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Reduced Risk of NSAID Gastropathy (GI Mucosal Toxicity) With Nonacetylated Salicylate (Salsalate): An Endoscopic Study

By Sanford Roth, Ralph Bennett, Paul Caldron, Ruby Hartman, Charles Mitchell, Marna Doucette, Bruce Ekholm, Barry Goldlust, Elizabeth Lee, and Richard Wilson

INDEX WORDS: Salsalate; naproxen; endoscopy; gastropathy.

THE GASTROPATHY associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs) is now recognized as a constellation of mucosal lesional responses of the upper gastrointestinal (GI) tract (primarily gastric antral and prepyloric regions), ranging from erosions through ulcer crater disease.[1] These responses to NSAID therapy can evolve to ulcers, bleeding, perforation, and death.[2] The US Food and Drug Administration now requires that class labeling warnings of these potentially serious consequences of NSAID therapy replace the simple mention of possible "gastric irritation" in previous package inserts.[3]

Compromise of the mucosal barrier allowing back diffusion of hydrogen ions can result in topical injury in patients treated with aspirin and some NSAIDS.[4] More importantly, the inhibition of gastroprotective prostaglandins by usual NSAIDs is now thought to have a central role in the development of the gastropathy associated with chronic NSAID therapy.[5] The risk of bleeding from damaged mucosa is further increased by NSAID-induced inhibition of platelet thromboxane, an arachidonate metabolite important in the aggregation of platelets.[6]

Among the available means directed at continued antiinflammatory action without altering gastric prostaglandin activity is the use of substituted or nonacetylated salicylates. One example, salsalate (salicylsalicylic acid), is an effective antiarthritic agent[7] that is insoluble at the acid pH of the normal stomach. Because salsalate does not dissolve in the stomach, local gastric injury is unlikely. Salsalate is less likely to affect platelet function[8] and is a relatively weak inhibitor of prostaglandin synthesis in vivo.[9,10] Salsalate should therefore be less likely to contribute to GI bleeding and should have less propensity to interfere with the cytoprotective activity of prostaglandins at antiinflammatory doses. These theoretical advantages are supported by the results of several clinical investigations. An open-label study showed resolution of preexisting peptic ulcer disease when a regimen of salsalate, combined with H_2-receptor antagonists, was substituted for other NSAIDs.[11] In a controlled study, fecal blood loss measured by the use of ^{51}Cr-labeled red blood cells was significantly greater in aspirin-treated than salsalate-treated patients, in whom the level of blood loss was equivalent to that seen with placebo.[12] A controlled endoscopic comparison in healthy subjects showed significantly less gastroduodenal mucosal damage with salsalate than with enteric-coated aspirin.[13]

To further evaluate the GI safety of salsalate, a prospective, randomized, investigator-blinded, parallel-group study was conducted in patients with rheumatoid arthritis (RA). In this investigation, endoscopic examination was used to compare the effects of salsalate and naproxen on the gastroduodenal mucosa.

METHODS AND MATERIALS

Patient Selection

Study participants were recruited from among patients with classical or definite RA receiving care at the Arthritis Center, Phoenix, AZ. The study population consisted of men and nonpregnant, nonlactating women at least 18 years of age who had been treated with a single NSAID for 6 months or longer. All patients gave voluntary written consent before entering the study. Patients with a history of major GI hemorrhage or ulceration greater than 20 mm in diameter; diffuse erosions or ulceration at baseline endoscopy (see screening observations below); conditions that might affect the absorption, distribution, biotransformation, or excretion

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of the study drugs; conditions that might compromise patient safety; or conditions that might obscure evaluation of study drug effects were not permitted to enter the study. Those receiving concomitant medication that could interfere with study drug assessments (antiulcer therapy, nonstudy NSAIDs, nonstudy antacids, or nonstudy analgesics) were also excluded. However, patients receiving stabilized dosage regimens of slow-acting antirheumatic drugs, low-dose pulse methotrexate, and/or systemic low-dose corticosteroids (≤7.5 mg/day prednisone or equivalent) were allowed to participate.

