GASTROENTEROLOGY 1990;99:1616-1621

Comparison of Salsalate and Aspirin on Mucosal Injury and Gastroduodenal Mucosal Prostaglandins

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The effects of a 7.5-day course of orally administered salsalate (3.0 g/day), aspirin (3.9 g/day), or placebo on gastroduodenal mucosal injury, mucosal prostaglandin content, and plasma prostaglandin concentrations in healthy, asymptomatic human volunteers were examined. Mean serum salicylate concentrations after these doses of salsalate and aspirin were nearly identical (≈15 mg/dL). When the gastroduodenal mucosa was assessed endoscopically 1 hour after the final dose of medication, there was minimal mucosal injury in placebo-treated or salsalate-treated subjects and considerable injury in the stomach and duodenum of aspirin-treated subjects ($P < 0.001$, aspirin vs. salsalate or placebo). In both the stomach and duodenum, aspirin lowered mucosal prostaglandin F_{2a} and E_2 content by > 90% ($P < 0.001$), whereas salsalate produced no significant change. Aspirin also lowered plasma prostaglandin F_{2a} concentrations by 58% ± 6%, whereas salsalate lowered them by only 11% ± 9% ($P < 0.001$). Thus, the nonacetylated salicylate, salsalate, produced much less gastroduodenal mucosal damage than aspirin at equivalent serum salicylate concentrations, possibly because salsalate did not inhibit mucosal prostaglandin synthesis.

Salsalate (salicylsalicylic acid), a nonacetylated salicylate, and aspirin (acetylsalicylic acid) have been reported to be equally effective in rheumatic diseases (1-4). Although more expensive than aspirin, salsalate produced fewer side effects (1-3,5). In addition, during short-term administration to healthy volunteers, salsalate caused less gastrointestinal blood loss than aspirin (6-8) and fewer gastric erosions (5,9).

Aspirin inhibits prostaglandin production by the gastroduodenal mucosa (10-12), and this effect, by removing protective prostanoids, may contribute to the development of gastric erosions and ulcerations (13). The effect of salsalate on prostaglandin production by the gastric mucosa of humans is unknown. In the present placebo-controlled study, we compared the acute effects of aspirin and salsalate on the gastroduodenal mucosa, assessed endoscopically, and the effects of these drugs on gastroduodenal mucosal prostaglandin content and on serum prostaglandin concentrations. Our hypothesis was that salsalate would cause less gastroduodenal mucosal injury than aspirin in association with a preservation of mucosal prostaglandin synthesis.

Materials and Methods

An investigational new drug number (33,634) for salsalate was obtained from the Food and Drug Administration on September 5, 1989 and studies were approved by a Human Research Committee on September 11, 1989. All subjects gave written informed consent before participation in this study.

Recruitment of Subjects

Healthy volunteers between the age of 18-65 were solicited through advertisement on the bulletin boards of our hospitals (Dallas Department of Veterans Affairs Medical Center and Parkland Memorial Hospital, Dallas, TX). Subjects were excluded if any of the following was present: heartburn, abdominal pain, indigestion, bloating, fullness, or nausea/vomiting; use of aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, H_2-blockers, sucralfate, misoprostol, antacids, or Pepto-Bismol (Norwich-Eaton, Norwich, NY) within the previous 2 weeks; history of

Abbreviation used in this paper: EGD, esophagogastroduodenoscopy.

0016-5085/90/$3.00

allergy to aspirin, diazepam, or topical tetracaine; a positive urine pregnancy test in premenopausal women; history of gastric surgery; history of peptic ulcer or other gastrointestinal disease; history of liver disease (including currently elevated liver function tests); or history or presence of anemia, thrombocytopenia, leukopenia, gout, coagulation disorder, or renal insufficiency (serum creatinine > 2.0). All subjects had a screening history and physical examination as well as a screening laboratory evaluation which included the following tests: complete blood count including platelet count, serum electrolytes, serum creatinine, and liver function tests. Twenty volunteers (9 men and 11 women) met all of the entry criteria and consented to participate as paid subjects in the study protocol (see below). Use of any medication other than study medication was not allowed during the study.

