Clinico-pharmacological studies and clinical evaluation of flurbiprofen*

A new non-steroidal antirheumatic agent

I. M. CHALMERS, B. J. CATHCART, E. B. KUMAR, W. CARSON DICK, AND W. WATSON BUCHANAN

From the Centre for Rheumatic Diseases and The University Department of Medicine, Royal Infirmary, Glasgow

Flurbiprofen (BTS 18 322, 2-(2-fluoro-4-biphenyl) propionic acid) is a member of the phenylalkanoic acid series. It differs from its predecessors (ibuprofen, ibufenac) in having a biphenyl nucleus (Fig. 1), but, like them, possesses analgesic, anti-inflammatory, and antipyretic properties. In animal experiments it has been found to be much more potent than ibuprofen, acetylsalicylic acid, and other nonsteroidal anti-inflammatory drugs. It has been shown to be devoid of glucocorticoid activity and has no demonstrable effect on the adrenal cortex (Adams and McCullough, 1971).

FIG. 1 Structural formula of flurbiprofen.

In this paper we report preliminary studies on flurbiprofen in patients with rheumatoid arthritis, including the results of a double-blind cross-over trial.

Materials and methods

Clinical pharmacological studies

These were conducted on 28 in-patients with 'definite' rheumatoid arthritis as defined by the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). The dosage schedules are summarized in Table I. All but two of the patients had positive tests for rheumatoid factor and all but one had articular erosions on x-ray examination of the joints. Three of the patients were males. The mean age of the 28 patients was 55 years (range of 22 to 79). All were Caucasian. Every patient was informed about the nature of the drug and consent was obtained before it was administered. All other antirheumatic therapy was stopped the day before flurbiprofen was commenced.

In addition to age and sex, the following clinical parameters were recorded: height, weight, duration of arthritis,

Table I Dosage schedules used in clinical pharmacological studies of flurbiprofen

Number of patients	Dose	Duration of treatment (days)
3	10 mg. three times a day	10
4	15 mg. twice a day	10
4	20 mg. twice a day	10
3	15 mg. three times a day	10
4	25 mg. twice a day	10
7	20 mg. three times a day	14
3	25 mg. three times a day	14

presence of subcutaneous nodules or keratoconjunctivitis sicca, functional capacity, and x-ray stage (Steinbrocker, Traeger, and Batterman, 1949). Full blood counts were performed before, during, and at the end of treatment with flurbiprofen. Liver function tests, serum electrolytes, blood urea, serum uric acid, serum creatinine, serum proteins, fasting blood sugar, serum cholesterol, serum calcium and phosphorus, and urine analysis were performed before and at the end of treatment in all cases. In addition, serum protein-bound iodine (11 patients), T_3 resin uptake (11 patients), bromsulphthalein retention (3 patients), faecal fat (11 patients), xylose absorption (8 patients), serum vitamin B_{12} (10 patients), and serum folate (10 patients) were measured.

Flurbiprofen blood levels were measured in three patients taking 15 mg. twice a day, in four taking 20 mg. twice a day, and in four taking 25 mg. twice a day. On the 1st day of therapy a blood sample was taken before the first dose of flurbiprofen was administered and thereafter at 1½, 3, 6, and 12 hrs. The 12-hr. sample was taken before the second dose of the drug was given. On the 10th day (i.e. the last day of therapy), a repeat of the procedure for the 1st day was carried out. Blood samples were also taken on the mornings of the 2 days following cessation of therapy to determine the persistence of the drug.

Flurbiprofen was measured by gas-liquid chromatography by Dr. W. Dickinson at the Chemical Sciences Laboratories of The Boots Company Ltd. (Dickinson, 1971).

Accepted for publication December 21, 1971.

* Flurbiprofen is not yet on the market as it is still undergoing extensive clinical trials in the United Kingdom and overseas.