Seventy-two patients were screened for eligibility to enter the study. Prestudy therapy consisted of naproxen in 18 of these patients, salsalate in 17, and other NSAIDs in 39 (two patients were receiving two NSAIDs). It is important to note that 15 of the 17 patients who did not qualify were excluded because of preexisting active ulcers (10 patients) or diffuse or hemorrhagic erosions (5 patients) on baseline endoscopy. The incidence of these lesions at the time of screening was 33% (6/18) of patients receiving naproxen, 6% (1/17) of patients receiving salsalate, and 26% (10/39) of patients receiving "other NSAIDs." Other NSAIDs included various forms of aspirin (4 patients), ibuprofen (3 patients), tolmetin (2 patients), and meclofenamate (1 patient). Seven of the 15 patients with significant lesions were asymptomatic, including a 68-year-old woman receiving naproxen, 500 mg twice a day along with aspirin 650 mg as required. Endoscopy in this patient revealed severe hemorrhagic erosive gastritis, for which she was immediately hospitalized.

Patients were discontinued from the study for use of prohibited drugs, significant changes in concomitant antirheumatic drug regimens, alcohol ingestion during the 72 hours preceding an endoscopy, and noncompliance with study drug. Noncompliance was defined as self-administration of less than 80% or greater than 120% of the total number of tablets prescribed.

Study Drugs

After eligibility was established, prestudy NSAIDs were discontinued. Patients were immediately randomized to receive, with no intervening washout period, either salsalate (Disalcid®, 3M Riker) or naproxen (Naprosyn®, Syntex Laboratories) for 3 months. Both drugs were administered in commercial tablet formulations at antiinflammatory doses. Randomization was stratified for three groups based on the patients' prestudy NSAIDs (salsalate, naproxen, or any other NSAID in the ratio 1:1:2). Patients were aware of their assigned treatments, but investigators, including the rheumatologists and the endoscopist (author C. Mitchell), remained blinded throughout the study.

Initial study drug doses were 3000 mg/d of salsalate (1500 mg twice a day) or 750 mg/d of naproxen (375 mg twice a day). Dosage titration within the ranges of 2000 to 4000 mg/d of salsalate and 500 to 1000 mg/d of naproxen was allowed as needed to maintain an adequate therapeutic response and to minimize adverse effects. An incremental schedule for dosage changes was preestablished. Upon receiving a general order from the rheumatologist to increase or decrease the dose, instructions regarding the specific number of tablets to take were conveyed by a study nurse to maintain physician blinding. Patients were allowed use of both acetaminophen (≤2600 mg/d) and aluminum hydroxide (≤2400 mg/d) as required. Compliance with study drug, acetaminophen, and aluminum hydroxide was monitored by tablet count and patient interview at each visit by a study nurse.

Clinical Assessments

Endoscopic evaluations were performed with a GIF-XQ10 Olympus flexible fiberoptic gastroscope (Olympus Optical Co., Tokyo, Japan) just before initiating treatment with the study drugs and after 1 and 3 months of therapy. The mucosa was viewed during advancement of the instrument to avoid recording trauma induced by the procedure. The entire gastroduodenal mucosa was assigned a single score according to the scale down in Table 1. Subjective GI complaints, elicited through indirect questioning at each study visit and through direct questioning at the time of each endoscopy, the use of aluminum hydroxide, and the presence of fecal occult blood (Hemoccult®, SmithKline Diagnostics) were used as additional indicators of GI effects.

General safety and efficacy evaluations were performed to assure that the doses of the study drugs were tolerated and provided an adequate therapeutic response. Safety was evaluated by physical examination, routine screening, concomitant medication requirements, and the incidence of adverse experiences. The adequacy of the therapeutic response was evaluated by quantification of both painful and swollen joints, physicians' and patients' global impressions, American Rheumatism Association (ARA) functional classification, and use of acetaminophen.

Patients were considered to have completed the study when one of the following endpoints occurred:

1. Grade 5 mucosal injury observed by endoscopy.
2. Grade 4 injury observed by endoscopy, if the injury had progressed by at least two grades from baseline.
3. Grade 3 or 4 injury observed by endoscopy, if the injury had progressed by at least one grade from baseline and was associated with intolerable symptomatology consistent with GI erosion or ulceration (ie, epigastric pain or burning).
4. Completion of 3 months on study drug, including the final endoscopy.

