An Endoscopic Comparison of the Gastroduodenal Injury Seen with Salsalate and Naproxen

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Abstract. **Forty endoscopically normal healthy subjects were randomized to receive either BID salsalate (3500 mg/day) or BID naproxen (750 mg/day) for 14 days followed by repeat endoscopic examination. Gastroduodenal lesions were found in 55% (11/20) of the subjects taking naproxen, and 10% (2/20) of those taking salsalate ($p=0.002$). Twenty-five percent (5/20) of the subjects taking naproxen and none of the subjects taking salsalate were noted to have severe gastric injury ($p=0.003$). There was no difference between the 2 groups in subjective gastrointestinal system adverse experiences. Overall, 95% (19/20) of subjects taking salsalate reported at least 1 adverse experience compared with 60% (12/20) of those taking naproxen ($p=0.02$). This was due primarily to the higher number of subjects taking salsalate reporting reversible tinnitus or hearing loss. There was no significant treatment difference in adverse experiences reported for any other organ system. The results of our study support previous observations in patients with rheumatoid arthritis that salsalate produces less gastroduodenal mucosal toxicity than the widely used antiinflammatory agent, naproxen. (*J Rheumatol 1989;***16:1570–4)**

Key Indexing Terms:
SALSALATE NONACETYLATED SALICYLATE NAPROXEN
ENDOSCOPY CLINICAL TRIAL GASTROPATHY

Nonsteroidal antiinflammatory drugs (NSAID) damage the gastroduodenal mucosae. This has been demonstrated in healthy volunteers[1,2], and in patients with rheumatoid arthritis (RA) presenting with life threatening complications, i.e., perforation or hemorrhage[3-10]. Nevertheless, the continued use of these drugs in patients with RA attests to their efficacy and underscores the need for development of NSAID with less gastroduodenal mucosal toxicity.

Salsalate (salicylsalicylic acid) is a nonacetylated salicylate which has been shown to be a weak prostaglandin inhibitor[11]. This drug also has demonstrated a lesser degree of mucosal injury compared with enteric coated aspirin in healthy volunteers[12] and when compared with naproxen in patients with RA[13]. Our purpose was to determine whether antiinflammatory doses of salsalate produced less gastroduodenal mucosal injury than antiinflammatory doses of naproxen in this healthy volunteer clinical model.

MATERIALS AND METHODS

Study design. This was a single blind (endoscopist), parallel group study in 40 healthy subjects. A single blind design was used so that the effects of physically unadulterated commercial tablets of both drugs could be studied. Placebo control was not used because of the absence of important gastroduodenal lesions with salsalate in a previous endoscopy study[13]. All subjects were screened with a complete history and examination, electrocardiogram, hemogram, blood chemistry profile and urinalysis. Subjects with any important abnormalities of these variables were excluded.

A baseline gastrointestinal (GI) endoscopy was carried out to verify the presence of normal gastroduodenal mucosae. Gastric aspirate was obtained from each subject at the time of initial endoscopy and pH was measured by pH meter. No subject was allowed to continue in the study with a baseline pH greater than 3.0. Men and nonpregnant, nonlactating women between 18 and 55 years of age, and who were within 15% of their ideal body weight[14], were included. Criteria for exclusion consisted of a history or presence of GI disease (i.e., peptic or duodenal ulcer, chronic constipation, inflammatory bowel disease, irregular bowel habits, previous endoscopy showing ulcer or > 10 erosions), known NSAID hypersensitivity, history of chemical dependency, including alcoholism, use of an investigational drug within the past 4 weeks, history or presence of important hepatic, renal, hematologic, cardiovascular, metabolic, or pulmonary disease or dysfunction, and ingestion of acetaminophen or antihistamine during the 24 h preceding baseline endoscopy. For 2 weeks before and during the course of the study, subjects were also prohibited from ingesting alcohol or any nonstudy drug with the exception of oral contraceptives, ovarian or thyroid hormone maintenance therapy, antihistamines and acetaminophen.

After the qualifying endoscopy, subjects were assigned sequential numbers in the order of accession. The study nurse then dispensed appropriate study drugs to subjects for self-administration during the next 2 weeks. Assignment of study drug was based on a computer generated list of random numbers. Subjects received either 3500 mg/day of salsalate (Disalcid®, 3M Riker, 500 mg tablets) as 3 in the AM and 4 in the PM, or 750 mg/day of naproxen (Naprosyn®, Syntex Laboratories, Inc, 375 mg tablets) as 1 in the AM and 1 in the PM. Dosing was started in the evening after baseline endoscopy and continued through the evening dose on Day 14. Subjects were instructed not to reveal identifying information about the study drug to the endoscopist. This was monitored at the time of endoscopy.

