Orudis in Management of Rheumatoid Arthritis and Osteoarthrosis of the Hip: Comparison with Indomethacin

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Summary

In double-blind cross-over studies in 46 patients with rheumatoid arthritis and in 42 patients with osteoarthrosis of the hip, Orudis—a new non-steroidal anti-inflammatory agent—has been shown to be well tolerated and to have comparable therapeutic efficacy with indomethacin when given in equal dosage. Side effects were less severe with Orudis. The results suggest that Orudis will prove valuable in the clinical management of rheumatic diseases.

Introduction

A major problem in the management of inflammatory and degenerative arthritis has been to find an anti-inflammatory analgesic drug which combines potency with safety. Thus the well-established agents in current use, including salicylates, corticosteroids, phenylbutazone, and indomethacin, have ulcerogenic properties as well as other serious toxic or side effects, while the efficacy of other, safer drugs such as ibuprofen has been questioned (Hart, 1972; Owen-Smith and Burry, 1972). Orudis, 2-(3-benzoylphenyl) propionic acid, is well tolerated by patients and has a very low incidence of side effects and toxic reactions (Cathcart *et al.*, 1972; Gomez, 1972; Mason *et al.*, 1972); in particular, overt gastrointestinal bleeding has not been reported. Laboratory studies have shown its potency as an anti-inflammatory agent in animals (Julou *et al.*, 1971), and recent double-blind cross-over studies against placebo have shown it to have great potency in man (Cathcart *et al.*, 1972; Mason *et al.*, 1972). The current studies were designed to compare Orudis with an established non-steroidal anti-imflammatory agent, indomethacin, in the management of rheumatoid arthritis and osteoarthrosis of the hip.

Method

Study 1 comprised 50 patients with classical or definite rheumatoid arthritis, as defined by the American Rheumatism Association criteria (Ropes *et al.*, 1959), who had not received systemic or intra-articular corticosteroid therapy, gold, or immunosuppressive therapy during the four weeks preceding the trial.

Study 2 comprised 44 patients with osteoarthrosis of the hip, the diagnosis satisfying the following criteria: (1) pain and limitation of range of movement in one or both hip joints, and (2) at least three out of four radiological features of osteoarthritis in one or both hip joints—(*a*) narrowing of joint space, (*b*) subchondral sclerosis, (*c*) osteophytosis, (*d*) deformity of the femoral head. Patients with protrusioacetabulae, gout, Paget's disease, or rheumatoid arthritis were excluded.

Children, women of child-bearing age in whom the possibility of pregnancy could not be excluded, patients with gastrointestinal or liver disease, and patients known to be intolerant of indomethacin were excluded from participation in both sections of the trial.

A double-blind cross-over technique was used, patients receiving two weeks' treatment with each trial drug in turn, the sequence being determined by random allocation. Drugs were supplied in capsules of identical appearance containing 25 mg of active agent, one capsule being taken four times daily with meals. Patients were given a measured supply of paracetamol tablets (0·5 g) to be used only for control of severe pain. All other antirheumatic and analgesic therapy was stopped at the time of the initial assessment.

All assessments were made by the same observer at the start of the trial, at two weeks, and again at four weeks, according to the following criteria.

Study 1.—Subjective assessments were based on answers to agreed standard questions. Severity of pain (nil, slight, moderate, severe, very severe), functional grading (modified after Steinbrocker *et al.* (1949), grade II being subdivided into two categories of severity of disability), global assessment of current clinical state (very poor, poor, fair, good, very good), and comparative global assessment (much worse, worse, unchanged, better, much better) were scored on a five-point scale grading severity of disease from 0 to 4. Duration of morning stiffness (more than 3 hours, 1-3 hours, less than 1 hour, nil) was based on a 0 to 3 scale. At the end of the trial patients were asked to state a preference for the treatment given. Objective assessments were of grip strength (based on the mean of three measurements obtained from each hand with the bag inflated to 30 mm Hg), articular index (Ritchie *et al.*, 1968), and joint size (Boardman and Hart, 1967). The number of paracetamol tablets used (rescue-drug count) provided an indication of the relative efficacy of study and reference drugs in suppressing pain.