Any patient who did not complete the study on the basis of one of these endpoints was replaced with another patient. The replacement patient was from the same prestudy NSAID group and was assigned to the same treatment group as the patient who was withdrawn.

Table 1. Endoscopy Grading Scale

Grade	Finding
1	Normal mucosa
2	Erythema (reddening or petechia of mucosa) without erosion or microbleeding
3	One or few erosions (flat) without microbleeding or ulceration. One or few hemorrhagic lesions without erosion
4	Diffuse erosions and/or diffuse microbleeding without ulceration
5	Ulceration (excavated)

Statistical Analysis

The intent of the statistical analysis was to compare the incidence of gastroduodenal injury in patients who completed the study. The cumulative incidence of ulcers and diffuse erosions was estimated by the Kaplan-Meier product limit method[14] for each treatment group. Incidence rates were compared using the logrank test.[15] The effect of the prestudy NSAID and the interaction of the prestudy NSAID with the study drug were tested using the logrank test. The change from the baseline to the final endoscopy score was calculated for each patient, and the significance of this change was tested for each treatment group using the Wilcoxon signed-rank test. The two treatment groups were compared using a categorical linear model (Statistical Analysis System Procedure for Categorical Data Modeling)[16] with treatment, prestudy NSAID, and the interaction of treatment and prestudy NSAID as factors in the model.

The incidence of adverse experiences in the two treatment groups was compared using a χ^2 test. To evaluate the therapeutic adequacy of drug doses, changes from baseline were tested using the Wilcoxon signed-rank test. The treatment groups were compared using an analysis of variance for continuous data (eg, number of painful joints) and a categorical linear model for discrete data (eg, global impressions). Both analysis of variance and the categorical linear model used treatment, prestudy NSAID, and the interaction of treatment and prestudy NSAID as factors in the models.

For all tests, a two-tailed P value of less than 0.05 was considered significant. All baseline data were collected before initiation of the study drugs.

RESULTS

Study Population

Fifty-five qualified patients entered the study. Thirty were assigned to the salsalate group and the other 25 to the naproxen group. Eighteen patients receiving salsalate and 21 patients treated with naproxen reached one of the endpoints designating completion of the study. Ten naproxen-treated patients did not complete the 3-month treatment period; of those, six patients were included in the analysis as completing patients based on the definition of ulcers/diffuse erosions as endpoints for study completions. Reasons for study withdrawal in the other four included an inadequate therapeutic response, intercurrent illness, or protocol violations. Twelve salsalate-treated patients did not complete the full 3 months of therapy, in spite of dosage adjustments when appropriate. Five discontinued because of reversible adverse experiences, four because of reversible adverse experiences combined with an inadequate therapeutic response, and three for other reasons, including noncompliance, personal reasons, or loss of follow-up.

Demographic characteristics and prestudy antirheumatic therapy were comparable for completing patients in the two treatment groups (Table 2). Eleven patients, five receiving salsalate and six receiving naproxen, had histories of gastroduodenal ulcer. Baseline RA status was similar with the exception of the physicians' global impressions, which were more favorable for patients randomized to salsalate (Table 3). There were no differences between treatment groups in the distribution of baseline endoscopy scores (Fig 1).

The median daily doses at the final visits were the same as the starting doses for both drugs, 3,000 mg/d of salsalate and 750 mg/d of naproxen. At study completion, the mean daily dose was 3,167 mg of salsalate and 821 mg of naproxen.