Compliance was evaluated on Days 8 and 15 by tablet count, and by screen-

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ing of urine samples for salicylic acid. Noncompliance was defined as a tablet count of less than 80% or more than 120% of the prescribed number. Subjects were also considered noncompliant by urine screen if those taking salsalate did not or those taking naproxen did test positive for salicylic acid. Subjects found to be noncompliant during the course of the study were replaced.

Endoscopic examination was repeated on Day 15 and the gastric and duodenal mucosae were each graded according to the scale shown in Table 1. All Day 15 procedures were done by the same endoscopist (FLL) with an Olympus GIF Q 10 panendoscope. The endoscopist was blinded to assignment of study drugs. The stomach was evaluated from proximal to distal so as to avoid error due to misinterpretation of artifacts caused by the passage of the instrument. At the conclusion of the study, assessment of general safety included a repeat examination and laboratory testing. Adverse experiences were elicited by means of indirect questioning on Days 8 and 15 by the study coordinator.

All subjects were informed of the risks and benefits and each gave voluntary written consent before entering the study. Study protocol and informed consent were reviewed and approved by an appropriate human use committee.

Statistical analysis. The baseline subject characteristics were compared using a χ^2 test for sex and race, and 2-tailed Student's t tests for age, weight, height, and pH of gastric aspirate. The distribution of final gastric and duodenal endoscopy scores for the 2 treatment groups were compared using a categorical linear model with mean score response function (SAS®PROC CATMOD[15]); 0.5 was added to each cell. The incidence of lesions (any endoscopy score greater than zero) and adverse experiences in the 2 treatment groups were compared using a χ^2 test. A p value of less than 0.05 was considered significant. No adjustments to the p value were done for multiple testing.

Table 1. *Endoscopy grading scale*

Grade	Finding
0	Normal
1	One submucosal hemorrhage or erosion
2	More than one submucosal hemorrhage or more than one erosion but not numerous or widespread ($\leq$ 10 erosions)
3	Extensive submucosal hemorrhages (throughout stomach and/or duodenum) or numerous areas ($>$ 10) with erosion
4	Widespread erosions with luminal bleeding or invasive ulcer of any size

RESULTS

Study group. Forty-one subjects entered the study, 21 taking salsalate and 20 taking naproxen. One subject taking salsalate was considered noncompliant for ingestion of alcohol in violation of the protocol and was replaced. Therefore, for the purpose of this report, there were 20 subjects in each group for analysis of endoscopic findings. Demographic characteristics for the 2 groups of subjects completing the protocol were similar, as expected in a randomized trial, and are shown in Table 2.

Gastroduodenal mucosal effects. The incidence of subjects with gastroduodenal lesions with naproxen (55%) was significantly ($p = 0.002$) greater than the incidence with salsalate (10%) (Table 3). Eleven of 20 subjects taking naproxen

Table 3. *Incidence of gastroduodenal lesions at final (Day 15) endoscopy*

	No. (%) of Subjects	
	Salsalate (n=20)	Naproxen (n=20)
Normal mucosa (Score = 0)	18 (90)	9 (45)
Gastroduodenal injury (Score >0 for stomach or duodenum)	2 (10)	11 (55)*

* Significantly greater incidence with naproxen by χ^2 test ($\chi^2 = 9.23$, df = 1, $p = 0.002$).

Table 2. *Characteristics of completing subjects*

	Salsalate	Naproxen	Test Statistic*	p Value
No. of subjects	20	20		
Sex:			0.13	0.72
Females (%)	14 (70)	15 (75)		
Males (%)	6 (30)	5 (25)		
Race:			0.78	0.38
White (%)	18 (90)	16 (80)		
Nonwhite (%)	2 (10)	4 (20)		
Age Mean ± SD (yrs)	29.1 ± 4.9	31.7 ± 6.1	−1.46	0.15
Height Mean ± SD (inches)	66.2 ± 3.7	65.1 ± 4.4	0.84	0.41
Weight Mean ± SD (lb)	146.1 ± 25.8	144.9 ± 25.6	0.14	0.89
pH of gastric aspirate Mean ± SD	1.4 ± 0.6	1.7 ± 0.7	−1.35	0.18

χ^2 test with 1 degree of freedom for sex and race; Student's t-test with 38 degrees of freedom for age, height, weight, and gastric pH.

had gastroduodenal lesions at the time of the Day 15 endoscopy. Three subjects taking naproxen had lesions in both the gastric and duodenal mucosae. The remaining 8 subjects taking naproxen had lesions in the gastric mucosa only. Two of the 20 subjects taking salsalate had lesions in the gastric mucosa only. No subjects in either treatment group developed gastric or duodenal ulceration.

