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

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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. Twenty-three patients were treated with 1.5 g salsalate twice daily and 20 with 20 mg piroxicam (taken after the evening meal) for a period of 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. Seven (37%) patients treated with salsalate complained of tinnitus. The results show that salsalate and piroxicam have equal efficacy in relieving the symptoms of arthritis.**

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

## INTRODUCTION

Salsalate is an ester of two molecules of salicylic acid and has been shown to have good analgesic anti-inflammatory activity and appears to be well tolerated by the gastro-intestinal tract. The drug was first synthesized in 1920, but only a few controlled clinical trials regarding its use in rheumatoid arthritis have been undertaken and there have been hardly any controlled endoscopic studies to document its true gastric safety in rheumatoid arthritis patients.[1 – 4]

In the USA, interest in salsalate has recently been revived and a multicentre comparative clinical trial of salsalate and aspirin in the treatment of the symptoms of rheumatoid arthritis showed that the two drugs offered similar efficacy but that the incidence of gastric side-effects was lower

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with salsalate (this was a clinical finding not an endoscopic investigation).[5]

There appear to have been no trials comparing salsalate with new non-steroid anti-inflammatory drugs (NSAIDs). It was, therefore, deemed to be of interest to set up a double-blind controlled trial, including clinical and endoscopic investigation, to compare the efficacy and gastric safety of salsalate and piroxicam in patients with rheumatoid arthritis. Piroxicam was selected as the reference drug as it can be considered one of the most effective new NSAIDs, and has an acceptable safety profile.[6]

## PATIENTS AND METHODS

### *Patients*

A total of 43 patients with stabilized rheumatoid arthritis (according to American Rheumatism Association criteria) were recruited to this study. No patients were allowed steroids or orally administered second-line drugs. Intramuscular gold salts were continued as maintenance therapy. Patients were instructed not to take any analgesics or other NSAIDs during the trial. The clinical characteristics of the patients are given in Table 1.

### *Treatments and study design*

Patients were randomly assigned to two treatment groups: 1.5 g salsalate given twice daily after meals (23 patients), and 20 mg piroxicam given after the evening meal (10 patients). The double-dummy technique was employed to ensure double-blind conditions. All treatments were given orally for 4 weeks.

### *Evaluation of therapy*

The following variables were recorded at baseline and at the end of the trial: Ritchie's index, morning stiffness, grip strength, subjective pain (visual analogue scale)[7] and patients' assessment of the efficacy of therapy (using a four-point rating scale). At the start and end of the trial, routine blood tests were made and gastroscopy was carried out.[8]

### *Statistical analysis*

Wilcoxon's signed-rank sum test and the Kruskal – Wallis test were used for statistical analysis.

## RESULTS

Both groups of patients presented a significant ($P<0.05$) improvement in all variables compared with baseline (Table 2). The between-drug comparison was not significant. Judgement of the efficacy of therapy was good or fair in 15/20 (75%) patients treated with piroxicam and 11/19 (58%) of those given salsalate (Table 3). Four patients in the salsalate therapeutic group stopped treatment before the end of the study: one because of a lack of therapeutic effect, one because of gastralgia and two because of tinnitus. None of the patients given piroxicam withdrew from treatment,

**Table 1**
**The clinical characteristics of the patients entered into this study**

| Treatment | Males/ females | Age (years) | Duration of disease (years) | Anatomical grade[a] I | II | III |
|---|---|---|---|---|---|---|
| 3.0 g/day salsalate | 3/20 | 54.5 (30 – 69) | 2.8 (0.6 – 9) | 6 | 10 | 7 |
| 20 mg/day piroxicam | 5/15 | 53.3 (32 – 70) | 3.9 (0.5 – 10) | 5 | 7 | 8 |

[a]Anatomical grades as defined by Steinbrocken *et al.*[9]

