Studies on 2-(3-benzoylphenyl) propionic acid (Orudis)

A double-blind cross-over trial in patients with rheumatoid arthritis and an assessment of its influence on hepatic drug-metabolizing enzymes

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In studies in experimental animals, Orudis* has been shown to have powerful analgesic, anti-inflammatory, and antibradykinin activities (Julou, Guyonnet, Ducrot, Garret, Bardone, Maignan, and Pasquet, 1971). It is not closely related structurally to established anti-inflammatory agents but bears a superficial similarity to ibuprofen in that it has a β -phenylpropionic group; to mefenamic acid in that two benzene nuclei are joined by a single bridging atom; and to indomethacin in that two cyclic groups are joined by a $-\text{CO}-$ bridge and one of the nuclei has an acidic substituent (Fig. 1). Preliminary clinical studies of Orudis, conducted mostly in France, in patients suffering from a variety of rheumatic diseases, have suggested that the drug has clinically useful analgesic and anti-inflammatory properties and a low incidence of side-effects.

FIG. 1 Chemical structural formula of 2-(3-benzoylphenyl) propionic acid (Orudis)

We have performed a double-blind controlled therapeutic trial of Orudis in fourteen patients with rheumatoid arthritis, in the course of which several haematological and biochemical parameters were followed in order to detect possible short-term toxic effects of the drug. In addition, the effect of Orudis on antipyrine clearance in twelve healthy young volunteers was studied in order to assess the

influence of the drug on hepatic drug-metabolizing enzymes. The results of these studies are reported below.

Material and methods

DOUBLE-BLIND TRIAL

Fourteen patients with 'definite' or 'classical' rheumatoid arthritis diagnosed according to the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) took part in the trial, having been selected on the basis of severe joint pain. Informed consent was obtained from all patients. They were all female Caucasians with ages ranging from 40 to 70 years (mean 54). The duration of the disease ranged from 1 to 22 years (mean 9.2) and in every case the disease was active at the time of the study, with functional classes ranging from II to IV (mode III) (Steinbrocker, Traeger, and Batterman, 1949). All had articular erosions on joint x ray (Stage III of Steinbrocker and others) and all but two had positive tests for rheumatoid factor. All anti-rheumatic therapy was discontinued before starting the trial. None of the patients had recently received corticosteroid therapy and none at any time had received gold or chloroquine.

The patients were randomly allocated to treatment for one week with Orudis or placebo, made up in identical capsules, and then crossed over to the alternative treatment for the second week. Seven patients received Orudis during the first week and the other seven received placebo first. The dose of Orudis was 25 mg. four times a day by mouth. Patients were told that they could take paracetamol if pain became unbearable but were instructed to abstain from other antirheumatic drugs.

Assessment was made at the end of each treatment week. General assessment of her progress by each patient was recorded on a 1 to 5 scale (1 = much better; 2 = better; 3 = no change; 4 = worse; 5 = much worse). A similar record was made of the physician's assessment of the patient's progress. Severity of pain and degree of morning

stiffness were each recorded on a 0 to 4 scale (0 = none; 1 = slight; 2 = moderate; 3 = severe; 4 = very severe), and the duration of morning stiffness in minutes was noted. Joint tenderness was assessed according to the method of Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieson, and Buchanan (1968). Grip strength was measured with a mercury sphygmomanometer, the cuff being replaced by a Boots grip-strength adaptor bag inflated to 30 mm. Hg.; the mean of three readings for each hand was recorded. The circumferences of the proximal interphalangeal joints of the fingers and interphalangeal joints of the thumbs were measured in mm. using the Geigy apparatus (Boardman and Hart, 1967). For the purpose of statistical analysis, the mean values for both hands for grip strength and joint circumference were used.

Radioactive technetium (^{99m}Tc) uptake over the right wrist and right knee was measured 15 minutes after the intravenous injection of a standardized dose in eleven patients at the end of each treatment week. The method has been previously described (Chalmers, Cathcart, Kumar, Dick, and Buchanan, 1972) and is a modification of that developed by Dick, Neufeld, Prentice, Woodburn, Whaley, Nuki, and Buchanan (1970) and Dick, Deodhar, Provan, Nuki, and Buchanan (1971).

A full blood count including platelet count, standard liver function tests, serum uric acid and blood urea estimations, and urine analysis were performed before starting the trial and at the end of each treatment week. Patients with evidence of hepatic or renal diseases were not included in the study.