GI Adverse Effects

No patients in the salsalate group showed endoscopic evidence of an active ulcer or diffuse erosions during the 3 months of therapy. Seven patients in the naproxen group had active ulcers and one had diffuse erosions (Tables 4 and 5). Six of the cases of mucosal injury in this group (five ulcers and the one case of diffuse erosions) were evident after 1 month of naproxen administration; the other two ulcers were apparent after 3 months. The cumulative risk of ulcers and/or diffuse erosions was significantly ($P = .003$)

Table 2. Baseline Characteristics of Patients who Completed the Study

Characteristics*	No. of Patients	
	Salsalate (n = 18)	Naproxen (n = 21)
Mean age ± SD (y)	51.1 ± 12.5	51.2 ± 15.2
Sex		
Men	5 (28%)	6 (29%)
Women	13 (72%)	15 (71%)
History of gastroduodenal ulcer	5 (28%)	6 (29%)
Mean duration of RA ± SD (y)	12.1 ± 11.0	10.1 ± 8.2
Prestudy NSAID		
Salsalate	6 (33%)	6 (29%)
Naproxen	4 (22%)	4 (19%)
Other	8 (44%)	11 (52%)
Other concomitant RA therapy	13 (72%)	14 (67%)
Single therapy	8 (44%)	8 (38%)
Multiple therapies	5 (28%)	6 (29%)

*P value determination by analysis of variance for continuous data and by categorical linear model for discrete data indicated no significant differences between treatments.

Table 3. Baseline RA Status for Patients who Completed the Study

Disease	Salsalate (n = 18)	Naproxen (n = 21)
Mean no. painful joints ± SD	15.3 ± 12.0	10.4 ± 8.3
Mean no. swollen joints ± SD	9.7 ± 8.8	7.2 ± 6.3
ARA functional class		
I	0 (0%)	3 (14%)
II	17 (94%)	14 (67%)
III	1 (6%)	4 (19%)
Patient's global impression (score)		
Very poor (0)	0 (0%)	0 (0%)
Poor (1)	2 (11%)	4 (19%)
Fair (2)	9 (50%)	10 (48%)
Good (3)	5 (28%)	6 (29%)
Very good (4)	2 (11%)	1 (5%)
Mean score ± SD	2.4 ± 0.8	2.2 ± 0.8
Physician's global impression (score)		
Very poor (0)	0 (0%)	0 (0%)
Poor (1)	2 (11%)	5 (24%)
Fair (2)	7 (39%)	10 (48%)
Good (3)	8 (44%)	5 (24%)
Very good (4)	1 (6%)	1 (5%)
Mean score ± SD	2.4 ± 0.8	2.1 ± 0.8*

*Significant difference ($P < .05$) between treatments by categorical linear model.

Table 4. Incidence of Significant Gastroduodenal Injury

Type of Injury	No. of Patients	
	Salsalate (n = 18)	Naproxen (n = 21)
Diffuse erosions	0 (0%)	1 (5%)
Active ulcers	0 (0%)	7 (33%)*
Total	0 (0%)	8 (38%)*

*Significant ($P < .01$) difference between treatments by categorical linear model.

greater with naproxen than with salsalate. Prestudy therapy in the eight naproxen-treated patients with ulcers or diffuse erosions included salsalate in two, naproxen in three, and ibuprofen, aspirin, and piroxicam in one each. Only two of the 11 patients with a history of gastroduodenal ulcer developed ulcers during the study.

In contrast to the pattern generally observed in classic peptic ulcer disease, the stomach was the predominant site of naproxen-induced injury in this study (Table 5). Lesions in seven patients occurred in the stomach, and one ulcer occurred in the duodenum. The size of ulcers ranged from 0.3 by 0.3 cm to 1.2 by 1.5 cm. Two patients had multiple ulcers.

In addition to the active ulcers and erosions, three patients showed healed lesions on endoscopy. One of these patients received salsalate and two were treated with naproxen.

Figure 2 shows the distribution of final endoscopy scores, and Figure 3 shows the changes from baseline. Naproxen-treated patients had a significant ($P < .05$) deterioration in endoscopy score from baseline to the final visit; the mean