**Table 2**
**Mean±SE values of the clinical variables before and after treatment of the symptoms of rheumatoid arthritis with salsalate or piroxicam**

| | Ritchie index | | Morning stiffness (min) | | Grip strength (mmHg) | | Pain | |
|---|---|---|---|---|---|---|---|---|
| Treatment | Before | After | Before | After | Before | After | Before | After |
| 3.0 g/day salsalate | 19.9 ± 6.3 | 16.3* ± 6.3 | 49.5 ± 26.0 | 35.0* ± 25.8 | 130.6 ± 30.4 | 136.8* ± 31.9 | 5.7 ± 0.8 | 3.8* ± 1.6 |
| 20 mg/day piroxicam | 18.0 ± 7.1 | 13.9* ± 6.8 | 43.5 ± 23.1 | 29.2* ± 25.3 | 146.0 ± 41.3 | 151.0* ± 42.5 | 5.1 ± 0.8 | 3.2* ± 1.4 |

*$P<0.05$ versus baseline.

**Table 3**
**Judgement expressed by patients who completed the trial on the efficacy of therapy with salsalate or piroxicam in treating the symptoms of rheumatoid arthritis**

| Treatment | Good | Fair | Scant | Nil | Total |
|---|---|---|---|---|---|
| 3.0 g/day salsalate | 8 | 3 | 2 | 6 | 19 |
| 20 mg/day piroxicam | 7 | 8 | 4 | 1 | 20 |

although one patient failed to attend the final visit for endoscopy due to personal reasons.

Among the patients who completed the trial, adverse reactions were presented by four (20%) in the piroxicam treatment group (one case of pruritus and three of gastralgia) and 13 (68%) in the salsalate treatment group (one case of pruritus, five of gastralgia and seven of tinnitus) (Table 4). Blood tests made at the start and end of therapy showed no noteworthy changes.

## DISCUSSION

This study confirms that salsalate and piroxicam are both effective in reducing signs and symptoms in patients with rheumatoid arthritis. Comparison of the two drugs showed no significant differences in therapeutic results, but the two treatment groups were different in terms of adverse reactions.

Analysis of the subjective symptoms involving the gastro-intestinal tract shows the difference between the groups (3/20 cases given piroxicam and 5/19 given salsalate). This was contradicted, however, by the endoscopic findings which showed that piroxicam had more harmful gastric effects.[8] This discrepancy between subjective symptoms and endoscopic findings in patients treated with salsalate is discussed further elsewhere.[8]

In the salsalate treatment group, seven patients complained of tinnitus; in two of these patients the symptom was so severe that treatment was stopped (no dose changes were allowed in this study). Tinnitus is an indication that an adequate blood level of

**Table 4**
**Drop-outs and side-effects following treatment of the symptoms of rheumatoid arthritis with salsalate or piroxicam**

| Drop-outs/ side-effect | 3.0 mg/day salsalate ($n$=23) | 20 mg/day piroxicam ($n$=20) |
|---|---|---|
| Dropped out | 4[a] | 0 |
| Pruritus | 1 | 1 |
| Gastralgia | 5 | 3 |
| Tinnitus | 7 | 0 |

[a]One because of lack of therapeutic effect, two because of tinnitus and one because of gastralgia.

salicylic acid has been reached and can be taken as a good clinical pointer that an effective anti-inflammatory dose has been administered. This is not a worrisome side-effect, because it usually disappears promptly on reducing the dose or on suspending therapy. This symptom, however, was not willingly tolerated by the patients of this study and, in fact, gave the affected patients reason to suspend the treatment.

The trial protocol did not include adjusting the dosage or assaying blood levels of salicylic acid. The mean dose of salsalate that was tolerated best could not, therefore, be established. On the basis of the data obtained, it appears that 3 g/day salsalate is a rather high dose for a Mediterranean population comprising people of small stature and low weight. Despite this high dose, however, the drug caused less gastric irritation than piroxicam and, thus, appears to offer good gastro-intestinal tolerability.

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