FLUFENAMIC ACID IN RHEUMATOID ARTHRITIS

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This is a report of a clinical trial comparing the effects in patients with rheumatoid arthritis of an anti-inflammatory drug, flufenamic acid, with the familiar anti-rheumatic drugs phenylbutazone and soluble aspirin.

Flufenamic acid, N-(*ααα*-trifluoro-*m*-tolyl) anthranilic acid, is a stable, weak carboxylic acid with the formula shown in Fig. 1.

Fig. 1.—Chemical formula of flufenamic acid.

It is a cream-coloured solid supplied in 200 mg. capsules. In experiments with guinea-pigs and rats its anti-inflammatory activity as determined by the ultra-violet erythema test has been shown by Winder, Wax, Serrano, Jones, and McPhee (1963) to be approximately 1·6 times that of phenylbutazone and 16 times that of aspirin. It has a dose-graded effect 3·6 times greater than phenylbutazone. Oral doses in excess of expected therapeutic levels are said to be very well tolerated and diarrhoea has been the commonest adverse effect. In a double-blind controlled trial comparing flufenamic acid with aspirin in a small number of patients with rheumatoid arthritis, Coodley (1963) found that the former, in a total daily dosage of 300 mg., was superior in its effect on strength of grip and other parameters. The total daily dose of aspirin, however, was only 1,800 mg. Higher daily doses of flufenamic acid (600 mg.) were found by Young (1963) to have an effect equal to that of oxyphenbutazone (400 mg.). More recently Simpson, Simpson, and Masheter (1966) completed a trial, of double-blind cross-over design, comparing flufenamic acid (600 mg.) with aspirin (2,700 mg.). Little difference was noted between the effect of the two drugs on strength of grip or

number of joints involved, but aspirin appeared to be more effective in reducing the erythrocyte sedimentation rate (ESR). The same authors observed a steady fall in the average ESR in a group of patients treated with flufenamic acid for longer periods, but this part of the trial was not controlled. In another trial, Fearnley and Masheter (1966) compared prednisone (7·5 mg. daily) with flufenamic acid (600 mg. daily) in two groups of patients with active rheumatoid arthritis. Prednisone proved more effective in reducing the number of joints involved and in increasing the strength of grip; it also markedly reduced the average ESR whereas flufenamic acid did not influence this measurement. Barnardo, Currey, Mason, Fox, and Weatherall (1966) compared mefenamic acid and flufenamic acid with aspirin and phenylbutazone in female out-patients with rheumatoid arthritis; phenylbutazone was preferred slightly but not significantly more often than any other drug and flufenamic acid was least popular, but again not significantly. The design of this trial provided for adjustment of dosage to the need of individual patients and equipotent daily doses of the trial drugs were estimated as 2·4 g. for aspirin, 0·33 g. for phenylbutazone, 1·7 g. for mefenamic acid, and 0·67 g. for flufenamic acid.

Purpose of Present Trial

In the trial now reported the ability of the three drugs, flufenamic acid, phenylbutazone, and aspirin, to lessen pain provided the principal basis for comparison. The trial was so designed as to allow it to be concluded as soon as a statistically significant difference had been established or a sufficient number of cases accumulated to show that no such difference existed. It was accepted that the number of observations might not suffice for a significant difference to emerge between the effects of the drugs on the other parameters which were to be measured.

Methods

Patients admitted to the trial all satisfied the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958) for a diagnosis of definite rheumatoid arthritis. All had pain in one or more joints and none had a history of any adverse reaction to aspirin or phenylbutazone. On entry to the trial patients already taking a corticosteroid continued this treatment without alteration of dose; otherwise only the trial drugs were administered.

The trial, which was double-blind, lasted 6 weeks and each drug was given for 2 weeks of this period. The sequence of drugs was varied according to a pre-determined random code and the total daily intake of each drug, divided into three equal doses, was as follows:

Flufenamic acid	600 mg.
Phenylbutazone	300 mg.
Aspirin	3.0 g.

Three capsules were required for a single dose of aspirin but only one for the other two drugs. To avoid varying the number of capsules forming a single dose patients were instructed to take a capsule from one bottle and two from a second. When aspirin was being administered the capsules in both bottles contained this drug but during other periods those in the second bottle contained an inert substance. All patients were seen at fortnightly intervals and were initially issued with numbered pre-packed bottles and instructions as to the number of capsules to be taken. They were asked to return the bottles at the end of the fortnight for which they had been earmarked and any unused capsules were then counted. Only two patients returned capsules, numbering four and six respectively. At each visit a record was made of the strength of grip measured in mm. Hg with a pneumatic bag inflated to 20 or 30 mm. Any adverse reactions were recorded and blood was taken for determination of the ESR by Westergren's method. At the end of 4 and 6 weeks patients were asked to say whether their pain had increased or decreased at the time of change-over of drugs. When the trial ended they were also asked to say whether they could identify any period as preferable to the others in terms of subjective relief. Wherever possible all assessments were made by one observer.

A sequential design was adopted for analysing subjective responses to the drugs, a separate chart being used for each of the possible three-way comparisons. The boundaries of these charts were drawn so that if one treatment was preferred 35 per cent. more than another there would be a 95 per cent. chance of detecting the difference. Such a design allows a trial to be concluded quickly if one treatment is overwhelmingly preferred to another. In the present instance a boundary on each chart had been crossed by the time 27 patients had completed the trial. Three patients failed to complete the trial: one suffered an acute exacerbation of her arthritis during the first week and had her treatment altered by her general practitioner, and the other two failed to attend for their fortnightly assessment. No patient had to stop the trial because of an adverse reaction to any of the three drugs.

