Orudis in the Management of Osteo-arthritis of the Knee

A DOUBLE-BLIND TRIAL

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SUMMARY

A controlled double-blind crossover trial of Orudis, a non-steroid anti-inflammatory drug, has been carried out in 98 patients with osteo-arthritis of the knee. The new preparation was tested against placebo (27 patients), paracetamol (42 patients) and acetylsalicylic acid (29 patients). It showed statistically significant superiority over placebo ($P<0,05$). Compared with paracetamol, the over-all results showed a marked trend in favour of Orudis, though this did not reach statistical significance ($0,1>P>0,05$). On the principal criteria for assessment there was no significant difference between Orudis and high-dosage salicylate ($P<0,05$); most of the patients, however, favoured the former.

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The use of systemic or intra-articular anti-inflammatory agents for the treatment of osteo-arthritis of the knee is based on the belief that the symptoms are in some measure due to an associated synovitis. The arthritic knee joint, moreover, is not nearly as amenable to reconstructive or replacement surgery as the hip joint; the result is that, as long as the joint remains stable, osteo-arthritis of either the patellofemoral or the tibiofemoral compartments is frequently managed by long-term analgesic and anti-inflammatory therapy. If this is to be the treatment of choice, the need for a drug with clear-cut anti-inflammatory and analgesic properties, unaccompanied by intolerable side-effects, is manifest.

Previous studies have shown that Orudis, 2-(3-benzoylphenyl) propionic acid, has marked anti-inflammatory and analgesic activities in experimental animals,[1] is well tolerated by man, and is therapeutically useful in the management of rheumatoid arthritis and osteo-arthritis of the hip.[2-4] In the present article we report the results of a controlled therapeutic trial of Orudis in 98 patients with osteo-arthritis of the knee.

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METHODS

Trial Design

Orudis was tested against three separate preparations: placebo, paracetamol and acetylsalicylic acid. It was intended that this should establish not only the over-all efficacy of the drug, but its relative potency in comparison with (*a*) a simple analgesic, and (*b*) a known anti-inflammatory agent.

In each section of the trial a double-blind crossover technique was used, the same patient having one week of treatment with each drug in turn. Assessments were carried out at the beginning of the trial and again after each 7-day treatment period. The results were plotted on a sequential analysis chart, only positive preferences for one or other drug being recorded.

Patients

Ninety-eight patients with osteo-arthritis of one or both knees completed the trial. There were 81 women and 17 men; their ages ranged from 28 to 78 years, the average being 53 years. The diagnosis of osteo-arthritis was established by a combination of clinical features, such as pain, tenderness, thickening of the joint margins, crepitus on movement and restricted mobility, together with the accepted radiological criteria of degenerative arthritis.[5] Excluded from the trial were pregnant women, patients with dyspepsia, hiatus hernia and peptic ulceration, patients with known intolerance to salicylates, and those with clinically obvious instability of the knee.

The distribution of patients in the 3 trial groups is shown in Table I.

TABLE I. DISTRIBUTION OF PATIENTS IN THE 3 TRIAL GROUPS

Trial group	Orudis during first period	Orudis during second period	Total
Orudis *v.* placebo	**14**	**13**	**27**
Orudis *v.* paracetamol	**20**	**22**	**42**
Orudis *v.* salicylate	**15**	**14**	**29**

Drug Administration

The two medications in each trial group were presented in identical form and administered in divided doses after meals. The daily dose of Orudis was 200 mg, of paracetamol 6 g, and of acetylsalicylic acid 5 g.

The order of drug administration was determined from tables of random numbers. After a 'wash-out' period during which the patient received no medication, each drug was given for 7 consecutive days, the crossover occurring without any further 'wash-out' period. No other analgesic or anti-inflammatory preparations were permitted during the trial; those patients who failed to adhere to the routine were excluded from the final assessment.

Assessment

Assessment was based on 5 principal criteria: (*a*) the degree of pain; (*b*) stiffness; (*c*) joint tenderness, all graded as 0 - 3; (*d*) maximum joint circumference; and (*e*) strength of knee extension from 90°, measured in kg with a specially constructed calibrated spring gauge.

The same investigator completed each trial period; his preference for either of the two coded medications used in the patient was established by a simple majority of the principal criteria in favour of one or other drug. Overall superiority of one drug over another was indicated by an appropriate breakthrough on the sequential analysis chart. In addition, each patient was asked to express his own subjective preference for either of the two medications. Details of side-effects were carefully recorded after each medication period.

RESULTS

Orudis versus Placebo

Twenty-seven patients completed this section of the trial; 14 received Orudis during the first week and placebo during the second, while 13 received placebo as the first and Orudis as the second drug.