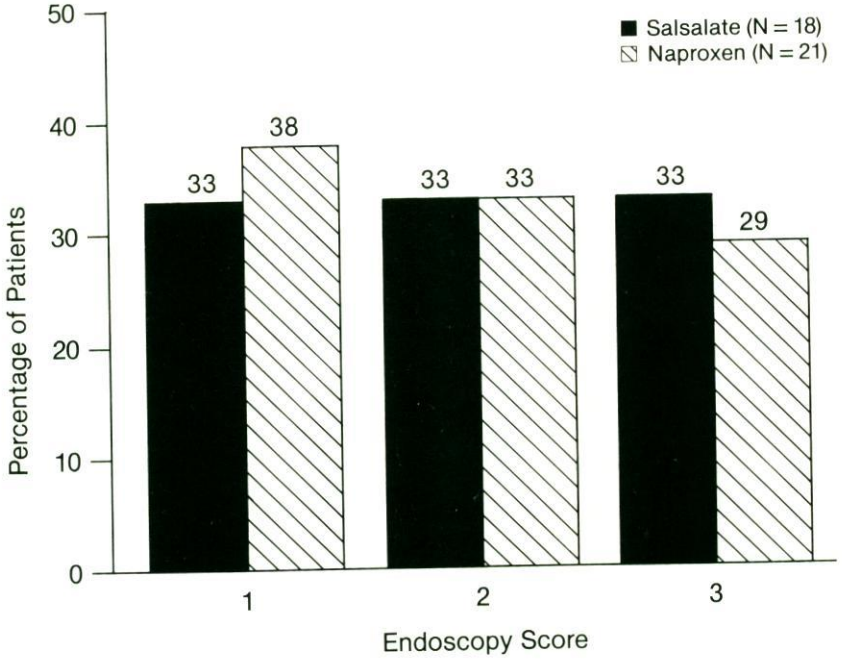

Fig 1. Distribution of baseline endoscopy scores in patients who completed the study. There was no significant difference between treatments.

Table 5. Status of Naproxen-Treated Patients Who Developed Ulcers or Diffuse Erosions

Patient No.	Prestudy NSAID	Final Concomitant Antirheumatic Therapy	Naproxen Dose (mg/d)	Duration of Naproxen Therapy (mo)	Baseline Endoscopy Score	Final Endoscopic Findings	Associated GI Symptoms
106	Salsalate	None	750	3	2	1 distal gastric antrum ulcer, 1.2 × 1.5 cm	None
114	Salsalate	Auranofin Prednisone	750	1	3	7 distal gastric antrum ulcers, 0.3 × 0.3 cm to 0.3 × 0.6 cm	None
205	Naproxen	Prednisone Methotrexate	750	1	3	1 apical duodenal ulcer, 1.2 cm	Epigastric pain
210	Naproxen	Methotrexate	875	1	3	Gastric antrum hemorrhagic erosions	None
211	Naproxen	None	750	1	1	1 distal gastric antrum ulcer, 0.2 × 0.5 cm	None
302	Ibuprofen	None	750	1	2	1 prepyloric gastric antrum ulcer, 0.3 cm	Epigastric burning; flatulence
305	Aspirin	Hydroxychloroquine	750	3	1	2 gastric angulus ulcers, 0.3 cm	Epigastric pain
313	Piroxicam	Hydroxychloroquine	750	1	1	1 prepyloric gastric ulcer, 0.4 cm	None

change was 1.2 (Fig 3). Patients treated with salsalate had a mean change of zero. The difference between the two groups was statistically significant ($P = .023$).

Of all patients exposed to the study drugs, 22 (79%) in the salsalate group and 18 (72%) in the naproxen group experienced adverse GI effects, either as symptomatic complaints reported in response to direct and indirect questioning or as endoscopically observed ulcers or diffuse erosions (Table 6). However, significant endoscopic lesional changes were not synchronous with complaints (Table 5). Only three of the eight naproxen-treated patients with significant gastroduodenal injury complained of epigastric pain. The remaining five were asymptomatic. There were no significant differences between treatments in the use of aluminum hydroxide during the study. The mean daily dose ranged from 180 to 240 mg with salsalate and from 60 to 300 mg with naproxen.

Three patients—two receiving naproxen and one receiving salsalate—had a single positive test for fecal occult blood during the study. On subsequent endoscopy (approximately 2 weeks after occult blood was detected), one of the naproxen-treated patients showed an ulcer and the other showed multiple hemorrhagic lesions; the gastroduodenal mucosa appeared normal in the salsalate-treated patient.

