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Location: SMITH PER

Article Information

Journal Title: J Int Med Res

Volume: 17: **Issue:**
Month/Year: 1989.**Pages:** 320-323.

Article Author: Porro GB, Petrillo M, Ardizzone S.

Article Title: Salsalate in the Treatment of Rheumatoid Arthritis: A Double-Blind Clinical and Gastroscopic Trial versus Piroxicam. II-Endoscopic Evaluation.

Loan Information

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Article Delivery Method: Mail to Address
Loan Delivery Method: Hold for Pickup
Electronic Delivery? Yes

The Journal of International Medical Research 1989; **17**: 320 - 323

Salsalate in the Treatment of Rheumatoid Arthritis: a Double-blind Clinical and Gastroscopic Trial versus Piroxicam. II – Endoscopic Evaluation

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A double-blind, double-dummy controlled study to compare the clinical efficacy and gastric tolerability of salsalate and piroxicam in the treatment of rheumatoid arthritis was performed. A total of 23 patients were treated with 1.5 g salsalate twice daily and 20 with 20 mg piroxicam (after the evening meal) for 4 weeks. Patients were submitted to gastroscopy at the start and end of treatment; only patients who presented a normal baseline gastroscopy were admitted to the trial. At the end of the planned treatment period, a statistically significant improvement of all clinical variables was observed in both treatment groups, the difference between the two drugs not being statistically significant. Five of 20 (25%) piroxicam treated patients and only 2/19 (11%) salsalate treated patients showed gastric lesions at final endoscopy. No relationship was found between dyspeptic symptoms and endoscopic lesions. The results show that salsalate and piroxicam have equal efficacy in relieving arthritic symptoms, but salsalate causes fewer gastric lesions.

KEY WORDS: Salsalate; piroxicam; rheumatoid arthritis; gastroscopy.

Received for publication 3 January 1989; accepted 9 January 1989.

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INTRODUCTION

The salicylates, particularly aspirin, are widely used in everyday clinical practice as non-steroidal anti-inflammatory drugs (NSAIDs), especially in alleviating the symptoms of rheumatic diseases. Despite

their therapeutic efficacy, however, one important drawback is that they produce frequent, and often severe side-effects on the upper digestive tract. Numerous studies have demonstrated that aspirin frequently induces ulcers and/or erosions and causes upper digestive tract haemorrhage.[1-3]

Salsalate is an ester of two molecules of salicylic acid with a clinical efficacy comparable with that of aspirin, but appears to cause less damage to the digestive tract. Studies have been conducted in which intestinal microbleeding was determined by using ^{51}Cr-labelled erythrocytes; 3000 – 5000 mg/day salsalate caused significantly less faecal blood loss than aspirin in various formulations (soluble, enteric coated and intravenous injectable). In this sense its effect is comparable to that of placebo.[4,5]

To date, however, few data comparing salsalate with NSAIDs other than aspirin are available. The present endoscopic study was designed to assess the effects of chronic treatment with salsalate on gastric and duodenal mucosa in patients with rheumatoid arthritis in comparison with piroxicam.

PATIENTS AND METHODS

Patients

The 43 patients admitted to this trial, according to the criteria set out previously,[6] underwent initial upper digestive endoscopy in order to ensure that there were no existing gastric mucosal lesions. Patients were admitted to the trial, only with grades 0 and 1, using an endoscopic rating scale (Table 1). Oral informed consent was obtained.

The following patients were considered ineligible: patients with a history of peptic ulcer, patients with digestive tract bleeding in the previous 6 months, patients receiving anti-ulcer therapy (H_2-antagonists, cytoprotectors) and patients with known hypersensitivity to salicylates.

Administration of therapy

Drug treatment was as described previously.[6]

Evaluation of therapy

At the end of the scheduled treatment period, endoscopy was repeated. Additional endoscopies were performed at any time during the trial in the event of painful dyspepsia lasting at least 48 h and refractory to antacid medication. Endoscopy was always performed by the same person in blind conditions, using an Olympus GIF Q10 direct vision endoscope. 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 grade on the rating scale.

Statistical analysis

Fisher's exact test was used to compare the prevalence of endoscopically detectable lesions in the two treatment groups. In addition, 95% confidence limits were calculated.