The investigator's preference, based on a combination of the 5 principal criteria, is represented in the sequential analysis chart (Fig. 1). Orudis showed a statistically significant superiority over placebo ($P<0,05$). In 5 instances no difference was detected in the response to the two drugs. Of the remaining 22 patients, 18 showed greater improvement on Orudis than on placebo.

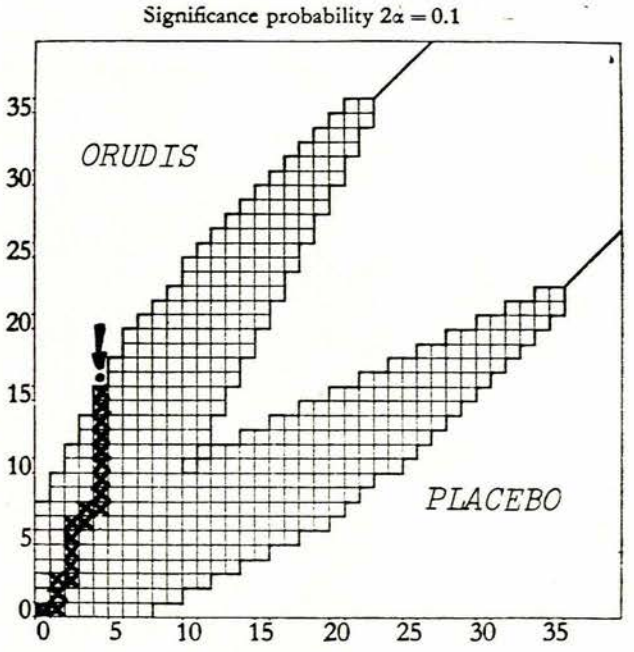

Fig. 1. Sequential analysis. Orudis shows statistically significant superiority over placebo ($P<0,05$).

The patients' subjective preferences also favoured Orudis, though the difference here was not as marked as indicated above; 15 preferred Orudis, 10 preferred placebo and 2 expressed no preference for either.

Four patients complained of side-effects while being

treated with Orudis: 2 experienced dizziness and 2 had episodes of excessive sweating, which was accompanied in one case by nausea. One patient complained of headaches during the placebo treatment period.

Orudis versus Paracetamol

This section of the trial was continued through a total of 42 patients, at which point a break-through occurred on the sequential analysis chart in favour of Orudis, but with a reduced significance probability (Fig. 2).

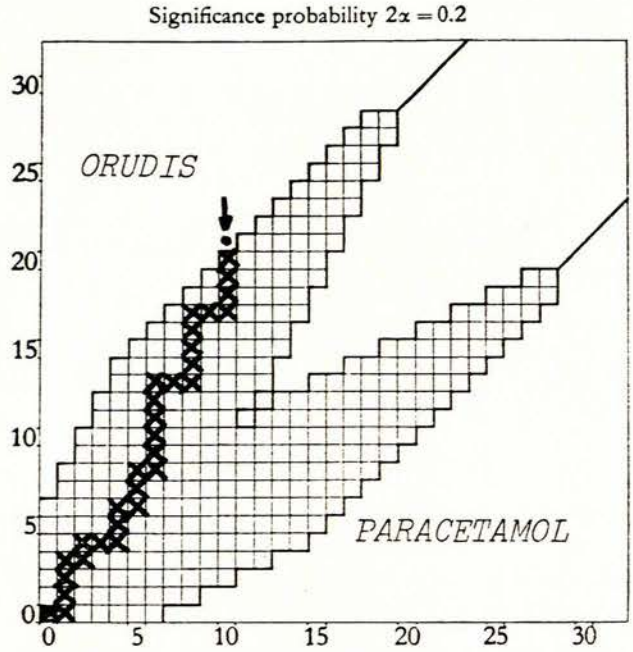

Fig. 2. Sequential analysis. Orudis *v.* paracetamol. There is a strong trend in favour of Orudis, though this does not reach statistical significance ($0,1>P>0,05$).

This indicated that there was a trend in favour of Orudis, though this did not achieve statistical significance ($0,1>P>0,05$). In 20 cases Orudis was taken during the first week, and in 22 cases paracetamol was taken first.

The patients' subjective preferences in this section of the trial paralleled the investigator's preference almost exactly; 25 preferred Orudis, 12 preferred paracetamol, and 5 expressed no particular preference.

Eight patients complained of side-effects while receiving Orudis. Usually this consisted of mild dizziness or tiredness; 2 patients experienced nausea and 2 had slight dyspepsia. Eleven patients had side-effects while on paracetamol; among the complaints were headaches (2 cases), nausea (2 cases), abdominal cramps (2 cases), lassitude and anorexia.

