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A short-term comparative trial of salsalate and indomethacin in rheumatoid arthritis

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Summary

A short-term, double-blind, placebo-controlled crossover study was completed in 15 patients with classical or definite rheumatoid arthritis to compare the antirheumatic activity of salsalate (3 g/day) with placebo and indomethacin (75 mg/day). Subjective and objective assessments showed that both salsalate and indomethacin were significantly superior to placebo. Grip strength was not improved by either of the drugs. Patient preference was in favour of indomethacin, but the difference between it and salsalate was insignificant.

Key words: Salsalate – salicylic acids – indomethacin – anti-inflammatory agents – arthritis, rheumatoid

Introduction

Salsalate (salicylsalicylic acid, disalicylic acid, 'Disalcid'†), synthesized in 1920 as an ester of salicylic acid, is insoluble in water and acid pH and on hydrolysis yields two molecules of salicylic acid. Salsalate has been shown to have significant anti-inflammatory activity[1] and markedly low gastric irritability compared with acetylsalicylic acid or sodium salicylate[1,5] and less occult gastro-intestinal bleeding than with acetylsalicylic acid.[13] Although commercially available in the United States of America as an analgesic in combination with acetylsalicylic acid, it has not received serious attention as an antirheumatic compound.

We wish to report the results of a short-term double-blind controlled trial to assess the antirheumatic activity of salsalate in patients with rheumatoid arthritis and to compare it with indomethacin and placebo.

Material and methods

Eighteen patients, 12 females and 6 males, suffering from 'definite' or 'classical' rheumatoid arthritis[11] entered the study after informed consent. Their ages ranged between 38 and 73 years (mean 56.5 years) and duration of disease ranged from

†trade mark, Riker

0.5 to 36.0 years (mean 11.6 years). All had a component of reducible disease activity as judged by the entry physician. Patients on second-line drugs, and those with hepatic/renal function impairment or a history of peptic ulcer disease or aspirin hypersensitivity were excluded. Before the start of the trial, all anti-inflammatory drugs were withdrawn and patients were allocated to a random treatment sequence of placebo, salsalate, and indomethacin. Each drug was prepared in an identical capsule and was administered 3-times a day for 1 week. Total daily salsalate and indomethacin received were 3 g and 75 mg respectively.

Patients were assessed by the same observer at the beginning of the study and at the end of each treatment period. Patients were required to make daily recordings of duration of morning stiffness (in minutes) and the degree of pain[3] on a prepared proforma which the patient completed. The weighting for the different degrees of pain were as suggested by Lee[7] (0 = nil, 1.5 = mild, 3 = moderate, 6 = severe, and 9 = very severe). Other assessments included articular index of joint tenderness,[10] grip strength in both hands,[6] and the patients' and observer's assessment of progress (5 = poor, 4 = slight improvement, 3 = moderate, 2 = much better, 1 = very much better).[4] At the end of the study, each patient's treatment preference was recorded. Pre-trial and weekly, full blood counts, erythrocyte sedimentation rate, hepatic and renal function tests and faecal occult blood were estimated.

Results

Of the 18 patients who entered the trial, 15 completed the study. Two patients withdrew while on placebo because of severe pain, and 1 on salsalate because of tinnitus.

Response to treatment

Details of observations on subjective and objective assessments are given in Table I.

Table I. Clinical and laboratory data on 15 patients with rheumatoid arthritis treated with placebo, indomethacin, and salsalate: mean ± S.E.M.

Assessment	Placebo	Indomethacin	Salsalate	p value	p value
Morning stiffness (duration in min)	157 ± 4.3	92 ± 3.7	46 ± 10	< 0.05	< 0.005
Pain score	6.9 ± 0.7	5.1 ± 0.8	4.7 ± 0.6	< 0.01	< 0.01
Articular index	27.2 ± 3.4	21.1 ± 3.7	18.0 ± 3.1	< 0.01	< 0.001
Grip strength (mmHg)	193 ± 20	215 ± 22	222 ± 22	N.S.	N.S.
Patients' assessment	3.4 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	< 0.01	< 0.002
Doctor's assessment	3.9 ± 0.3	2.6 ± 0.3	2.4 ± 0.2	< 0.01	< 0.01
Patients' preference (first choice)		7	5		
Erythrocyte sedimentation rate (mm/hr)	36.2 ± 9.1	41.6 ± 12.9	38.1 ± 10.7	N.S.	N.S.

Note: statistical analysis carried out by Student's t-test for paired values. p values in the column on the left refer to analysis between placebo and indomethacin; those in the right column between salsalate and placebo. N.S. = not significant

Both salsalate and indomethacin were significantly better than placebo in all the parameters tested, except grip strength and erythrocyte sedimentation rate. The mean duration of morning stiffness was less with salsalate than with indomethacin. In all other respects, however, there were no significant differences between the two active drugs.

Patient preference

One patient had no drug preference, 2 considered indomethacin and salsalate comparable, 5 considered salsalate to be the drug of first preference, and 7 preferred indomethacin.

Tolerance

Details of the side-effects reported are given in Table II.

Table II. Side-effects reported during the trial

Treatment	Side-effect	Patient No.
Salsalate	Diarrhoea	4
	Pruritus	8
	Tinnitus	11, 12
Placebo	Dyspepsia	4, 16
	Pruritus	8
Indomethacin	Headache	16
	Dyspepsia	16, 17
	Burning in mouth	4

During the study period there was no significant change in haemoglobin, hepatic function or renal function, and occult blood in the stools was negative.

Discussion

In the past, analgesic activity of salsalate has been tested in *combination* with acetylsalicylic acid.[2,9] The present study confirms that the antirheumatic activity of salsalate is comparable to that of indomethacin. Neither of the drugs studied significantly improved grip strength. This is possibly due to the short study period. Also, many of the patients had had their disease for a long period (mean 10.6 years) with destructive changes in the small joints of the hand.

Salsalate, therefore, seems to have significant antirheumatic activity. The reported lower incidence of gastric bleeding[8] and gastric erosion[5] compared with acetylsalicylic acid may merit its use as a preferable first-line drug for some patients. Furthermore, in view of the apparently slow absorption and rise in plasma concentration of salicylate following salsalate in combination with aspirin,[12] it would be worthwhile to observe the relative efficacy of salsalate in terms of its antirheumatic/anti-inflammatory activity and toxicity, if any, in long-term studies. As salsalate may well be used for the prolonged treatment of rheumatoid arthritis, it would be useful to

have information on salicylate plasma levels during long-term administration. Such studies are now in progress, as are comparisons of long-term clinical tolerance with other first-line non-steroidal anti-inflammatory analgesics.

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