Study Protocol

Each subject, after an overnight fast, had a baseline venous blood sample drawn for measurement of serum salicylate and plasma prostaglandin F_{2a} concentrations. Salicylate concentration was measured to exclude the possibility of surreptitious salicylate ingestion. Subjects then underwent a baseline esophagogastroduodenoscopy (EGD) using an Olympus GIF-Q-10 instrument (Olympus Corp., New York, NY) after pharyngeal anesthesia with tetracaine hydrochloride (Pontocaine; Winthrop Pharmaceutical, New York, NY) and light sedation with IV diazepam (Valium; Roche Laboratories, Nutley, NJ). The procedure was videotaped, and gastroduodenal mucosal injury was scored by two independent blinded observers. One scorer was present at the endoscopy, and the other scorer assessed injury through a review of the videotapes after all of the procedures. The following endoscopic scoring system, slightly modified from Lanza et al. (17), was used to score each of four mucosal regions, namely, the gastric fundus, the gastric antrum, the duodenal bulb, and the postbulbar duodenum: 0, normal gross appearance; 1, erythema and/or edema; 2, 1–10 submucosal hemorrhages only; 3, numerous (>10) submucosal hemorrhages, with or without one or two discreet erosions; 4, large areas of submucosal hemorrhage or more than two erosions; grade 5, ulceration.

After each region was scored, gastric and duodenal mucosal biopsies were obtained using 4-mm biopsy forceps. Four biopsies were taken from fundic mucosa 5 cm below the squamocolumnar junction; four from antral mucosa, 2 cm proximal to the pylorus; four from duodenal bulbar mucosa; and four from postbulbar duodenal mucosa. Each mucosal biopsy specimen was frozen within 10–15 seconds with liquid nitrogen to arrest further prostaglandin synthesis. The specimen was stored at −90°C until PGs were extracted and then assayed for PGF_{2a} and PGE_2 concentrations by radioimmunoassay, according to a previously described method (18).

Seven days after baseline endoscopy (day 8), subjects were randomized to receive for the next 7.5 days either placebo (six subjects), unbuffered aspirin (seven subjects), or salsalate (seven subjects). Dosages of medications were as follows: placebo, three dextrose capsules four times a day; aspirin (Eli Lilly & Co., Indianapolis, IN), three 325-mg capsules four times a day (total daily dose, 3.9 g); or salsalate (Disalcid; Riker Laboratories, Inc., St. Paul, MN), three 500-mg capsules twice a day (total daily dose, 3.0 g). Times of doses were 6 AM, noon, 6 PM, and 11 PM. In the salsalate group, three 500-mg salsalate capsules were taken at noon and 11 PM. To maintain blinding in this group, three placebo capsules were taken at 6 AM and 6 PM. Placebo, aspirin, and salsalate capsules were identical in appearance. Doses of aspirin and salsalate were chosen to produce similar mean serum salicylate concentrations which were in the lower range of salicylate concentrations expected to provide an antiinflammatory effect (i.e., 15–30 mg/dL) (1,4,5,7,8,14–16). Additionally, these doses are within the recommended dosage range for treatment of rheumatic conditions (16).

Subjects returned to the endoscopy laboratory at 1 PM on day 15, 1 hour after their final dose of medication, for venous blood sampling (for repeat serum salicylate and plasma prostaglandin F_{2a} measurements) and EGD, with mucosal scoring and mucosal biopsies for prostaglandin content as described above. Also, on day 15 subjects were asked by questionnaire to report any symptoms they may have experienced during the preceding week of drug therapy.

Prostaglandin Measurements

Mucosal and plasma prostaglandins were measured as described below by an investigator blinded to treatment group.

Mucosal PGF_{2a} and PGE_2 assays. Tissue extraction of prostaglandins and measurements of prostaglandins by radioimmunoassay were performed according to a previously described method (18). Briefly, frozen biopsy specimens were crushed, homogenized in ethanol, and then centrifuged. The resultant supernatant was then acidified with acetic acid. Prostaglandin fractions were then extracted by column elution through a reverse-phase octadecylsilane-bonded silica gel and reconstituted in a phosphated saline buffer. Radioimmunoassay was performed by incubating the reconstituted tissue prostaglandins with the corresponding ^{3}H-prostaglandin and the corresponding antisera. After incubation, bound counts were determined by liquid scintillation spectrometry. Standard curves using known amounts of PGF_{2a} or PGE_2 were used to quantitate prostaglandin concentrations in study samples. Previous studies in our laboratory have shown that PGF_{2a} and PGE_2 are the two major prostaglandins in the human gastric mucosa (18). We have also previously reported intraassay variations of 7.1% and 6.5% for radioimmunoassays of PGF_{2a} and PGE_2, respectively, and interassay variations of 10.5% and 12.4%, respectively (18).