Clinical trial

A further twenty patients participated in a double-blind cross-over trial of flurbiprofen against placebo. They were selected on the basis of severe symptoms at the time of entry into the trial and informed consent was obtained from each patient. Eighteen of the patients had 'definite' rheumatoid arthritis, although four were seronegative for rheumatoid factor. Of the two remaining patients one was a 21-year-old with Still's disease and the other had psoriatic arthropathy. Two of the patients were males. The age range was from 21 to 67 years (mean 51). The duration of disease varied from 1 to 20 years (mean 8). The patients had had a wide variety of nonsteroidal anti-inflammatory drugs, but none had had recent corticosteroid therapy. Antirheumatic therapy was withdrawn the day before entry into the trial. Six patients were receiving drugs other than antirheumatic agents; these included phenobarbitone, rauwolfia root, chlorpropamide, digoxin, bendrofluazide, ampicillin, and meprobamate.

The patients received flurbiprofen in a dose of 15 mg. three times a day orally for 1 week and were then given identical placebo capsules for another week. The patients were randomly allocated to flurbiprofen and placebo for the 1st week and then crossed over to the alternative treatment for the 2nd week of the trial. Nine patients received flurbiprofen first and eleven placebo first.

Assessment was made at the end of each treatment week. The patient's own impression of pain was recorded on a scale of 0 to 4 (0 = no pain; 1 = slight; 2 = moderate; 3 = severe; and 4 = very severe). Similarly, the severity of morning stiffness was recorded on a 0 to 4 scale and the duration of morning stiffness was recorded in minutes. Grip strength was estimated in each hand as the mean of three attempts at gripping a rolled sphygmomanometer cuff with the pressure at a basal level of 30 mm. Hg. The circumference of the proximal interphalangeal joints of the fingers and interphalangeal joint of the thumb were measured on each hand using the Geigy apparatus. An articular index of joint tenderness was estimated as described by Ritchie, Boyle, McInnes, Jasani, Dalakos, Grievson, and Buchanan (1968). In addition, the pair of most severely involved large joints was assessed for pain, tenderness, swelling, stiffness, and heat, each item being scored on a 0 to 3 basis (0 = nil; 1 = slight; 2 = moderate; 3 = severe). The patient's and physician's assessment of the patient's progress were recorded, the scoring being on a 1 to 5 scale (1 = much worse, 2 = worse, 3 = no change, 4 = better, 5 = much better). The erythrocyte sedimentation rate (Westergren method) was measured at the end of each treatment week.

Those aspects of the patient's assessment which required an estimate of a subjective symptom were performed in a standard manner. For example, subjective impression of pain was elicited by the question: 'Have you at this moment, very severe pain, severe pain, moderate pain, slight pain, or no pain?', and the degree of morning stiffness by the question: 'Did you on waking this morning have very severe stiffness, severe stiffness, moderate stiffness, slight stiffness, or no stiffness?'

Possible side-effects of the drug were also sought. Those volunteered spontaneously or in reply to the question: 'Have you experienced anything unusual during the past week?' were recorded separately from those elicited by specific questioning.

Full blood count, standard liver function tests, serum uric acid and urea, and urine analysis were performed before entry into the trial and at the end of each treatment week. No patient with evidence of gross hepatic or renal disease was admitted to the trial.

In twelve patients, radioactive technetium studies were performed at the end of each treatment week. A slight modification of the procedure described by Dick and his colleagues was used (Dick, Neufeld, Prentice, Woodburn, Whaley, Nuki, and Buchanan, 1970; Dick, Deodhar, Provan, Nuki, and Buchanan, 1971). Approximately 200 μ Ci of ^{99m}Tc (as sodium pertechnetate) was standardized by counting for 2 min at 30 cm., using a thallium-activated sodium iodide scintillation crystal and photo-multiplier. The pulses were fed through a pulse-height analyser (EKCO M5050) and digital rate-meter (EKCO M5183A) and read out 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 and 90 mins after injection, counting was performed over a wrist and a knee (always in that order and always on the same side for a given patient). Each count lasted for 2 mins. The scintillation counter was positioned 2.5 cm. above the joint being examined. In the case of the wrist, the counter was aligned with a point on the dorsum midway between the radial and the ulnar borders at the level of the distal end of the ulnar styloid, and in the case of the knee, with the midpoint of the upper pole of the patella. Counts over the joints were expressed as a percentage of the dose.