Adverse Experiences by Body System

During the study, 93% (26/28) of the patients receiving salsalate and 76% (19/25) of those treated with naproxen experienced at least one adverse effect (Table 6). The difference between

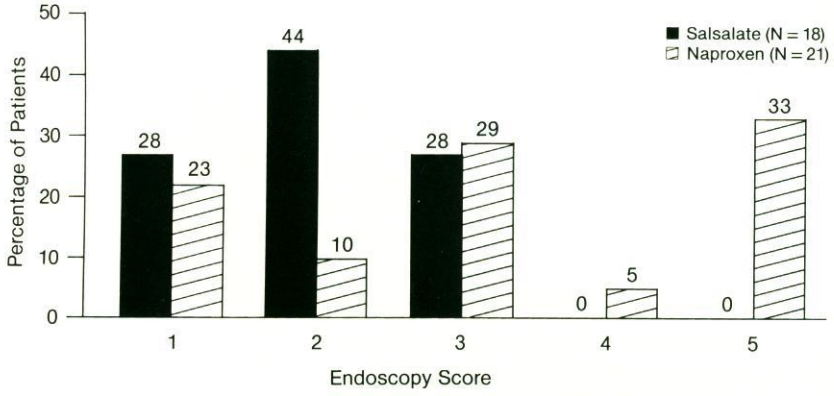

Fig 2. Distribution of final endoscopy scores for patients who completed the study. Distributions were significantly different ($P = .019$) between treatments by categorical linear model.

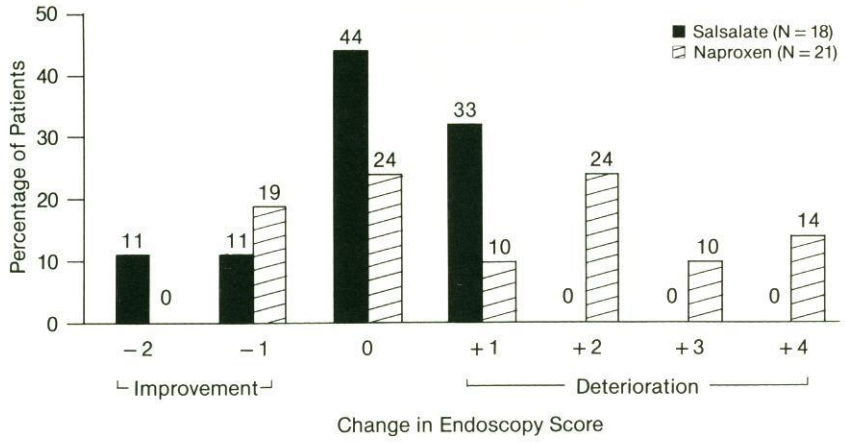

Fig 3. Distribution of changes from baseline endoscopy scores for patients who completed the study. The mean change (±SD) of 0.0 (±1.0) with salsalate was not significant by Wilcoxon signed-rank test ($P = 1.0$) or by sign test ($P = .38$). The mean change (±SD) of 1.2 (±1.7) with naproxen was significant both by Wilcoxon signed-rank test ($P = .005$) and by sign test ($P = 0.038$). The changes were significantly different ($P = .023$) between treatments by analysis of variance. The distributions were significantly different ($P = 0.039$) between treatments by categorical linear model.

treatments was not statistically significant. Because adverse experience reports included responses to direct questioning regarding GI symptoms at the time of endoscopy as well as indirect questioning at each visit, the incidence of total adverse experiences, and, more specifically, of subjective GI complaints, was higher than expected based on clinical experience with both drugs. The only significant difference between treatments other than the higher rate of gastroduodenal injury with naproxen was a higher rate of reversible otologic complications with salsalate ($P = 0.01$). All cases of tinnitus and decreased hearing reported with salsalate resolved spontaneously when the dose was reduced or the drug was discontinued.

Table 6. Adverse Experiences by Body System

Body System†	No. of Patients* Salsalate (n = 28)	Naproxen (n = 25)
Body as a whole	5 (18%)	6 (24%)
Central and peripheral nervous system	2 (7%)	1 (4%)
Gastrointestinal‡	22 (79%)	18 (72%)
Hearing and vestibular	9 (32%)	1 (4%)§
Liver and biliary	3 (11%)	2 (8%)
Psychiatric	2 (7%)	0 (0%)
Other‖	4 (14%)	3 (12%)
Total no. patients reporting adverse experiences	26 (93%)	19 (76%)

*Number reporting adverse experience at least once.