Side-effects were recorded at the end of each treatment week. Those volunteered spontaneously or in reply to the question 'Have you felt anything upsetting you during the past week?' were recorded separately from those specifically asked for, such as dyspepsia, diarrhoea, constipation, headache, visual upset, tinnitus, paraesthesiae, and pruritus.

ANTIPYRINE METABOLISM STUDY

The experimental subjects were twelve healthy young volunteers; ten were Caucasian males, one an Asian male, and one a Caucasian female. Their ages ranged from 21 to 31 years (mean 24). The experimental procedure was similar to that described previously (Chalmers, Bell, and

Buchanan, 1973), but only one pretreatment antipyrene half-life estimation was performed on each subject. After the pretreatment estimation, each subject was issued with a 2-week supply of Orudis in the same dosage as that used in the clinical trial (four 25 mg. capsules daily). At the end of the 14-day treatment period, antipyrene half-lives were again estimated.

Results

DOUBLE-BLIND TRIAL

The results of the double-blind therapeutic trial are summarized in Table I. All clinical parameters, with the exception of joint circumference, showed highly significant improvement on Orudis compared with placebo. Radioactive technetium uptake by the wrist joint showed a significant decrease after Orudis therapy but the same change was not evident in the knee. The mean erythrocyte sedimentation rate was virtually identical at the end of each treatment period and none of the other laboratory investigations showed significant change with Orudis therapy. All values were within normal limits before entry and remained so throughout the trial. Volunteered side-effects were slightly more common during treatment with placebo than with Orudis. Five patients on placebo complained of toe cramps, nausea, anorexia, dizziness, and headache, respectively, and of the three patients who volunteered symptoms while on the active drug, two had heartburn and one had lightheadedness. Sought-after side-effects were recorded once for each treatment period. One patient on placebo had paraesthesiae and one on Orudis had vertigo. Consumption of paracetamol (2 to 4g./day) because of intolerable pain was reported by four patients while on placebo, but by none during treatment with Orudis. In addition, two patients who were receiving placebo required to be assessed before completion of the treatment week because of the extreme severity of their rheumatic symptoms.

Table 1 Results of double-blind cross-over trial

Figures are the means $\pm$ S.E.M. for fourteen patients at the end of each treatment week (11 patients for ^{99m}Tc study). Values of t obtained by the Student's 't'-test for paired values.

Treatment	Placebo	Orudis	t	P value
Assessment of progress Patient	3.9 $\pm$ 0.3	2.4 $\pm$ 0.2	6.9	<0.001
Doctor	3.5 $\pm$ 0.2	2.1 $\pm$ 0.2	5.3	<0.001
Subjective impression Pain	3.0 $\pm$ 0.1	2.2 $\pm$ 0.2	4.2	<0.005
Morning stiffness	3.0 $\pm$ 0.2	2.1 $\pm$ 0.2	5.6	<0.001
Duration of morning stiffness (min.)	350 $\pm$ 77.5	137 $\pm$ 47.6	2.2	<0.05
Articular index of joint tenderness	22.0 $\pm$ 2.9	13.5 $\pm$ 1.8	3.6	<0.005
Grip strength (mm./Hg)	87.1 $\pm$ 7.9	104 $\pm$ 12.3	2.9	<0.02
Joint circumference (mm.)	57.4 $\pm$ 1.2	57.0 $\pm$ 1.1		NS
^{99m}Tc uptake at 15 min. Knee	13.1 $\pm$ 1.2	12.2 $\pm$ 1.6		NS
Wrist	14.7 $\pm$ 1.3	11.4 $\pm$ 1.2	2.2	<0.05
Erythrocyte sedimentation rate (mm./1st hr)	49 $\pm$ 7.9	47.2 $\pm$ 8.4		NS

N.S. = not significant at 5 per cent. level.

ANTIPYRINE METABOLISM STUDY

The plasma half-lives of antipyrine for the twelve subjects before and after administration of antipyrine are set out in Table II. The mean post-treatment value of 15.1 hrs $\pm$ 1.8 (standard error of mean) does not differ significantly from the pretreatment value of 13.9 hrs. $\pm$ 1.3 ($t = 0.92$; $P > 0.1$).