Study 2.—Subjective assessments were based on answers to agreed questions. Severity of overall pain, night pain, and morning pain, functional grading, global assessment of current clinical state, and comparative global assessment were based on a five-point scale as for study 1, and, similarly, patients were asked to state a preference for one of the two treatments given. Objective assessments were of intermalleolar straddle and intercondylar distance (Owen-Smith and Burry, 1972), and were recorded as the mean of measurements taken when first pain started and at maximum displacement tolerated by the patient. The rescue-drug count, as with study 1, provided an indirect objective assessment.

In both studies all medicine containers were returned at the end of each treatment period, any remaining capsules and tablets were counted, and the number taken during the trial was calculated.

Side effects were noted at each assessment in response to the questions: Has the treatment upset you in any way during the past two weeks? If yes, in what way?

Laboratory investigations undertaken at each assessment were: full blood count, E.S.R. (Westergren), plasma alkaline phosphatase, bilirubin, urea, aspartate transferase, serum hydroxybutyric dehydrogenase, and urine analysis.

Results

Forty-six patients with rheumatoid arthritis completed the trial (Table I). Of the four patients excluded from the analysis two developed exacerbation of symptoms, one during the Orudis

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treatment and the other when on indomethacin, and two were withdrawn after administrative errors. Side effects were experienced by 22 patients—in 4 cases only when on Orudis, in 5 only when on indomethacin, and in 12 when on both drugs. The results are summarized in Tables II and III.

Of the patients with osteoarthrosis 42 completed the trial (Table IV). Two others were excluded—one developed exacerbation of symptoms during treatment with Orudis and one took aspirin in addition to the trial drug and paracetamol. Altogether 15 patients had side effects—3 only when on Orudis, 7 only when on indomethacin, and 5 when on both drugs. The results are summarized in Tables V and VI.

TABLE I—*Details of the 46 Patients with Rheumatoid Arthritis who Completed the Trial*

Trial Drug Sequence	No. of Patients			Age (Years)		Duration of Illness (Years)		
	M.	F.	Total	Range	Mean	<1	1-5	>5
Indomethacin/Orudis	10	12	22	34-74	56	0	9	13
Orudis/indomethacin	8	16	24	32-71	58	0	11	13

TABLE II—*Drug Preference and Subjective Assessment of Condition among the 46 Patients with Rheumatoid Arthritis Completing Trial*

	No Improvement or Drug Preference	Patients Preferring Orudis	Patients Preferring Indomethacin	P Value
Pain	27	8	11	N.S. (0·65)
Duration of morning stiffness	27	7	12	N.S. (0·36)
Current clinical state	22	11	13	N.S. (0·84)
Comparative clinical state	13	14	19	N.S. (0·49)
Functional dependency	26	8	12	N.S. (0·50)
Overall drug preference	5	23	18	N.S. (0·63)

N.S. = Not significant.

TABLE III—*Observer Assessment of Results in the 46 Patients with Rheumatoid Arthritis according to Subjective Drug Preference. Mean Values given*

	Preferred Drug		P Value
	Orudis	Indomethacin	
Total grip strength of both hands (mm Hg)	318	319	N.S. (0·80)
Articular index	18·01	16·51	N.S. (0·30)
Joint size	589	588	N.S. (0·50)
Rescue-drug count (No. taken)	40	34	<0·05

N.S. = Not significant.

TABLE V—*Drug Preference and Subjective Assessment of Condition Among the 42 Patients with Osteoarthrosis Completing Trial*

	No Improvement or Drug Preference	Patients Preferring Orudis	Patients Preferring Indomethacin	P Value
Overall pain	19	8	15	N.S. (0·21)
Night pain	17	12	13	N.S. (1·00)
Morning pain	13	12	17	N.S. (0·35)
Current clinical state	15	12	15	N.S. (0·7)
Comparative clinical state	13	10	19	N.S. (0·14)
Functional dependency	29	2	11	<0·004
Overall drug preference	6	17	19	N.S.

N.S. = Not significant.

TABLE VI—*Observer Assessment of Results in the 42 Patients with Osteoarthrosis according to Subjective Drug Preference. Mean Values given*

	Preferred Drug		P Value
	Orudis	Indomethacin	
Intermalleolar straddle	133	134	N.S.
Intercondylar distance	83	84	N.S.
Rescue-drug count (No. taken)	30	28	N.S.