Plasma prostaglandin assay. Prostaglandins were extracted from plasma, and a radioimmunoassay, which was similar to the procedure described above, was performed. However, an additional chromatographic step was required to eliminate nonspecific interference of plasma components in the radioimmunoassay. This involved the use of silicic acid chromatography as described by Jaffe et al. (19). Silicic acid slurry in solvent 1 (toluene/ethyl acetate, 60:40 vol/vol) was packed into columns and washed with 5 mL of solvent 2 (toluene/ethyl acetate/methanol/water, 60:40:20:0.1 vol/vol) and 4 mL of solvent 1. Prostaglandins extracted from

octadecysilane-bonded silica gel were dissolved in solvent 1 and added to the column. Prostaglandins were then eluted off the column by addition of 12 mL of solvent 3 (toluene/ethyl acetate/methanol/water, 60:40:5.0:0.1, vol/vol) and 10 mL of solvent 2. Solvents were evaporated to dryness and then radioimmunoassayed for PGF_{2a} in a fashion similar to that described above.

In preliminary experiments, a fraction of prostaglandins that was pure enough to reliably reproduce by radioimmunoassay standard curves with PGF_{2a} was extracted. Our extraction techniques for PGE_2 produced a prostaglandin fraction that was contaminated with other measured substances. We therefore chose to assay plasma samples only for PGF_{2a} concentration.

Serum Salicylate Concentration

Serum salicylate assay was measured using the Cobas-Mira kit (Sigma, St. Paul, MN) which determines salicylate concentrations by a quantitative, colorimetric assay (20). Using this assay, values $\leq$ 2 mg/dL are considered negative (undetectable).

Statistical Analysis

Results are expressed as mean ± SE. There was good correlation between endoscopic mucosal injury scores of the two blinded scores ($r = 0.83$, $n = 160$, $P < 0.001$). Therefore, the mean of the two scores for each subject in each region was used. When determining differences between mean results in the different treatment groups, analysis of variance was used. When determining differences before and after drug therapy, paired t tests were used. When determining differences in symptom frequency between treatment groups, adjusted χ^2 analysis was used. P values < 0.05 were considered statistically significant. Mucosal prostaglandin concentrations were normalized by using $\log_{10}$ or the square root of the concentrations. These two methods gave nearly identical P values. Therefore, the P values cited for comparison of mucosal prostaglandin concentrations represent those for $\log_{10}$ concentrations.

Results

Before initiation of drug treatment, there were no significant differences among groups in mean age, mucosal injury scores, mucosal PGF_{2a} and PGE_2 concentrations, plasma PGF_{2a}, or serum salicylate concentrations (Table 1).

After 7.5 days of drug treatment, salsalate, and aspirin-treated subjects had nearly identical mean serum salicylate levels (14.9 ± 3.1 and 15.3 ± 2.1 mg/dL, respectively), whereas the placebo group had a mean serum salicylate level of 0.9 ± 0.1 mg/dL ($P < 0.001$; salsalate or aspirin vs. placebo). After drug treatment, aspirin produced significantly more mucosal injury in every region when compared with either salsalate or placebo (Figure 1, Table 2). The sum of the injury scores for the four separate regions averaged 11.6 ± 0.9 after aspirin compared with 4.6 ± 1.0 and 3.9 ± 0.6 after salsalate and placebo, respectively ($P < 0.001$). There was no significant difference in mean mucosal injury scores between the placebo or salsalate groups in any region. No mucosal erosions were visualized before drug therapy in any treatment group. After drug therapy, mucosal erosions were present in none of the six placebo-treated subjects, in one of the seven salsalate-treated subjects (duodenum only), and in six of seven the aspirin-treated subjects (in both stomach and duodenum in five subjects and in duodenum only in one subject).