†World Health Organization nomenclature.

‡Includes reports elicited through direct questioning at endoscopy plus ulcers and diffuse erosions detected by endoscopy.

§Significant difference ($P = .01$) between treatments by χ^2 test.

‖Includes those systems with less than 5% incidence, ie, metabolic and nutritional, red blood cell, resistance mechanism, respiratory, skin and appendage, urinary, and visual.

The rate of discontinuation, because of adverse experiences alone and adverse experiences with inadequate therapeutic response, was comparable in the two treatment groups, 30% (9/30) with salsalate and 24% (6/25) with naproxen. All six discontinuations for naproxen were because of gastroduodenal injury. None of the salsalate discontinuations were for GI injury. Six of the nine discontinuations in the salsalate group were related to reversible otologic problems. One patient each discontinued because of diarrhea, elevated liver enzyme activity, and a complex of symptoms that included wheezing, shortness of breath, rash, confusion, headache, and eye pain. In each case, symptoms resolved with discontinuation of salsalate.

There were no clinically significant mean changes from baseline in vital signs or body weight in either treatment group. The only laboratory test to show a significant mean change from baseline and significant deviation from the normal range was serum uric acid, that decreased significantly with salsalate. Such a reduction in uric acid is a known effect of high-dose salicylates.

Therapeutic Response

Measurements of RA status in patients who completed the study showed no significant differences between the two treatment groups. The therapeutic response to both study drugs was generally comparable to that achieved with prestudy NSAIDs (Table 7). The only significant changes from baseline were a decrease in the mean number of swollen joints at the final visit for salsalate-treated patients and an improvement in the physicians' global impressions for those treated with naproxen. At the final visit, 89% of the patients receiving salsalate and 90% of the patients receiving naproxen rated their ability to perform usual daily activities (patients' global impressions) as fair, good, or very good. The physicians' global impressions of the patients' general condition were good or very good for 50% of those receiving salsalate and 62% of those receiving naproxen. The mean daily requirements for acetaminophen during the study were comparable in the two treatment groups, ranging from 325 to 423 mg with salsalate and 325 to 488 mg with naproxen.

Table 7. RA Status at Final Visit for Patients who Completed the Study

Disease Status*	Salsalate (n = 18)	Naproxen (n = 21)
Mean improvement in no. painful joints ± SD	4.5 ± 16.2	0.8 ± 10.9
Mean improvement in no. swollen joints ± SD	4.1 ± 7.6†	0.4 ± 6.0
ARA functional class		
I	0 (0%)	3 (14%)
II	18 (100%)	18 (86%)
III	0 (0%)	0 (0%)
Patient's global impression (score)		
Very poor (0)	0 (0%)	0 (0%)
Poor (1)	2 (11%)	2 (10%)
Fair (2)	5 (28%)	6 (29%)
Good (3)	9 (50%)	12 (57%)
Very good (4)	2 (11%)	1 (5%)
Mean improvement in score ± SD	0.2 ± 0.9	0.4 ± 0.9
Physician's global impression (score)		
Very poor (0)	0 (0%)	1 (5%)
Poor (1)	2 (11%)	0 (0%)
Fair (2)	7 (39%)	7 (33%)
Good (3)	8 (44%)	12 (57%)
Very good (4)	1 (6%)	1 (5%)
Mean improvement in score ± SD	0.0 ± 1.0	0.5 ± 0.7†

*P value determined by analysis of variance for continuous data and by categorical linear model for discrete data indicated no significant differences between treatments.

†Significant improvement ($P < .05$) from baseline by Wilcoxon signed-rank test.