Results

(a) *Subjective Response.*—The sequential charts (Fig. 2a, b and c, opposite) show the three two-way comparisons between the drugs used in the trial, based on the patients' own assessment of the severity of symptoms. No significant difference emerged in any comparison, though there was a tendency for phenylbutazone to be preferred by more patients than either of the other two drugs. Formal analysis (Table I) confirms that there was little to choose between aspirin and flufenamic acid and that the lead of phenylbutazone over each of the other drugs was not significant ($P > 0.1$).

TABLE I
COMPARISONS OF THE PATIENTS' PREFERENCE BETWEEN
PAIRS OF DRUGS

Preference	Observed No. of Patients	Expected No. on Null Hypothesis	χ^2	P(>)
A better than B B better than A	14 12	13 13	0.15	0.50
TOTAL	26	26		
A better than C C better than A	10 17	13.5 13.5	1.88	0.10
TOTAL	27	27		
B better than C C better than B	9 17	13 13	2.46	0.10
TOTAL	26	26		

A = Flufenamic acid
B = Aspirin
C = Phenylbutazone

Less weight can be attached to the patients' overall preferences recorded at the end of the trial, since this involved the difficult task of casting back over the whole period. In fact nine chose flufenamic acid, seven aspirin, and eleven phenylbutazone.

(b) *Strength of Grip.*—The effect of the trial drugs on strength of grip was examined in a similar way to that used in assessing the subjective response. Separate analyses were also made for each pair of drugs given consecutively or separated by a period of treatment with the third drug. No statistically significant difference emerged from any of these analyses. There was a tendency for the grip to improve more during treatment with phenylbutazone, but the results for each hand considered separately were inconsistent in assigning the other two drugs to second and third place.

(c) *Erythrocyte Sedimentation Rate.*—A similar analysis of the ESR again showed no statistically significant difference, though there was a greater tendency for the rate to decrease during treatment

2 (a)

2 (c)

Fig. 2.—Sequential charts showing patients' preference in three comparisons of pairs of drugs:
 (a) Flufenamic acid compared with phenylbutazone.
 (b) Flufenamic acid compared with aspirin.
 (c) Aspirin compared with phenylbutazone.

TABLE II
SIDE-EFFECTS

Complaints	Flufenamic Acid	Aspirin	Phenylbutazone
Nausea	1	2	1
Vomiting	—	1	—
Diarrhoea	2	—	2
Giddiness or Tinnitus	—	2	1
Indigestion	3	—	2
Depression	1	2	—
Marked Stiffness	—	—	1
Subconjunctival Haemorrhage	—	1	—
Swelling of Legs	—	1	—
TOTAL*	7	9	7

*Since some patients experienced more than one side-effect the total number of such effects recorded exceeds the number of patients who reacted adversely.

difference was found in the response of patients to the three drugs and the results were in line with those reported by Simpson and others (1966) and Barnardo and others (1966).

Discussion

The subjective response is a relatively crude yardstick for comparing the value of anti-rheumatic drugs. Nevertheless it is reasonable to submit a new drug to a trial of its ability to make patients more comfortable, in the belief that any major gain in potency will be detected. An effective drug may also be expected to make joints less tender and to strengthen the grip. A new anti-rheumatic drug which

2 (b)

with aspirin than with either of the other two drugs, and for phenylbutazone to be more active than flufenamic acid.

(d) *Adverse Effects.*—These are detailed in Table II. Most patients escaped adverse reactions and none experienced any one effect throughout all phases of the trial.

Thus, within the limits of this investigation, no

patients are unable to appreciate as a superior source of relief of pain and which fails in the short-term to increase strength of grip more than older drugs may have other virtues. Thus it may influence favourably the natural history of the disease or produce fewer and less severe adverse effects. The short trial described above was not designed to explore either of these possibilities in the case of flufenamic acid. Neither of the two drugs used as controls has been proved to modify the disease in any fundamental way, and the new drug was used for too short a time and in too few patients for its toxicity to be assessed. That no difference could be found between flufenamic acid, aspirin, and phenylbutazone in their ability to lessen pain, assessed subjectively, or to influence strength of grip or ESR may mean either that the drugs were equally potent or that the measurements used were insufficiently sensitive to detect any difference between them.

Flufenamic acid is likely to find a modest but useful role in the management of rheumatoid arthritis as a substitute for aspirin in patients with dyspepsia, providing more extensive use uncovers no new long-term adverse effects.

Summary

A double-blind clinical trial comparing flufenamic acid, aspirin, and phenylbutazone in patients with rheumatoid arthritis failed to reveal any difference between these drugs in their ability to relieve symptoms, improve strength of grip, or reduce the erythrocyte sedimentation rate.

We wish to acknowledge the help of Parke Davis and Company and of Geigy (U.K.) Pharmaceutical Division in supplying the drugs used in this trial. We are also indebted to Dr. P. V. Pigott and Dr. P. D. Fowler for invaluable assistance in designing and completing the investigation.

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L'acide flufénamique dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

Une étude comparative par la méthode de *double-blind* de l'acide flufénamique, de l'aspirine et de la phénylbutazone chez les malades atteints d'arthrite rhumatismale parvint à mettre en évidence aucune différence entre ces médicaments en ce qui concerne leur efficacité sur les symptômes, la force de préhension et le taux de la vitesse de sédimentation globulaire.

El ácido flufenámico en el tratamiento de la artritis reumatoide

SUMARIO

Un estudio comparativo por el método de *double-blind* del ácido flufenámico, de la aspirina y de la fenilbutazona en enfermos con artritis reumatoide no llegó a evidenciar diferencia alguna entre estos productos en su efecto sobre la sintomatología, la fuerza de presa de la mano y de la velocidad de sedimentación globular.