In every region, aspirin-treated subjects had signifi-

Table 1. Baseline Group Characteristics

	Placebo (n = 6)	Salsalate (n = 7)	Aspirin (n = 7)
Age (yr) (range)	30.3 ± 5.2 (18–55)	36.1 ± 4.1 (21–57)	39.6 ± 4.4 (26–60)
Endoscopy score			
Fundus	0.6 ± 0.4	0.9 ± 0.4	1.0 ± 0.5
Antrum	0.7 ± 0.7	0.8 ± 0.4	1.3 ± 0.4
Bulb	1.1 ± 0.4	0.4 ± 0.4	0.7 ± 0.4
Postbulbar	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1
PGF_{2a} content (pg/mg)			
Fundus	299.7 ± 77.8	262.3 ± 39.5	325.5 ± 111.2
Antrum	366.8 ± 162.9	507.7 ± 101.1	301.2 ± 66.2
Bulb	262.5 ± 90.0	242.6 ± 43.5	346.7 ± 90.7
Postbulbar	470.9 ± 122.2	643.5 ± 174.9	578.4 ± 169.7
PGE_2 content (pg/mg)			
Fundus	142.0 ± 40.4	86.3 ± 14.7	79.1 ± 12.6
Antrum	94.2 ± 34.1	155.7 ± 41.6	105.7 ± 27.6
Bulb	68.6 ± 11.9	87.3 ± 18.7	113.4 ± 23.7
Postbulbar	158.1 ± 54.1	257.0 ± 97.4	227.8 ± 76.7
Plasma PGF_{2a} concentration (pg/mL)	470.4 ± 40.0	503.2 ± 20.1	512.0 ± 54.8
Serum salicylate concentration (mg/dL)	0.8 ± 0.1	0.9 ± 0.1	1.6 ± 0.8

NOTE. Results before drug therapy, expressed as mean ± S.E. None of these differences was significant by analysis of variance.

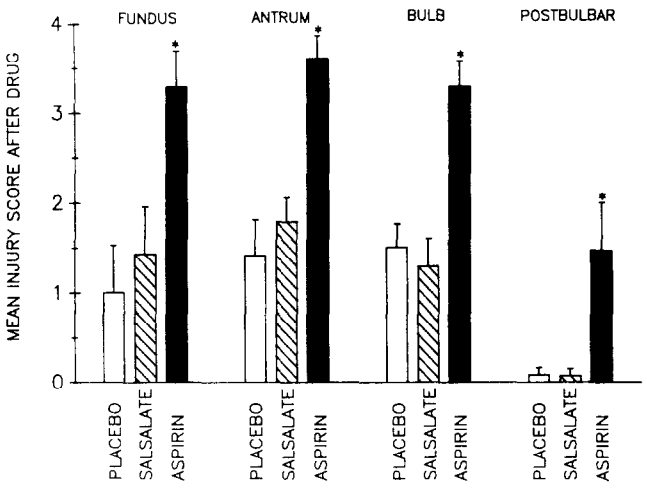

Figure 1. Mean (± SE) mucosal injury scores after 7.5 days of drug therapy with placebo (n = 6), salsalate (n = 7), or aspirin (n = 7). *Significant differences ($P < 0.01$ to 0.001) for aspirin vs. salsalate or placebo.

cantly lower mucosal PGF_{2a} and PGE_2 concentrations than prostaglandin concentrations of salsalate-treated or placebo-treated subjects (Figure 2). Mucosal prostaglandin concentrations were not significantly different after salsalate or placebo. Aspirin therapy also

Table 2. Number of Subjects Grouped by Endoscopy Score Before and After Drug Therapy

	No. of subjects					
	Before			After		
	P	S	A	P	S	A
Endoscopy score by region[a]						
Fundus						
0	4	3	4	3	3	0
0.1-1	1	2	0	1	0	1
1.1-2	0	1	1	1	2	0
2.1-3	1	1	2	1	2	1
3.1-4	0	0	0	0	0	5
Antrum						
0	4	4	1	1	0	0
0.1-1	0	1	3	1	2	0
1.1-2	2	1	2	3	4	0
2.1-3	0	1	1	1	1	2
3.1-4	0	0	0	0	0	5
Bulb						
0	2	6	3	0	1	0
0.1-1	1	0	2	2	2	0
1.1-2	3	1	2	4	3	1
2.1-3	0	0	0	0	1	1
3.1-4	0	0	0	0	0	5
Postbulbar						
0	5	7	6	5	6	2
0.1-1	1	0	1	1	1	1
1.1-2	0	0	0	0	0	2
2.1-3	0	0	0	0	0	1
3.1-4	0	0	0	0	0	1

P, placebo (n = 6); S, salsalate (n = 7); A, aspirin (n = 7).
[a]The average of the scores of two observers.