Results*Clinical pharmacological studies*

None of the 28 patients developed any abnormality in any of the haematological or biochemical tests during or after flurbiprofen therapy. In those patients in whom xylose absorption was measured, a consistent increase in urinary xylose was noted after treatment. Two patients had subnormal figures before treatment, but in both cases normal values were obtained after treatment (Table II). The mean value before treatment was 1.1 ± 0.2 g and after was 1.9 ± 0.2 g: the difference is highly significant by the paired 't'

Table II *Results of xylose absorption tests*

g. xylose in a 5-hr urine collection after a 5-g. oral loading dose

Patient	Before treatment	After treatment
M.M.	1.5	2.5
E.F.	0.3*	1.7
M.R.	1.1	2.1
C.M.	1.1	1.7
J.M.	1.4	2.3
E.F.	1.9	2.4
H.C.	0.5*	1.0
M.A.	1.0	1.6
Mean $\pm$ S.E.M.	$1.1 \pm 0.2^\dagger$	$1.9 \pm 0.2^\dagger$

* Subnormal figures. (Lower limit of normal 1 g.)

† Difference highly significant by paired 't' test ($t = 6.77$; $P < 0.001$).

test ($t = 6.77$; $P < 0.001$). No patient showed any significant deterioration in his arthritis and the severity of the arthritis did not appear to influence the reaction to the drug in any way.

Two patients volunteered side-effects, both while receiving 10 mg. flurbiprofen three times a day. One patient reported 'hissing noises' in her ears which began on the 2nd day of therapy and persisted through to the 6th day when therapy was discontinued. The level of flurbiprofen, estimated in a sample of this patient's serum withdrawn 2 hrs after the first dose on the 4th day of treatment, was found to be $0.3 \mu\text{g./ml.}$ The 'hissing' had completely disappeared 4 days after therapy had ceased. The second patient reported 'buzzing in the head' which began on the 3rd day of therapy. Flurbiprofen was discontinued on Day 5 and placebo capsules substituted. 'Buzzing' continued on Days 6 and 7, but had begun to diminish on Day 8 and had disappeared by Day 10. In both these cases, detailed otological studies (including audiograms and tests of vestibular function) were completely negative. No other side-effects were noted.

Serum levels of flurbiprofen are shown in Table III and illustrated in Fig. 2.

Clinical trial

The results of the double-blind cross-over trial are shown in Table IV (overleaf). Of the twenty patients who entered the trial, three had to be withdrawn: one experienced nausea and vomiting while receiving the active drug, the second was found to have a urinary tract infection and raised blood urea, and the third developed an urticarial skin rash while on placebo.

Table IV shows that flurbiprofen was significantly better than placebo in the following assessments: subjective impression of pain, severity and duration of morning stiffness, grip strength, articular index, doctor's assessment of progress, and patient's

FIG. 2 Serum levels of flurbiprofen

assessment of progress. No significant difference was found in estimates of joint size, special joint score, ^{99m}Tc uptake, or erythrocyte sedimentation rate. None of the assessment indices revealed placebo to be superior to the active drug.

Side-effects in these patients are shown in Table V (overleaf). Eleven experienced side-effects while taking placebo compared with ten on flurbiprofen. In most instances, the side-effects were slight and did not greatly worry the patient. Withdrawal from the trial was necessitated in only one instance by a severe side-effect attributable to the drug.