DISCUSSION

The objective of this study was to define and compare the risks of salsalate and naproxen treatment with regard to upper GI mucosal toxicity. The incidence of GI symptomatic complaints were comparable with these two drugs. However, a significantly higher incidence of ulcer formation was observed with naproxen, while no active ulcers were observed after 3 months of salsalate therapy. The NSAID-associated gastropathy seen in this and other studies[17-19] is often not associated with overt symptoms and is usually apparent only by endoscopy. Asymptomatic ulcers and erosions may pose a risk for undetected progression to serious sequelae, such as hemorrhage or perforation. The risk of hemorrhage is increased by impairment of platelet aggregation, a complication associated with most NSAIDs[20] but not with salsalate.[8]

Patient discontinuation rates for adverse experiences were comparable. The six discontinuations in the naproxen group were for endoscopically shown gastric lesions. Discontinuations from salsalate were predominantly due to reversible otologic problems (six of the nine discontinuations), which, although not medically serious, represent the major potential disadvantage of this drug. These problems, commonly associated with salicylate use, are readily apparent and easily resolved with dosage reductions or drug discontinuation. Endoscopic findings of diffuse erosions and ulceration were responsible for most discontinuations from naproxen. The lower risk of GI mucosal toxicity with salsalate outweighs the higher incidence of otologic problems. The medical importance of NSAID-induced gastropathy demonstrates the desirability of selecting a first-line agent such as salsalate for patients with RA or osteoarthritis, including those at increased risk for GI complications.

Previous studies of the resilient cytoprotective adaptive response of healthy mucosa in both animals and adult humans demonstrated that the mucosal impact of NSAID therapy was transient.[21] However, subsequent long-term, double-blind endoscopy experiences have documented that adaptation is evanescent and eventually

fails, leading to the progression of mucosal lesions.[1,22] Evidence of ulcers after 1 and 3 months of naproxen therapy in the present study indicates that gastric adaptation, if it occurs, is insufficient to completely protect against the gastropathy associated with long-term NSAID therapy.

NSAID gastropathy has now been recognized as a specific iatrogenic disorder that can progress to ulcers, bleeding, perforation, and death. In fact, complications of NSAID-induced gastropathy are believed to be responsible for 2,000 to 4,000 potentially preventable deaths annually in patients with RA.[1,23] Furthermore, hundreds of millions of dollars are lost each year because of disability, hospitalization expenses, and costs of complications from NSAID gastropathy.[24] Multiple large-scale, long-term, endoscopy-controlled studies have reported that ulcer crater disease actually occurs in at least one of five patients receiving chronic NSAID therapy.[1,22,25-28] Thus, the high incidence of ulcers associated with naproxen in this study both on screening endoscopy at the time of admission (33%) and on repeat examination during controlled treatment (also 33%), as well as the 26% incidence of such lesions in the "other NSAID" group at prestudy screening, are all consistent with the usual frequency of ulcers detected by endoscopy in chronic NSAID users. By comparison, the 6% incidence of ulcers in the salsalate group at the prestudy screening and the complete lack of progression to serious gastropathy during the three months of the study indicate a safer outcome, probably because of a combination of drug dissolution and absorption outside the stomach and the relatively prostaglandin-sparing effect of salsalate.

Based on the results of this study, it is concluded that patients treated with salsalate are at a lower risk for developing significant gastropathy (GI mucosal lesions) than patients receiving naproxen. Therefore, it is possible to differentiate GI safety at therapeutic doses of these two drugs in patients with RA who require long-term NSAID therapy.

SUMMARY

This randomized, investigator-blinded, parallel group endoscopic study evaluated the effects of salsalate and naproxen on the gastroduodenal mucosa over a 3-month period in patients with RA. Using therapeutic doses of the drugs, 8 of 21 patients (38%) in the naproxen group had endoscopically shown active ulcers (seven patients) or diffuse erosions (one patient), whereas none of the 18 patients treated with salsalate (0%) had such lesions ($P = .003$). Five of the eight naproxen-treated patients with evidence of GI damage were asymptomatic at the time of endoscopic verification of their lesions. The most significant disadvantage of salsalate was its higher incidence of otologic problems accounting for six of the nine discontinuations with salsalate. However, the findings of this study suggest that patients receiving salsalate are at lower risk for developing significant gastropathy than those treated with naproxen. The relative benefit-to-risk ratio of salsalate indicates that this drug should be considered as a significant alternative NSAID therapy.

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