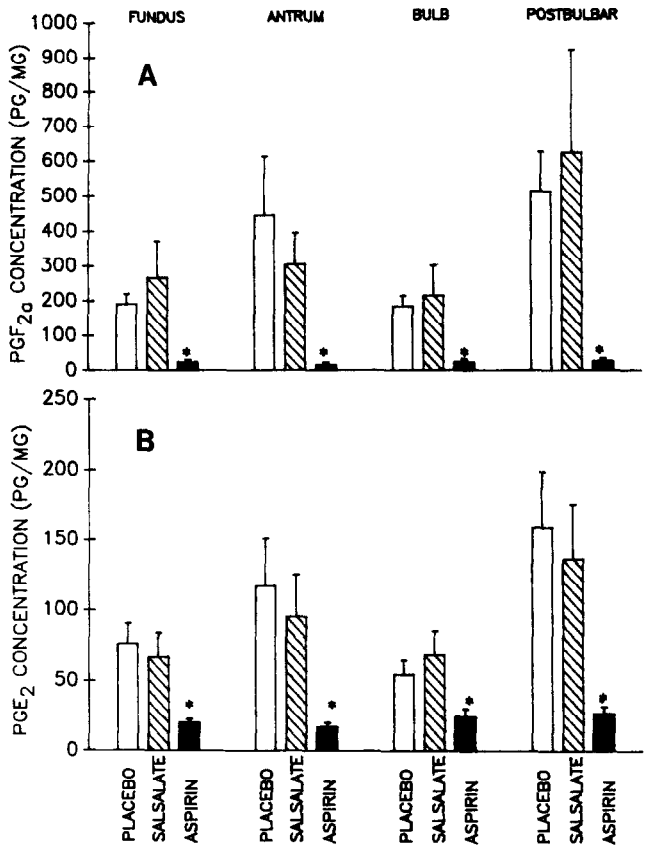

Figure 2. Mean (±SE) gastroduodenal mucosal concentration of PGF_{2a} (A) and PGE_2 (B) after 7.5 days of drug therapy with placebo (n = 6), salsalate (n = 7), or aspirin (n = 7). *Significant differences ($P < 0.01$ to <0.001) for aspirin vs. salsalate or placebo. Please note different scales for PGF_{2a} and PGE_2 concentrations.

significantly decreased plasma PGF_{2a} concentrations from 512.0 ± 54.8 pg/mL to 181.4 ± 31.5 pg/mL ($P < 0.001$). Salsalate and placebo therapy resulted in plasma PGF_{2a} concentrations of 443.5 ± 36.4 and 477.2 ± 64.3 pg/mL, respectively, which were similar to one another and not significantly different from pretreatment values (Table 1).

As shown in Table 3, the most common symptoms reported were abdominal pain, indigestion, abdominal cramping, and heartburn. One or more of these symptoms was reported by all of the aspirin-treated subjects, by four of seven of the salsalate-treated subjects, and by none of the six placebo-treated

Table 3. Number of Subjects With Symptoms After Drug Therapy

	Placebo	Salsalate	Aspirin
Indigestion	0	4	7
Abdominal pain	0	3	7
Abdominal cramping	0	3	5
Heartburn	0	1	3
Pruritus	1	1	0
Tinnitus	1	0	0

subjects ($P < 0.01$). Pruritus was reported by two subjects; one had received salsalate and the other placebo. One subject who had received placebo reported tinnitus.

Discussion

Inhibition of mucosal prostaglandin synthesis is thought to be an important factor in the pathogenesis of gastric and duodenal mucosal damage by aspirin and NSAIDs (12,13,18,21,22). In the present study, significant differences in mucosal prostaglandin content observed after salsalate and aspirin administration are probably explained by differences in molecular structures of the two compounds. Salsalate differs from aspirin in that it is a dimer of salicylic acid and lacks an acetyl group. The acetyl group of aspirin may impart certain properties that are lacking in the nonacetylated salicylate, salsalate. For example, after oral administration, aspirin is known to inhibit platelet aggregation through an irreversible acetylation of cyclooxygenase, resulting in decreased levels of thromboxane in platelets (23). A previous study of healthy human volunteers by Morris et al. showed that serum PGE_2 and thromboxane concentrations were minimally affected by salsalate but profoundly suppressed by aspirin (24); this is in agreement with our present findings with plasma PGF_{2a} concentrations.