The haematological and biochemical results are shown in Table VI (overleaf). With one exception, none of the individual figures was abnormal, and

Table III Serum levels of flurbiprofen at different dosage levels on the first and last days of a 10-day treatment course and on the mornings of the two days after cessation of treatment ($\mu\text{g./ml.}$)

Name	Dose (mg: twice daily)	Day 1					Day 10					Day 11	Day 12
		Hours following first dose					Hours following first dose					0900 hrs	0900 hrs
		0	1½	3	6	12	0	1½	3	6	12		
A.F.	15	0	0.1	1.5	0.2	—	0	0	0.6	1.0	0	0	0
M.M.		0	1.2	1.0	0.2	0	—	1.4	—	—	—	0	0
A.S.		0	2.1	1.3	0.3	0	—	—	0.8	—	—	—	—
M.M.	20	0.1	1.9	1.4	0.6	0.3	0.6	1.8	2.4	0.8	0.3	—	—
A.H.		0	0.3	—	0.1	0	0.5	2.0	1.7	1.0	0.4	—	—
D.D.		0	2.1	0.7	0.1	0	0.7	3.1	2.0	0.9	—	—	—
A.K.		0	2.8	1.7	0.9	—	—	3.1	2.2	3.6	3.5	0.6	0.1
R.A.	25	0	4.2	2.8	0.9	—	—	5.6	5.3	1.5	—	0.6	0
E.M.		0	3.8	3.5	0.7	0.1	0.3	3.9	2.0	1.5	—	0.5	0
R.D.		0	3.4	3.1	0.5	—	0.5	4.4	1.7	1.1	—	0.4	0.1
A.M.		0.1	2.6	3.1	1.0	—	0.5	3.6	2.6	1.5	—	0.6	0.2

—: result not available.

Table IV *Results of double-blind crossover trial*Figures are means ($\pm$ S.E.M.) for seventeen patients at end of each treatment week. Values of *t* obtained by the paired *t*-test

Assessment index	Placebo	Flurbiprofen	<i>t</i>	<i>P</i>
Subjective impression of pain	2.9 $\pm$ 0.2	2.3 $\pm$ 0.3	2.86	<0.02 > 0.01
Degree of morning stiffness	3.3 $\pm$ 0.2	2.2 $\pm$ 0.3	4.37	<0.001
Duration of morning stiffness (min.)	308 $\pm$ 76	160 $\pm$ 53	2.38	<0.05 > 0.02
Grip strength (mm. Hg)	67.9 $\pm$ 5.3	78.4 $\pm$ 5.6	2.30	<0.05 > 0.02
Joint size (mm.)	54.9 $\pm$ 0.9	54.7 $\pm$ 0.8	1.30	N.S.
Special joint score	13.5 $\pm$ 1.4	12.7 $\pm$ 1.5	1.55	N.S.
Articular index	39.1 $\pm$ 3.3	27.7 $\pm$ 3.6	4.58	<0.001
Patient's assessment of progress*	2.3 $\pm$ 0.3	3.5 $\pm$ 0.3	3.78	<0.01 > 0.001
Doctor's assessment of progress*	2.2 $\pm$ 0.2	3.7 $\pm$ 0.3	4.24	<0.001
99 mTc uptake	{ Knee 15 min. Wrist 15 min. Knee 90 min. Wrist 90 min.	{ 19.4 $\pm$ 1.8 15.4 $\pm$ 1.5 17.3 $\pm$ 1.3 13.6 $\pm$ 1.3	{ 0.56 0.31 0.25 0.85	{ N.S. N.S. N.S. N.S.
Erythrocyte sedimentation rate (mm./1hr)	53 $\pm$ 10	46 $\pm$ 8	1.40	N.S.

* No significant difference between patient's and doctor's assessments.

Table V *Side-effects elicited during double-blind cross-over trial*

Name	Placebo		Flurbiprofen		Comment
	Volunteered	Sought after	Volunteered	Sought after	
A.L.	Thirst, dry mouth	Nausea	Nil	Nil	
M.J.	Nil	Nil	Nil	Nil	
T.P.	Nil	Nil	Nil	Nil	
A.C.	Nil	Headache	Slight anorexia	Nil	
M.C.	Nil	Nil	Nil	Dry mouth	
G.P.	Giddiness	Peripheral paraesthesiae	Slight heartburn	Nil	
J.C.	Nil	Nil	Nil	Nil	
J.C.	Dry mouth	Nil	Flushing of face	Nil	
H.C.	Nausea, tight chest, depression, burning feet, insomnia	Headache, heartburn, paraesthesiae in feet	Leg cramps, profuse sweating	Headache, dry mouth, palpitations, paraesthesiae in feet	Patient subsequently found to be thyrotoxic
M.M.	—	—	Severe nausea and vomiting	Nil	Withdrawn from trial
M.N.	Nil	Constipation	Nil	Constipation	
M.C.	Chest pain	Nil	Nil	Nil	
B.G.	Headache, nausea	Nil	Nil	Nil	
E.R.	—	—	—	—	Withdrawn from trial because of urinary tract infection
E.R.	Urticarial skin rash	Nil	—	—	Withdrawn from trial
M.G.	Dizziness	Nil	Headache	Nil	
F.T.	Nil	Nil	Nil	Nil	
G.G.	Nausea	Nil	Constipation	Nil	
M.S.	Nil	Nil	Nil	Nil	

