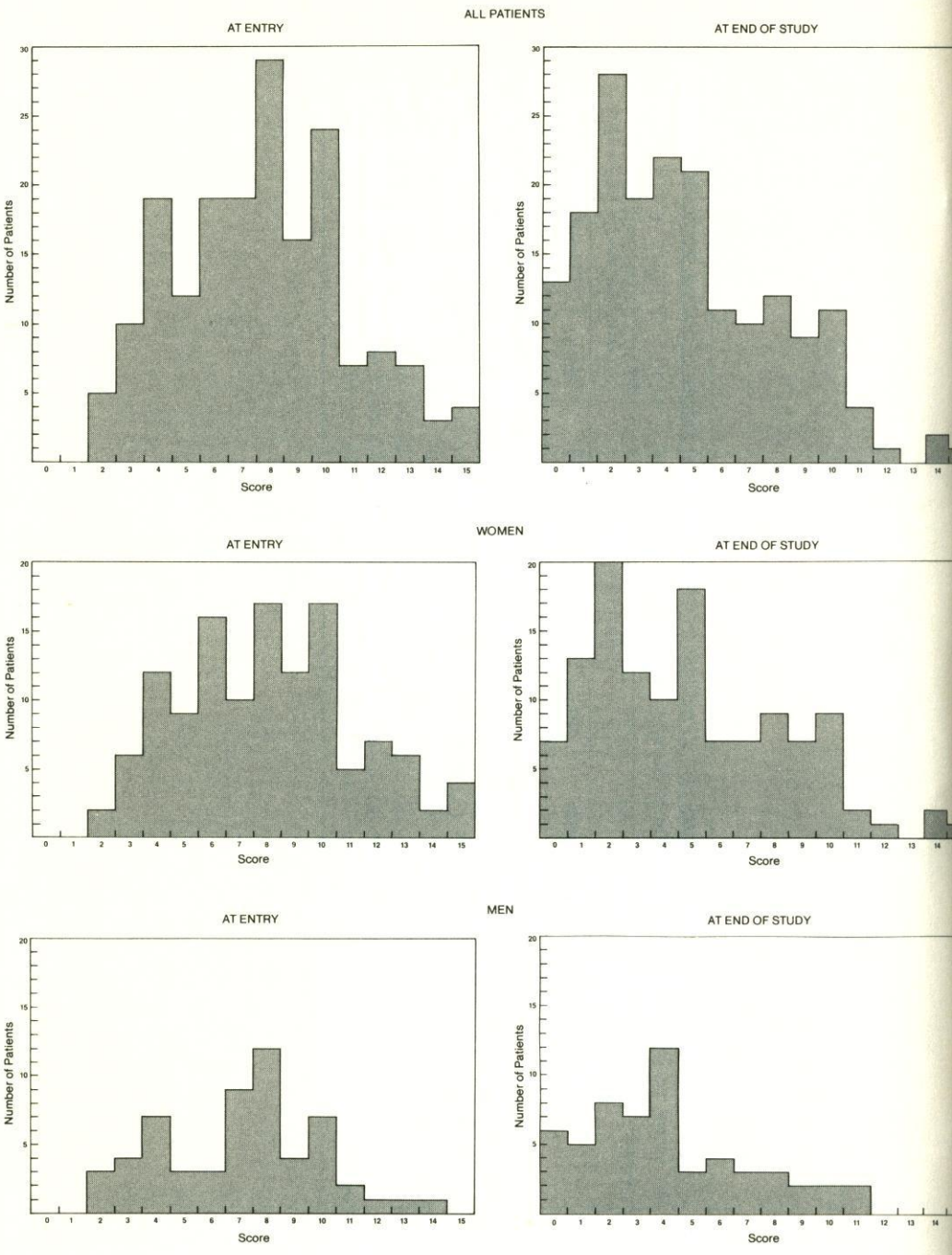

Figure 1. Combined disease indices scores: frequency distribution. (A preponderant shift to lower scores following salsalate treatment is evident.)

Table VIII. Global evaluations made by patients and physician: Men, women, and all patients.

	Men				Women				All Patients			
	Patient (n = 51)		Physician (n = 49)		Patient (n = 96)		Physician (n = 92)		Patient (n = 147)		Physician (n = 141)	
Evaluation	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Worse	2	4	1	2	3	3	3	3	5	3	4	3
No change	25	49	28	57	48	50	50	54	73	50	78	55
Improved	24	47	20	41	45	47	39	42	69	47	59	42

Table IX. Side effects experienced with antarthritic drugs.

Side Effect	Men		Women		All Patients		
	Previous Therapy (n = 27)	Salsalate (n = 10)	Previous Therapy (n = 67)	Salsalate (n = 38)	Previous Therapy (n = 94)	Salsalate (n = 48)	Percent Reduction
Epigastric distress/ pain	18	7	40	26	58	33	43
Dizziness	9	1	19	0	28	1	96
Tinnitus	7	3	19	13	26	16	38
Disorientation	0	2	5	1	5	3	40
Headache	9	1	27	1	36	2	94
Miscellaneous	4	1	15	5	19	6	68
Total	47	15	125	46	172	61	65

number of patients experiencing side effects (Table IX). The 125 side effects noted in 67 women at the beginning of the study decreased to 46 side effects in 38 women during salsalate administration, a 63% reduction in the number of side effects and a 43% reduction in the number of patients reporting side effects. Headache and dizziness showed the most impressive declines in incidence (94% and 96%, respectively). The change of greatest clinical significance, however, was the 43% reduction in the incidence of epigastric distress/upper abdominal pain. This symptom must be viewed as a possible harbinger of more serious iatrogenic gastric disease and is certainly one of the least tolerable side effects of antarthritic therapy. With the possible exception of tinnitus, there was no correlation between the dosage of salsalate and the occurrence of side effects.

Compliance with Therapeutic Regimen

More than half of the patients took two 750-mg salsalate tablets twice daily throughout the 15-day study period. A small number of patients required five or six tablets daily, and the remainder were given lower doses. Only 5% of the patients were rated by their physicians as noncompliant.

DISCUSSION

Nearly all of the patients in this study had previously received aspirin or at least one of the newer NSAIDs, or both, for the treatment of arthritis. Nearly 70% of the patients rated these drugs as unsatisfactory. In this context, the improvements observed during this study in specific indices of disease are particularly noteworthy. The severity of symptoms decreased during the 15-day course of salsalate therapy in 79% of the treated patients. Of equal importance was the remarkable decrease (65%) in the number of drug-related side effects when salsalate was substituted for the drug used previously. This reduction in side effects may have accounted for the exceptionally good compliance rate achieved in these patients. Differences in the compliance of patients within the study group did not appear, however, to be related to the presence or absence of side effects, suggesting that most side effects occurring during the trial did not compromise therapy.

The results of this study agree with previously reported clinical evidence of the analgesic and anti-inflammatory efficacy and superior safety of salsalate in the treatment of arthritis.[16–26] The effectiveness and convenience of twice-daily dosing (usual dosage, 3 gm/day), combined with a significantly lower potential for serious adverse effects, suggest that salsalate should be used as first-step therapy and that a change to another NSAID is not likely to be necessary.

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