Table II Plasma antipyrine half-lives (hrs) before and after treatment with Orudis in twelve healthy subjects

Subject no.	Value		Percentage change after treatment
	Pretreatment	Post-treatment	
1	13.7	14.9	+8.8
2	19.0	18.1	-4.7
3	20.8	16.3	+21.6
4	12.8	13.0	+1.6
5	8.4	8.4	0
6	10.7	11.4	+6.5
7	22.0	31.9	+45.0
8	13.2	6.7	-49.2
9	10.2	15.7	+53.9
10	10.5	11.0	+4.8
11	14.2	15.8	+11.3
12	11.1	17.8	+60.4
Mean $\pm$ S.E.M.	13.9 $\pm$ 1.3	15.1 $\pm$ 1.8	13.3 $\pm$ 8.5

Fig. 2 illustrates the composite regression lines for the pre- and post-treatment antipyrine levels in the twelve subjects. The close similarity between the two lines is evident.

FIG. 2 Effect of Orudis (19583 RP) on plasma antipyrine

Discussion

In the present double-blind cross-over trial in fourteen patients with rheumatoid arthritis, Orudis has been shown to have significantly superior analgesic and anti-inflammatory activity compared with placebo.

The trial was primarily designed as an initial screening test to determine whether Orudis was clinically active and, for this reason, particularly

stringent criteria were adopted with regard to patient selection. The patients mostly had chronic severe disease and were further selected on the basis of severity of pain rather than on evidence of joint inflammation. Thus many patients had long-standing arthritis with little or no soft-tissue swelling of the finger-joints and it is possibly for this reason that joint size was not significantly reduced in the course of this study, despite evidence as to the anti-inflammatory activity of Orudis. Similarly, with regard to the radiotechnetium studies, trial design probably influenced the outcome of this investigation in that it might not have been appropriate to measure ^{99m}Tc uptake over the same joints (*i.e.* right wrist and knee) in every patient, rather than in joints having evidence of active inflammation. It is relevant, however, that ^{99m}Tc uptake was significantly reduced over the wrist joint, even though the values for the knee joint did not show similar change. Reduction in the severity and duration of morning stiffness is regarded as an index of anti-inflammatory activity (Ingpen, 1968) and significant changes in these parameters were produced by Orudis.

No serious side-effects were encountered in this small number of patients and spontaneous and sought-after side-effects were trivial in those securing Orudis. No haematological or biochemical abnormalities were detected. No serious side-effects have been recorded in clinical studies carried out in France and Germany on approximately 1,000 patients or in studies conducted in the United Kingdom in over 200 patients (Bloch, 1972).

The results of this double-blind controlled trial in patients with rheumatoid arthritis strongly suggest that this new drug may be a valuable adjunct to existing non-steroidal antirheumatic agents. If Orudis finds a place in the therapeutic armamentarium, it will undoubtedly be used with other drugs and the possibility of interaction then arises. The aim of the second part of our study was to examine the influence of Orudis on an important site of interaction, namely the microsomal drug-metabolizing enzymes of the liver. Of the commonly-used antirheumatic drugs, only phenylbutazone appears to have been studied widely in man from the point of view of drug interaction, and this has a well-documented inducing effect on hepatic microsomal enzymes (Chen, Vrindten, Dayton, and Burns, 1962; Conney, 1967; Kitagawa, Kamataki, and Yoshida, 1968).

The measurement of the plasma half-life of antipyrine is probably the most suitable method at present available for studying drug interactions at the hepatic microsomal level in man (McEwen and Stevenson, 1972), and it is this method that we have applied in the present study. No significant change in mean antipyrine half-life was evident after 14 days' treatment with Orudis in twelve healthy young volunteers in comparison with the mean control value. Individual

subjects showed quite marked variation between the pre-and post-treatment values, but these variations are the same order of magnitude as those exhibited by another group of normal subjects over a 2-week control period on no specific medication (Chalmers and others, 1973). It can be concluded, therefore, that Orudis probably has no effect on drug-metabolizing enzymes in the liver, and is unlikely to produce significant interactions with other drugs at this level.

Summary

In a double-blind cross-over study in fourteen patients with rheumatoid arthritis, Orudis was found to have significant analgesic and anti-in-

flammatory activity compared with placebo. Side-effects were few and trivial. A further study on plasma antipyrine half-lives in twelve normal subjects showed no significant change in the mean value after 14 days' treatment with Orudis. This new drug may prove to be a useful antirheumatic agent and is unlikely to interact with drugs metabolized by the liver.

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