no significant change was produced by the active drug. The single exception was the pre-treatment level of alkaline phosphatase in Patient 20, which was found to be 27 K.A. units per 100 ml. serum. Ordinarily, this would have been considered grounds for exclusion from the trial, but the result came to light only at the end of the trial, and the post-treatment levels were found to have subsided. Other tests of liver function in this patient were normal, and the patient had no symptoms or signs of liver disease.

Discussion

On the basis of the short-term studies reported here, flurbiprofen appears to be a safe, relatively non-toxic drug. The incidence of side-effects was low and, in the double-blind trial, those experienced in association with ingestion of the active drug were not markedly different from those associated with placebo. There was only one instance of side-effects (nausea and vomiting) sufficiently severe to warrant withdrawal of the drug. No satisfactory explanation can be

Table VI Laboratory results obtained during double-blind crossover trialFigure are means ($\pm$ S.E.M.) for all patients on whom estimations were performed

Laboratory test	Before treatment	Placebo	Flurbiprofen
Haemoglobin (g./100 ml.)	13.0 $\pm$ 0.4	12.6 $\pm$ 0.4	12.8 $\pm$ 0.3
White cell count (10^3 /c.mm.)	7.6 $\pm$ 0.4	7.2 $\pm$ 0.6	7.8 $\pm$ 0.5
Platelet count (10^3 /c.mm.)	271 $\pm$ 20	297 $\pm$ 24	298 $\pm$ 19
Bilirubin (mg./100 ml.)	0.32 $\pm$ 0.03	0.38 $\pm$ 0.04	0.38 $\pm$ 0.05
SGOT (U./l.)	13.1 $\pm$ 1.4	11.1 $\pm$ 0.6	12.6 $\pm$ 0.6
SGPT (U./l.)	9.1 $\pm$ 1.3	8.1 $\pm$ 1.0	9.1 $\pm$ 1.1
Alkaline phosphatase (K-A U./100 ml.)	11.8 $\pm$ 1.2	11.9 $\pm$ 1.2	12.1 $\pm$ 1.1
Uric acid (mg./100 ml.)	4.1 $\pm$ 0.2	4.2 $\pm$ 0.3	4.1 $\pm$ 0.4
Urea (mg./100 ml.)	36.7 $\pm$ 3.3	30.0 $\pm$ 2.0	34.6 $\pm$ 1.8

No significant change produced by flurbiprofen in any of these estimations.

advanced for the two cases of possible ototoxicity which occurred early in these studies. Subsequent patients received much higher dosages of the drug, but none of them reported any symptoms referable to the inner ear. In addition, the serum level of flurbiprofen measured in one of the patients with tinnitus was very much lower than some of those recorded for asymptomatic patients.

Laboratory investigations did not reveal any adverse effect of flurbiprofen on haemopoiesis, hepatic, renal, or thyroid function, uric acid metabolism, glucose tolerance, or intestinal absorption. The short-term nature of these studies must again be emphasized, however. Three parameters of intestinal function (faecal fat, serum vitamin B₁₂, and serum folate) were unchanged by the drug, but one, namely xylose absorption, appeared to be enhanced. The reason for this is not clear, but it may be artefactual. Some commonly-used antirheumatic drugs, namely aspirin and indomethacin, have been shown to affect the xylose test adversely (Kendall, Nutter, and Hawkins, 1971), and it may be that the apparent enhancement of xylose absorption by flurbiprofen merely represents recovery from the deleterious effects of a previous drug. On the other hand, a positive effect of flurbiprofen on the intestinal absorption or renal handling of xylose cannot be discounted without further study.