Hydrolysis of aspirin yields salicylate and acetic acid, whereas hydrolysis of salsalate yields only salicylate. The salicylate ion per se does not inhibit cyclooxygenase activity in the gastric mucosa, as has been shown with sodium salicylate (25). Therefore, the acetylated form of salicylate, aspirin, seems to be responsible for the inhibition of mucosal cyclooxygenase activity. The mucosal and prostaglandin-sparing activities of salsalate may be thus explained, in part, by its lack of acetylation of cyclooxygenase.

Prostaglandin inhibition is not the only mechanism by which aspirin causes gastric mucosal injury. Aspirin is also known to be directly toxic to the mucosa by disrupting the mucosal barrier, as measured by ionic flux or transmucosal potential difference (22). Aspirin, because of its pKa of 3.5, remains mostly undissociated in acidic gastric juice and is, therefore, lipid soluble. Lipid solubility allows high gastric absorption and direct toxic effects on the cells of the gastric mucosa. Salsalate is one-twentieth as soluble as aspirin at acidic pH values (1). In the more basic environment of the duodenum, salsalate is soluble and is absorbed in the upper small intestine (1). Because of its low solubility in gastric juice, salsalate is not as likely as aspirin to damage the gastric mucosa from the luminal side. Because salsalate is absorbed in the small intestine rather than the stomach, it might cause injury in the small bowel, as has been observed with enteric-coated aspirin preparations (17,26). However, in the present study there was no endoscopic evidence of a significant increase in mucosal injury in either the first or second portions of the duodenum in salsalate-treated subjects.

A recent multicenter, double-blind study compared the antiinflammatory efficacy of salsalate and aspirin in 233 patients with rheumatoid arthritis (3). Responses to drug therapy were assessed by changes in physical examination and laboratory parameters, and side effects of treatment were monitored. The investigators found that salsalate and aspirin had equal therapeutic effectiveness, whereas aspirin was associated with more clinically evident side effects, namely gastrointestinal bleeding, erosions, and ulcerations. In the present study, every aspirin-treated subject and most of the salsalate-treated subjects experienced gastrointestinal symptoms. One could speculate that some symptoms occurring after salicylate therapy may be attributed to the metabolic derivative of both aspirin and salsalate, the salicylate ion, whereas mucosal damage and inhibition of prostaglandin synthesis may be caused by the acetyl group of aspirin. For this reason, mucosal damage and gastrointestinal symptoms may not necessarily correlate in patients receiving salicylates.

Inhibition of prostaglandin synthesis has long been considered to be the mechanism of action through which aspirin and other NSAIDs exert their antiinflammatory effects. With salsalate, however, an alternative mechanism for its antiinflammatory effect must be proposed because it does not reduce prostaglandin content in serum or gastroduodenal mucosa. Inhibition of neutrophil activation has been suggested as a mechanism by which both aspirin and sodium salicylate, a nonacetylated salicylate, exert their antiinflammatory effects (27). Whether this mechanism applies to salsalate remains to be investigated.

Differences in gastroduodenal mucosal injury scores and in prostaglandin content after salsalate or aspirin were observed after 1 week of therapy and in a group of healthy individuals. While no gastric or duodenal ulcers were observed after 1 week of any medication in this study, a longer treatment period with aspirin would probably result in ulcer formation (28,29). The effects on the gastroduodenal mucosa of salsalate therapy for more than 1 week are unknown (5). However, if sparing of gastroduodenal mucosal injury and preservation of mucosal prostaglandin content were to persist after prolonged treatment with salsalate and this mucosal sparing also occurred in patients with rheumatologic disease, salsalate could be of benefit to arthritis patients who depend on large doses of antiinflammatory medications for symptomatic relief.

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Received April 25, 1989. Accepted July 5, 1990.

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This work was supported by Grant No. DK 16816 from the National Institutes of Health and the Department of Veteran Affairs.

The authors thank Mary Walker and Cora Barnett for their technical assistance, Dr. Barry Goldlust of 3M-Riker Laboratories for providing salsalate (Disalcid) and placebo capsules, and Dr. Linda Katz of the Food and Drug Administration for her assistance and recommendations.