Table 1
Endoscopic rating scale for gastric mucosal lesions

Grade	Description
0	Normal mucosa or hyperaemia
1	1 - 3 petechiae, submucosal haemorrhage or erosions
2	≤10 petechiae, submucosal haemorrhage or erosions
3	>10 petechiae, submucosal haemorrhage or erosions
4	Active ulcer

RESULTS

As specified previously,[6] of the 43 patients admitted to the trial, only 39 were included in the final analysis, 19 in the salsalate treated group and 20 in the piroxicam treated group. Four patients in the salsalate treated group spontaneously stopped taking the drug, one because of lack of therapeutic benefit, two because of tinnitus and one because of gastralgia. The post-treatment endoscopy envisaged in the protocol could not be performed in the latter case, as the patient did not contact the Centre in time.

The endoscopic findings are shown in Table 2. Lesions were detected in 2/19 (11%) patients in the salsalate treated group (one grade 2 and one grade 3) and in 5/20 (25%) in the piroxicam treated group (all grade 4: four patients with duodenal ulcer, one with gastric ulcer). This difference was not significant ($P>0.05$, 95% confidence interval -0.14 to $+0.42$).

No correlation was found between the endoscopic results and dyspeptic symptoms. In the salsalate treated group, 7/19 (overall prevalence 37%) complained of gastralgia, four of these presenting grade 0 lesions at final endoscopy and one of each of grades 1, 2 and 3. In the piroxicam treated group, painful dyspepsia was reported by 8/20 patients (overall prevalence 40%), two presenting grade 2 lesions, three grade 1 and three grade 4.

DISCUSSION

To date only one endoscopic study has been performed in patients with rheumatoid arthritis.[7] This compared salsalate doses of 2500 – 4000 mg/day with naproxen at doses of 750 – 1500 mg/day for up to 3 months in 39 patients. At the end of treatment, 0/18 (0%) patients given salsalate presented active lesions, while 8/21 (38%) patients in the naproxen treated group had ulcers (seven patients) or diffuse erosions (one patient) ($P<0.05$).

The present findings show that chronic treatment with salsalate in patients with rheumatoid arthritis is associated with a lower prevalence of endoscopically detectable lesions than piroxicam treatment (11% versus 25%). This difference, however, is not statistically significant, probably only because of the relatively small number of patients included in the trial. It must be emphasized, however, that the lesions found

Table 2
Endoscopic assessment of gastric tolerability after 4 weeks of treatment with 3.0 g/day salsalate and 20 mg/day piroxicam in patients with rheumatoid arthritis

Endoscopic measure	Salsalate (n=19)	Piroxicam (n=20)
Normal mucosa		
Grade 0	15	12
Grade 1	2	3
Total	17/19 (89%)[a]	15/20 (75%)
Pathological mucosa		
Grade 2	1	-
Grade 3	1	-
Grade 4	-	5
Total	2/19 (11%)[a]	5/20 (25%)

[a] $P>0.05$ versus piroxicam treatment (Fischer's exact test).

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treatment with 3.0 g/day
arthritis

iroxicam (*n*=20)
12
3
5/20 (75%)
-
-
5
/20 (25%)

endoscopically in the patients given piroxicam were all grade 4 (active ulcer). In addition, salsalate caused a lower degree of gastric damage than did aspirin. As a matter of fact, in an earlier study by the present group[8] in a series of 26 patients treated chronically with aspirin, ulcers and/or erosions were observed in 13 (50%) patients (versus 11% in the present trial with salsalate).

No real difference was observed in the prevalence of gastro-intestinal symptoms (gastralgia, heartburn) in the two treatment groups. There appeared to be no correlation between the presence of subjective symptoms and endoscopically detectable lesions. This suggests that investigating gastro-intestinal symptoms is of little value in assessing the tissue toxicity of any single NSAID and only of limited use in evaluating the comparative toxicity of several such drugs. It does confirm, however, the need for periodic endoscopic controls of the upper digestive tract in rheumatic patients under chronic NSAID treatment.

In conclusion, salsalate has the same clinical efficacy as piroxicam but appears to cause less gastric irritation. The high frequency of tinnitus observed at the dosage of salsalate employed in this study, however, suggest that further studies are needed with larger groups and different drug dosages. This will help establish the efficacy and gastric safety profile of salsalate.

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