Serum levels of the drug were measured in too small a number of patients for any firm conclusions to be drawn and the suggestion of accumulation in the blood from the Day 10 levels is within the limits of error of the experimental technique used. However further studies are needed to answer this problem fully.

The double-blind trial showed flurbiprofen to be significantly better than placebo in most of the parameters measured and flurbiprofen may be regarded as a useful analgesic for rheumatoid arthritis. Two

assessments that failed to show significant change were joint size and special joint score. The former may have failed to alter because of the long duration of disease in many of the patients studied, who therefore probably had irreversible structural changes in the joints measured. Special joint score concentrates on a pair of severely-involved large joints. It was sometimes difficult to find a suitable pair of joints in patients who were selected on the basis of overall severity of the disease, and this assessment is thus probably best reserved for studies of specific joints. Those measurements which may be considered indices of inflammation (^{99m}Tc uptake and erythrocyte sedimentation rate) were also unchanged after a week on the active drug. That ^{99m}Tc uptake is influenced by anti-inflammatory therapy has been shown conclusively by measurements of uptake before and after intra-articular corticosteroid injections into rheumatoid arthritic knees (Dick and others, 1970). It may be that time in excess of one week is necessary for the development of a demonstrable anti-inflammatory effect, and long-term studies will be needed to clarify this point.

Summary

Preliminary studies of a new drug, flurbiprofen, are presented. When used on a short-term basis in patients with rheumatoid arthritis it appeared to be well-tolerated and non-toxic. A double-blind crossover trial showed the drug to be significantly superior to placebo in most of the assessment indices. Further, more prolonged, studies are warranted.

The authors are grateful to Drs. A. A. J. Goldberg and J. Warwick Buckler of the Boots Company Ltd. for helpful criticism and assistance in conducting these studies, and to the Arthritis and Rheumatism Council for Research for financial support.

References

- ADAMS, S. S., AND McCULLOUGH, K. F. (1971) In 'Abstracts of the VII European Rheumatology Congress'. British Branch of the European League against Rheumatism, Faraday House, 8 Charing Cross Road, London (2-(2-fluoro-4-biphenyl) propionic acid, a non-steroidal antiinflammatory agent)

- DICK, W. C., DEODHAR, S. D., PROVAN, C. J., NUKI, G., AND BUCHANAN, W. W. (1971) *Clin. Sci.*, **40**, 327 (Isotope studies in normal and diseased knee joints: ^{99m}Tc uptake related to clinical assessment and to synovial perfusion measured by the ^{133}Xe clearance technique)
- , NEUFELD, R. R., PRENTICE, A. G., WOODBURN, A., WHALEY, K., NUKI, G., AND BUCHANAN, W. W. (1970) *Ann. rheum. Dis.*, **29**, 135 (Measurement of joint inflammation)
- DICKINSON, W. (1971) Personal communication (Determination of phenylalkanoic acids in biological fluids using the XAD-2 column method)
- KENDALL, M. J., NUTTER, S., AND HAWKINS, C. F. (1971) *Brit. med. J.*, **1**, 533 (Xylose test: effect of aspirin and indomethacin)
- RITCHIE, D. M., BOYLE, J. A., MCINNES, J. M., JASANI, M. K., DALAKOS, T. G., GRIEVESON, P., AND BUCHANAN, W. W. (1968) *Quart. J. Med.*, **37**, 393 (Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis)
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A. (1959) *Ann. rheum. Dis.*, **18**, 49 (Diagnostic criteria for rheumatoid arthritis: 1958 revision)
- STEINBROCKER, O., TRAEGER, C. H., AND BATTERMAN, R. C. (1949) *J. Amer. med. Ass.*, **140**, 659 (Therapeutic criteria in rheumatoid arthritis)