Clinical evaluation of niflumic acid (Squibb) in rheumatoid arthritis

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Summary

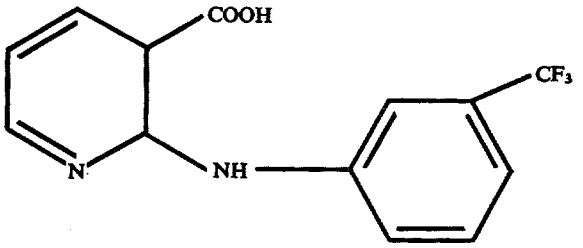
The effect of 750 mg. of niflumic acid per day administered orally was studied in 15 patients with active rheumatoid arthritis in a double-blind cross-over trial. The patients were followed over a 2-week period with 3 assessments of joint pain and tenderness, duration and severity of morning stiffness, digital joint circumference, grip strength and radioactive pertechnetate (99m Tc) knee and wrist joint uptakes.

The results show that niflumic acid was more effective in relieving pain than placebo. Anti-inflammatory effects could not be demonstrated.

Key words: Arthritis, rheumatoid – niflumic acid – radioisotope scanning

Niflumic acid is a new, non-steroidal anti-inflammatory analgesic, which is a derivative of nicotinic acid. Chemically it is designated trifluoromethyl-3-phenylamino-2-nicotinic acid and its structural formula is shown in Fig. 1. The molecular formula is C_{13} H_9 O_2 N_2 F_3 and the molecular weight is 282.1. Animal studies have demonstrated considerable anti-inflammatory and analgesic activity and a slight antipyretic effect.[1,2]

Figure 1. Structural formula of niflumic acid



Several clinical studies of niflumic acid have been reported in a number of different rheumatic diseases.[3-8] In none of the papers, however, was the drug compared with placebo. The object of the present study, therefore, was to compare the analgesic and anti-inflammatory action of niflumic acid with placebo in patients with active rheumatoid arthritis.

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Methods

All 15 patients taking part in this trial had 'definite or classical' rheumatoid arthritis according to the criteria of the American Rheumatism Association.[9] Their mean age was 55 ± 2.2 years, with a range of 42 to 72 years. There were 5 male and 10 female patients. Nine of the patients had subcutaneous nodules present and all 15 patients had Grade III X-ray changes.[10] The mean duration of arthritis was 10.5 ± 2.6 years, with a range of 1.5 years to 35 years. The average functional capacity[10] was 2.13 ± 0.16. Two of the patients had keratoconjunctivitis sicca.

A record was taken of past and current antirheumatic therapy. None of the patients previously had or was receiving corticosteroid therapy. Any known drug allergies were noted.

Patients with a recent diagnosis of an active peptic ulcer, regional enteritis, ulcerative colitis, or evidence of bleeding from the gastro-intestinal tract, renal or hepatic disease, were excluded from the study, as were women of child bearing age. All patients agreed to participate in this study after a full explanation of its content and implications.

The design of the trial was that of a double-blind cross-over. All current therapy was discontinued 7 days before starting the trial, after which patients were randomly allocated niflumic acid or placebo, with the cross-over taking place after 7 days. The dosage of niflumic acid administered was 250 mg., by mouth, 3 times a day. The patients' subjective impression of pain was recorded as a scale of 0 to 4 (0 = no pain, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). The degree of morning stiffness was assessed on a similar scale and the duration of morning stiffness was established in minutes.

The patient's own assessment of general progress was calculated from a scale 0 to 4 (where 0 = total remission, 1 = excellent, 2 = considerable, 3 = moderate, and 4 = slight remission). An assessment of the patient's progress was also made by the physician employing the same scale.

An articular index[12] of joint tenderness was performed and grip strength was estimated in each hand as the mean of 3 grip strength values using a rolled sphygmomanometer cuff with an initial reading at a basal level of 30mm.Hg.[13] The circumference of the proximal interphalangeal joints of the fingers and the interphalangeal joints of the thumbs were measured on each hand using the plastic spring apparatus supplied by Geigy Limited.[14]

In addition, radioactive technetium studies were performed at the commencement of the study and also at each later assessment. A slight modification of the procedure described by Dick and his colleagues[15,16] was used. Approximately 200μ Ci of 99m Tc (as sodium pertechnetate) was standardized by counting for 2 minutes at 30 cms., using a thallium activated sodium iodide scintillation crystal and photomultiplier. The pulses were fed through a pulse height analyser (EKCO M5050) and digital rate meter (EKCO M5183A) and read from the latter. Thereafter, the dose was injected intravenously into an antecubital vein, great care being taken to ensure no extravasation of the dose at the time of injection. At 15 minutes

after injection, counting was performed over both knees and both wrists (always ensuring that each joint was measured in the same order on each occasion). Each count lasted 2 minutes. The scintillation counter was positioned 2.5 cms. above the joint being examined and counts over the joints were expressed as a percentage of the administered dose.