When gastric and duodenal mucosae were considered separately, there were significant differences in the incidence and severity of lesions in the gastric mucosa (Figure 1) but not in the duodenal mucosa (Figure 2).

One subject taking salsalate was discontinued from the study after 1 week due to alcohol ingestion. At that time after endoscopy, she was found to have a score of 0 for both the gastric and duodenal mucosae. No other subjects were found to be noncompliant with the requirements of the protocol or with self-administration of study drug.

Adverse experiences. Reports of adverse experiences were elicited at Days 8 and 15. No subject discontinued the study

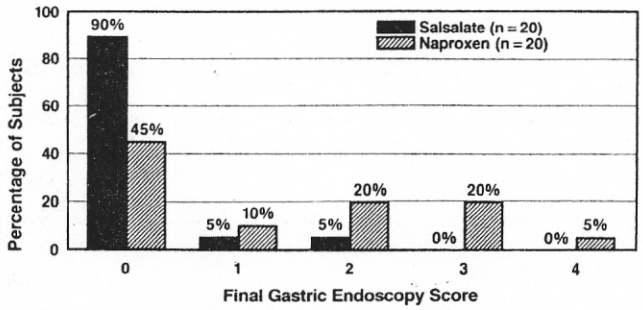

Fig. 1. Distribution of final gastric endoscopy scores. Significant difference between treatments (χ^2 = 8.90, df = 1, p = 0.003).

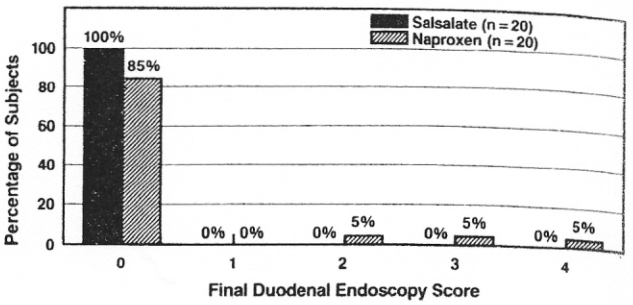

Fig. 2. Distribution of final duodenal endoscopy scores. No difference between treatments (χ^2 = 1.66, df = 1, p = 0.20).

because of adverse experiences and all adverse experiences resolved spontaneously during the study or after drug discontinuation at the completion of study. Twelve of 20 subjects taking naproxen (60%) and 19/21 subjects taking salsalate (90%) reported at least 1 adverse experience during study participation (Table 4). The difference between treatment groups was significant (p = 0.02).

Adverse experiences were grouped by body system (Table 4). Subjects taking salsalate had significantly (p = 0.01) more hearing and vestibular disorders (i.e., reversible tinnitus and hearing loss) than subjects taking naproxen. The profiles of reported adverse experiences were otherwise comparable between the 2 treatment groups.

Adverse experiences relating to the GI system are further described in Table 5. There was no relationship between GI subjective symptomatology and visualized mucosal injury. Only 6/13 subjects that had gastroduodenal lesions reported GI symptoms at the time of the second endoscopy and all had received naproxen. The 2 subjects with the most severe gastric and duodenal lesions did not complain of GI pain.

Table 4. *Adverse experiences by body system during 2 weeks of therapy*

	No. (%) of Subjects*			
Body System**	Salsalate (n=21)	Naproxen (n=20)	Test Statistic***	p Value
Body as a whole	6 (29)	2 (10)	2.25	0.13
Central & peripheral nervous	2 (10)	1 (5)	0.31	0.58
GI	10 (48)	11 (55)	0.22	0.64
Hearing and vestibular	14 (67)	0 (0)	20.25	0.001
Heart rate and rhythm	2 (10)	0 (0)	2.00	0.16
Metabolic and nutritional	1 (5)	0 (0)	0.98	0.32
Psychiatric	5 (24)	2 (10)	1.38	0.24
Respiratory	1 (5)	0 (0)	0.98	0.32
Skin and appendages	2 (10)	1 (5)	0.31	0.58
Vision	1 (5)	1 (5)	0.00	0.97
No. reporting at least 1 adverse experience	19 (90)	12 (60)	5.16	0.023

* No. (percentage) reporting at least once; includes all subjects who received study drug.
** WHO nomenclature[16].
*** χ^2 test with 1 degree of freedom.