Orudis versus Acetylsalicylic Acid

After 29 patients had completed this part of the trial, the central barrier of the sequential analysis chart was pierced, indicating no significant difference between the two drugs on the basis of the 5 principal criteria for assessment ($P<0,05$). Fifteen patients had received Orudis as the first medication and 14 had received salicylate as the first medication.

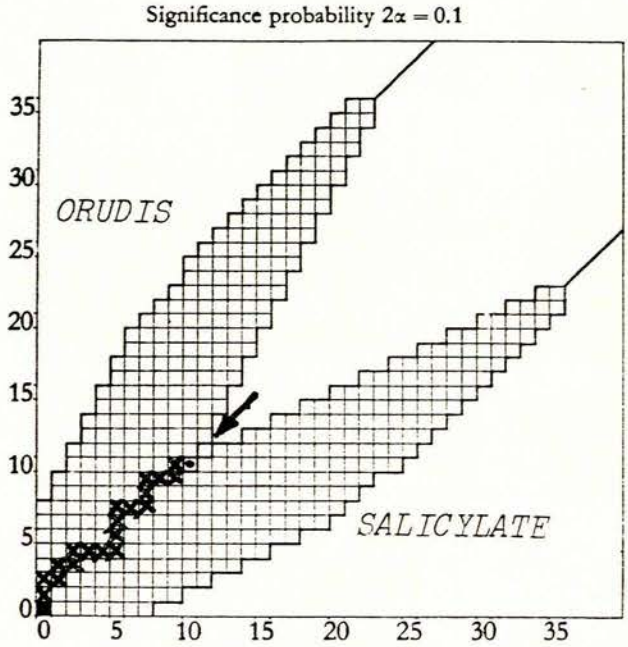

Fig. 3. Sequential analysis. Orudis *v.* salicylate. There is no appreciable difference between the responses to these two drugs ($P<0,05$).

Orudis and salicylate showed superior effectiveness over each other in an equal number of cases (11 patients each); in the remaining 7 patients there was no difference in response during the two treatment periods. Subjective preferences, however, favoured Orudis in 17 cases, salicylate in 10, and neither drug in 2 instances.

Nine patients developed side-effects while on Orudis; 4 had some degree of nausea and 2 had moderately severe dyspepsia. Seventeen patients experienced side-effects while receiving salicylates; 6 of these had gastro-intestinal symptoms, and 3 complained of tinnitus or deafness.

DISCUSSION

Purely objective criteria for the assessment of the patient's response to the treatment of a painful osteo-arthritis are not only difficult to attain but may be quite unrealistic as a practical guide to therapy. A diminished awareness of pain will favourably influence such objective parameters as stiffness, and even muscular power, while the most impressive response to medication may be mitigated by the occurrence of intolerable side-effects.

In the present trial more weight was given to over-all responses than to isolated changes, and in addition the patients' personal preferences were recorded without critical analysis. The results suggest that Orudis has therapeutic properties superior to those of paracetamol,

and similar to those of salicylate in high dosage. The patients themselves, however, favoured Orudis above salicylate, doubtless because the efficacy of the latter was to some extent offset by its unpleasant side-effects.

Altogether 21 of the 98 patients complained of side-effects while being treated with Orudis (Table II). In only 5 cases, however, were these described as severe: 1 patient complained of excessive drowsiness, and 1 of profuse sweating, 1 of dizziness and 2 of dyspepsia. In no case did these symptoms cause the patient to stop taking Orudis.

TABLE II. SIDE-EFFECTS OF ORUDIS (98 PATIENTS)

Side-effects	No. of patients
No side-effects	77
Dizziness	4
Nausea	7
Dyspepsia	4
Sweating	2
Drowsiness	4
Insomnia	2
Slight diarrhoea	2

It still remains to be shown whether the superior therapeutic effects of salicylate and Orudis are due to anti-inflammatory activity or to purely analgesic activity. Both drugs appeared to be capable of reducing knee-joint swelling, salicylate somewhat more effectively than Orudis (Table III): while this occurred also in some patients after taking paracetamol (3 cases), and even after placebo (1 case) it was uncommon and invariably of small degree.

TABLE III. NUMBER OF PATIENTS SHOWING A REDUCTION IN JOINT CIRCUMFERENCE AFTER TREATMENT WITH ORUDIS OR SALICYLATE

Response to treatment	Orudis	Salicylate
Reduced joint size after first week of treatment	3	7
Reduced joint size after second week of treatment	5	3

It is probable, therefore, that the effect of Orudis in osteo-arthritis of the knee is due, at least in part, to anti-inflammatory activity, and this would account for its superior behaviour over a simple analgesic like paracetamol.

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