N.S. = Not significant.

Results from the two trials showed that there was little difference between the two drugs, the only variables—out of 20 investigated—in which differences reached statistically significant proportions were in respect of the number of paracetamol tablets taken for pain relief in the rheumatoid arthritis trial ($P < 0.05$) and the changes in functional dependency in the osteoarthrosis trial ($P < 0.004$). Both these results favoured indomethacin. Significant improvement in functional dependency was seen only in the group starting treatment with indomethacin, and was absent in the group taking the drugs in the reverse order. Since the two treatment groups were not well matched with regard to functional dependency, in that the group taking indomethacin first contained fewer patients in the more severely incapacitated grades, it seems likely that the result was related to this disparity.

Despite the fact that patients known to be intolerant of indomethacin were excluded from the trial side effects were more frequent with indomethacin and tended to be more severe, particularly with regard to symptoms referable to the central nervous system (Table VII). In no case, however, were they sufficiently severe to warrant stopping treatment.

Biological Monitoring.—In a number of instances with either drug the serum hydroxybutyric dehydrogenase concentration became increased above the normal range. These changes were not associated with change in bilirubin, alkaline phosphatase, or aspartate transferase concentration, and probably were not significant. Significant changes did not occur elsewhere.

TABLE VII—*Incidence of Symptoms Developing in 94 Patients* Admitted to Rheumatoid Arthritis and Osteoarthrosis Studies*

Symptoms	Orudis	Indomethacin
Dyspeptic:		
Epigastric discomfort: Transient or mild	2	1
Epigastric discomfort: Prolonged or severe	—	1
Nausea	4	6
Vomiting	—	2
Indigestion, regurgitation, flatulence, distension	7	3
Hunger, anorexia	—	2
Diarrhoea, loose stools	3	8
Constipation	1	1
Sore tongue, mouth ulcers, dry mouth	4	3
Total	21	27
Central nervous system:		
Headache: Transient or mild	—	8
Headache: Prolonged or severe	—	4
Lethargy, fatigue, tiredness, malaise	2	3
Dizziness, giddiness, "woolly" head	1	5
Depression, irritability	3	2
Forgetfulness	1	—
Total	7	22
Others:		
Weight gain	2	4
Sweating, mild impotence, facial pain, facial rash, bruising, puffiness of foot	4	2
Total	6	6
Grand total	34	55

*Including patients withdrawn from the trials.
Symptoms were absent in 51 patients.

TABLE IV—*Details of the 42 Patients with Osteoarthrosis who Completed the Trial*

Trial Drug Sequence	No. of Patients			Age (Years)		No. with Both Hips Involved	No. with One Hip Involved	Duration of Illness (Years)		
	M.	F.	Total	Range	Mean			<1	1-5	>5
Indomethacin/Orudis	10	12	22	42-81	64	17	5	1	14	7
Orudis/indomethacin	10	10	20	30-80	65	12	8	0	14	6

Discussion

Studies conducted elsewhere in the United Kingdom (Cathcart *et al.*, 1972; Gomez, 1972; Mason *et al.*, 1972) have indicated that in the dosage used in the present study Orudis is well tolerated, causes only occasional and minor side effects, and has statistically significant superiority ($P < 0.01$) in anti-inflammatory and analgesic activity when compared with placebo.

Indomethacin is a powerful anti-inflammatory and analgesic drug (Percy *et al.*, 1964; Hart and Boardman, 1965; Thompson and Percy, 1966), its principal disadvantage being a relatively high incidence of side effects.

The present studies suggest that in equal dosage clinical efficacy of Orudis is comparable with that of indomethacin. The results marginally favour the latter drug but side effects were less severe with the former. Preliminary results from studies with higher dosages of Orudis (Gomez, 1972; Mason *et al.*, 1972) indicate that 150 mg daily is well tolerated. This finding considered together with the above results suggests that Orudis is likely to have an important part to play in the clinical management of rheumatic disease.