Table 5. *GI symptoms*

Symptom	No. (%) of Subjects* Salsalate (n=21)	Naproxen (n=20)	Test Statistic**	p Value
Abdominal pain	4 (19)	3 (15)	0.12	0.73
Constipation	3 (14)	4 (20)	0.24	0.63
Nausea	3 (14)	1 (5)	1.00	0.32
Diarrhea	2 (10)	3 (15)	0.29	0.59
Dyspepsia	2 (10)	1 (5)	0.31	0.58
Flatulence	1 (5)	0 (0)	0.98	0.32
Vomiting	1 (5)	0 (0)	0.98	0.32
Stomatitis	0 (0)	2 (10)	2.21	0.14
No. reporting at least 1 GI symptom	10 (48)	11 (55)	0.22	0.64

* No. (percentage) reporting at least once; includes all subjects who received study drug.
** χ^2 test with 1 degree of freedom.

The only clinically important laboratory changes were elevations of hepatic enzyme levels in 4 subjects in the salsalate group. Three of the 4 subjects had elevations of aspartate transaminase (AST) and alanine transaminase (ALT) only, and it was felt that all 3 of these cases were probably drug related. All enzyme levels returned to normal for these 3 subjects at followup testing 13 to 17 days after discontinuance of the medication. The fourth subject had marked elevations of AST, ALT, and lactic dehydrogenase (LDH). At the completion of the 2 weeks of study, the AST and ALT were 774 IU/l and 534 IU/l, respectively, with an LDH of 603 IU/l. At that time the patient complained of intermittent nausea and moderate abdominal bloating. The symptoms persisted for 8 days after discontinuance of salsalate and hepatic enzyme levels peaked at 9 days after discontinuance of the drug, with AST and ALT levels of 1784 and 1856 IU/l, respectively. Hepatitis antibody profile was negative and other liver function tests (i.e., total bilirubin, alkaline phosphatase, total protein, albumin) were within normal limits. The patient was followed carefully on a weekly basis and 10 weeks after discontinuance of the study drug, all abnormalities had fully corrected and the subject was asymptomatic.

All subjects completing the study in both treatment groups were judged compliant by both tablet count and urinary screening for salicylic acid at Days 8 and 15.

DISCUSSION

Our data support the results seen in normal volunteers in which salsalate was compared with enteric coated aspirin[12]. In that study, only 1/10 subjects taking salsalate developed mild mucosal damage and in the current study, only 2/20 subjects had mild to moderate damage. In the comparison with enteric coated aspirin, salsalate caused significantly less gastroduodenal mucosal damage than the aspirin. It has also been shown in both normal subjects[17,18] and patients[19,20] that enteric coated aspirin is less injurious to the gastroduodenal mucosae than either plain or buffered aspirin. These data suggest that patients treated with salsalate are at less risk for GI mucosal toxicity than patients treated with these available aspirin formulations.

Results of the present study in normal volunteers are also remarkably similar to a study in patients with arthritis in which salsalate was also compared to naproxen[13]. In that study, 18 patients taking salsalate for 3 months showed no evidence of ulceration or diffuse erosions compared with ulceration in 7/21, and diffuse erosions in 1/21 patients taking naproxen. Moreover, since naproxen has also been shown to be an NSAID of only mild to moderate mucosal toxicity in a normal volunteer clinical model[2], salsalate also appears to offer an alternative in patients who demonstrate susceptibility to nonaspirin NSAID toxicity.

Reversible elevation of hepatic enzymes, as seen in 4 salsalate subjects in our study, has been previously observed in controlled clinical trials (unpublished observations). Similar findings have also been associated with aspirin therapy[21].

Although the overall reported adverse experiences were significantly greater with salsalate than with naproxen, the vast majority of this disparity was accounted for by reversible tinnitus or hearing loss seen with salsalate. The incidence of otologic complaints with salsalate in our study was about 2-fold greater than in previous studies (unpublished observations), possibly due to the higher dose used. From the standpoint of reported GI symptomatology, there was no significant difference between the 2 groups. However, the statistical power of this comparison was small since the intent of the study was not to compare incidences of symptoms. With the study sample size the probability of detecting a difference of 20% in the incidence of GI symptomatology was 0.25.

As has been the case in previous studies in both volun-

teers[2] and patients[22], no correlation existed between the subjective GI symptomatology reported by the subjects and the endoscopically observed toxicity. Therefore, it would appear that, unless endoscopic examinations are performed regularly in high risk arthritic patients taking these agents, asymptomatic gastric lesions may remain undetected and possibly increase the risk of progression to hemorrhage or perforation. Our data suggest that reduction of this risk might be accomplished by initial use of agents such as salsalate which appear to be less toxic to the gastroduodenal mucosae. With reversible otologic problems as the most important disadvantage of salsalate, the relative benefit-to-risk indicates this drug should be considered an important alternative NSAID therapy.

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