Statistical analysis of the results obtained was carried out employing Student's t-test for paired samples.

Results

The results are shown in Table I.

Table I. Clinical laboratory data after 250 mg. niflumic acid 3-times daily

Assessment		Pre-trial assessment	Placebo week	Niflumic acid week	t	p
		Mean ± SEM	Mean ± SEM	Mean ± SEM		
Pain level		2.8 ± 0.2	2.1 ± 0.3	1.5 ± 0.2	2.59	<0.025
Morning stiffness		3.0 ± 0.2	2.21 ± 0.26	1.8 ± 0.2	1.33	N.S.
Duration of morning stiffness (mins.)		132.7 ± 33.8	140.7 ± 47.1	95.3 ± 29.6	1.6	N.S.
Patient's assessment		4.2 ± 0.2	3.2 ± 0.3	1.9 ± 0.2	5.08	<0.001
Physician's assessment		4.2 ± 0.2	3.14 ± 0.3	1.8 ± 0.2	3.65	<0.005
Articular index		20.8 ± 2.6	18.7 ± 2.3	13.7 ± 1.8	3.28	<0.005
Grip strength	Right	101.3 ± 11.7	99 ± 7.1	122.2 ± 11.3	2.8	<0.02
	Left	96.5 ± 8.3	100.1 ± 8.4	109.2 ± 10.7	1.65	N.S.
Joint circumference (cms.)	Right	289.9 ± 6.5	288.7 ± 6	289.8 ± 6.3		N.S.
	Left	284.7 ± 7.6	282.5 ± 7	282 ± 6.2		N.S.
Technetium studies (% uptake) knee	Left	185.6 ± 18.2	168.9 ± 19.8	161 ± 16.7	0.78	N.S.
	Right	180.2 ± 20.5	170 ± 16	161 ± 13.6	0.97	N.S.
Wrist	Left	212 ± 19.5	280 ± 33	256 ± 21	0.26	N.S.
	Right	398 ± 50	374 ± 35	340 ± 24	0.74	N.S.

Note: SEM = Standard error of the mean. N.S. = not significant

It will be seen that there was a highly significant improvement in the pain scores, and in the patients' as well as the physician's assessment of overall improvement. The articular index and the grip strength in the right hand also showed significant improvement. Joint circumference measurement and 99m Tc uptake of the left wrist showed no significant change with treatment.

In the remainder of the parameters tested there was a tendency towards improvement, but the differences did not reach statistical significance.

Discussion

This study was designed to answer the simple question whether niflumic acid had analgesic and anti-inflammatory effects in patients with rheumatoid arthritis. The

design of the study was simple, and the results show clearly significant improvement with niflumic acid compared with placebo in patients' assessment of their pain and overall well-being, the physician's assessment of the patient's progress, the articular index of joint tenderness, and grip strength in the right hand. Morning stiffness showed improvement both in duration and severity with niflumic acid, but the differences were not significant. Grip strength improved in the left hand, but again the differences were not statistically significant. These results indicate that the drug has analgesic properties in rheumatoid arthritis.

The problem of assessing an anti-inflammatory effect in patients with rheumatoid arthritis is bedevilled by the lack of sensitive indices.[17] No change was recorded in digital joint circumference, but it should be noted that the patients were selected on the basis of persistent pain in their joints, and not because they had soft-tissue swelling in their finger joints. Much of the swelling in the small joints of the fingers in rheumatoid arthritis can be due to other than soft-tissue swelling, and this, of course, will not be reduced by an anti-inflammatory drug.[14] Consequently, because no change was observed in reduction of digital joint circumference, it cannot be concluded that the drug has no anti-inflammatory action. Similarly, it cannot be concluded that the drug has no anti-inflammatory action because no statistical difference in joint 'uptake' of 99m Tc could be demonstrated. However, it is noteworthy that both knee and wrist joints showed a reduction of 99m Tc uptake with niflumic acid compared to placebo. Clearly further studies are indicated to determine whether the drug has an anti-inflammatory action in rheumatoid arthritis.

The conclusions of this study are that niflumic acid has an analgesic effect superior to placebo in an oral dose of 750 mg. daily in patients with rheumatoid arthritis. Further clinical therapeutic trials are now clearly indicated to compare niflumic acid with other standard antirheumatic agents such as aspirin. The anti-inflammatory effects of the drug remain to be demonstrated.

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