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References

Boardman, P. L., and Hart, F. D. (1967). *British Medical Journal*, **4**, 264.
Cathcart, B. J., Vince, J. D., Gordon, A. J., Bell, M. A., and Chalmers, I. M. (1972). In press.
Gomez, G. (1972). Personal communication.
Hart, F. D. (1972). *Practitioner*, **208**, 10.
Hart, F. D., and Boardman, P. L. (1965). *British Medical Journal*, **2**, 1281.
Julou, L., *et al.* (1971). *Journal de Pharmacologie*, **2**, 3, 259.
Mason, R. M., Zutshi, D. W., Marr, S., and Bloch, M. (1972). Personal communication.
Owen-Smith, B. D., and Burry, H. C. (1972). *Rheumatology and Physical Medicine*, **2**, 281.
Percy, J. S., Stephenson, P., and Thompson, M. (1964). *Annals of Rheumatic Diseases*, **23**, 226.
Ritchie, D. M., *et al.* (1968). *Quarterly Journal of Medicine*, **37**, 393.
Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. (1959). *Annals of Rheumatic Diseases*, **18**, 49.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *Journal of the American Medical Association*, **140**, 659.
Thompson, M., and Percy, J. S. (1966). *British Medical Journal*, **1**, 80.

Hypercalcaemia, Hypophosphataemia, and Inability to Excrete Hydrogen Ions

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Summary

Investigation of a patient with hypercalcaemia, hypophosphataemia, and nephrocalcinosis failed to lead to a clear diagnosis. Neither primary hyperparathyroidism nor primary incomplete renal tubular acidosis could explain all the biochemical features, and it seems that more than one fundamental abnormality may have been present.

Introduction

Biochemical changes produced by excessive parathyroid hormone and their effects on several organs and tissues are well known. Hypercalcaemia, hypophosphataemia, and nephrocalcinosis are common in advanced cases, and inability to eliminate hydrogen ions in the urine has been reported in a number of patients (Fourman *et al.*, 1960).

The case of a patient with all these conditions is reported here in whom a diagnosis of primary hyperparathyroidism was rejected on the basis of suppressed serum parathyroid hormone levels and normal response to parathyroid extract infusion (Becker *et al.*, 1964), prednisone administration (Thomas *et al.*, 1958), and intravenous calcium infusion (Goldsmith and Forland, 1964).

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This patient's disorder, while similar to the late type of incomplete renal tubular acidosis (Elkinton *et al.*, 1960), was associated with hypercalcaemia, which has not been reported previously in that syndrome.

Case Report

An 18-year-old man was admitted to the Instituto Nacional de Cardiologia for investigation of nephrocalcinosis. He had been well until six months previously, when he complained of dysuria and polyuria. His physician found a urinary infection and prescribed antibiotics. Nephrocalcinosis, hypercalcaemia, and hypophosphataemia were also discovered and the patient was referred to this Institute. There was no family history of renal disease but his father has essential hypertension. Physical examination showed nothing abnormal. His weight was 68 kg, height 178 cm, body surface area 1·82 m^2, blood pressure 120/80 mm Hg, heart rate 88/min, and ventilatory rate 18/min.

Serum calcium was high in numerous determinations, with levels varying from 11·0 to 12·0 mg/100 ml, while the serum phosphorus was low, with values ranging from 1·4 to 2·7 mg/100 ml. Alkaline phosphatase was 3·6 Bodansky units. Blood urea nitrogen was 42 mg/100 ml, and serum creatinine 1·0 mg/100 ml. Maximum tubular reabsorption of glucose was 191 mg/min, and maximum tubular secretion of para-aminohippurate (PAH) 56 mg/min. Glomerular filtration rate was 77 ml/min (inulin clearance), and renal plasma flow 286 ml/min (PAH clearance). Serum albumin was 4·55 g/100 ml, and globulins were 2·68 g/100 ml. Paper electrophoresis showed normal plasma proteins. Total serum carbon dioxide was 26 mEq/l, and pH was 7·42. Haemoglobin was 15·6 g/100 ml, and the haematocrit reading 49%. Leucocyte count was 7,400/mm^3. Urine analysis showed low densities from 1004 to 1014. Urinary pH ranged from 6 to 7. Several urine cultures were negative.

A shortening of the S-T interval was present on the electrocardiogram. *X*-ray films of the chest, long bones, hands, feet, skull, and teeth showed no bone lesions. An intravenous pyelogram confirmed bilateral renal calcifications distributed diffusely on the parenchyma (Fig. 1) without alterations in the ureters or bladder.