Feprazone, a new anti-inflammatory agent

Studies of potency and gastrointestinal tolerance

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Fletcher, M. R., Loeb, W., and Scott, J. T. (1975). *Annals of the Rheumatic Diseases*, 34, 186. Feprazone, a new anti-inflammatory agent. Studies of potency and gastrointestinal tolerance. Two studies are reported; a double-blind cross-over trial of feprazone 600 mg daily and aspirin 3.6 g daily in the treatment of rheumatoid arthritis, and an uncontrolled open study of gastrointestinal tolerance in twenty rheumatoid arthritis patients with known intolerance to other drugs. The first study showed that feprazone was significantly superior to aspirin in all the parameters tested. In the second study all twenty patients showed an improvement of their gastrointestinal symptoms, nineteen reporting no symptoms at all when taking the new preparation.

In the management of inflammatory or degenerative joint disease treatment with salicylates, phenylbutazone, or indomethacin may be accompanied by symptoms due to gastrointestinal irritation. Those drugs causing less gastrointestinal intolerance, such as ibuprofen, tend to be less potent anti-inflammatory and analgesic agents (Hart, 1972; Owen-Smith and Burry, 1972).

Gefarnate is an ulcer-healing drug, the effect of which has been ascribed to its possession of a terpenyl grouping (Casadio, Mantegani, Coppi, and Pala, 1967). The introduction of such a grouping into the basic chemical structure of phenylbutazone gives feprazone (4-prenyl-1,2-diphenyl-3,5-pyrazolidinedione (DA 2370).

Feprazone has been shown by Casadio and his colleagues (Casadio, Pala, Morazzi-Uberti, Lumachi, Crescenzi, Donetti, Mantegani, and Bianchi, 1972) in animal experiments to possess a similar analgesic, anti-inflammatory, and antipyretic activity compared with the unsubstituted compound, phenyl-

butazone, but to have a markedly reduced ulcerogenic activity.

In the present studies the analgesic and anti-inflammatory effects of feprazone have been compared with those of aspirin. In addition, the incidence of gastrointestinal irritation caused by feprazone was assessed in a group of patients in whom a tendency to develop gastrointestinal intolerance with other drugs had previously presented problems in the management of their joint disease.

Patient selection and study design

The analgesic and anti-inflammatory potency of feprazone was assessed by a double-blind comparison with aspirin. Twenty-two outpatients with classical or definite rheumatoid arthritis according to the American Rheumatism Association criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), who had not received systemic corticosteroid, ACTH, or gold therapy in the previous 6 months, were admitted to the trial. The study was a double-blind, cross-over comparison, the administration sequences (ASP-FEP or FEP-ASP) being allocated randomly. After a 'run in' period of one week, during which only paracetamol was given, identical capsules containing either feprazone 150 mg (three 50 mg capsules) of aspirin 900 mg (three 300 mg capsules) were administered four times daily for 2 weeks. After this there was a second week-long 'run in' period of paracetamol only and the other drug was then administered. During treatment with both drugs the patient was also allowed to take paracetamol, in free dosage, for severe pain.

At the end of weeks 1, 3, 4, and 6 the following parameters were assessed by the same observer: patient's

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assessment of pain, patient's and physician's assessment of progress, articular index (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieverson, and Buchanan, 1968), grip strength in both hands, duration of morning stiffness, walking time, average daily paracetamol consumption, body weight, blood pressure, pulse rate, full blood count, erythrocyte sedimentation rate, blood transaminases, alkaline phosphatase, bilirubin, urea, bicarbonate, and electrolyte levels. The results were analysed by analysis of variance test, Wilcoxon test, and Binomial test (Steel and Torrie, 1960).

In the second study 22 outpatients with inflammatory or degenerative joint disease, who had developed moderate or severe gastrointestinal intolerance to other nonsteroidal anti-inflammatory drugs, were admitted to the trial. Patients were excluded if they were pregnant, had received systemic corticosteroid therapy in the previous year, gave a history of peptic ulceration, or were sensitive to pyrazoles (e.g. had had a skin rash with phenylbutazone). Symptoms of gastrointestinal intolerance were: abdominal or retrosternal pain or discomfort, nausea, and vomiting. All other anti-inflammatory analgesic drugs were withdrawn at the time of initial assessment and the patients were given feprazone 150 mg four times daily.

Subjective assessment of the severity of gastrointestinal symptoms was made on the 1st, 7th, and 28th days of the trial by the same observer, at the same time of day for every patient. A full blood count, erythrocyte sedimentation rate, blood urea and electrolytes, and urine testing for protein were performed at each assessment.

Severity of gastrointestinal symptoms was scored on a 4-point scale as 'nil', 'mild' (may be continuous or not but does not disturb daily routine or disturb sleep), 'moderate'

(not normally constant but distressing when it occurs, disturbs sleep some nights but not more than once), and 'severe' (constant and disturbing at least once per night).

Results

(1) DOUBLE-BLIND STUDY OF POTENCY

There were two withdrawals from the trial (see below) and these cases are excluded from the statistical analysis of results.

(a) Clinical assessment

The two treatment groups (ASP-FEP and FEP-ASP sequences) were homogeneous with regard to their clinical data at the end of the first 'run in' period (Table I). Improvement during a treatment period was assessed by the difference between the value of any parameter at the ends of the run-in period and the treatment period. There is a difference in favour of feprazone between the two treatments (Table II) as assessed by all measured parameters of progress.

(b) Side effects

Two patients were withdrawn from the trial, one developed a maculopapular eruption during feprazone treatment; the other defaulted while on aspirin therapy. The side effects while on feprazone were few and none were serious (Table III).

(c) Laboratory data

The two treatment groups were homogeneous with regard to the laboratory parameters at the beginning

Table I Evaluation of group homogeneity at end of first 'run-in' period

Variables	Sequences		Homogeneity test	P
	ASP-FEP	FEP-ASP		
Age (years)	56.63 $\pm$ 2.49	62.09 $\pm$ 3.21	t = 1.34	NS
Duration of RA (years)	13.68 $\pm$ 2.23	15.18 $\pm$ 2.43	t = 0.54	NS
Sex	M 3; F 7	M 5; F 5	t = 0.196	NS
Nodules	Present 6 Absent 4	Present 7 Absent 3	t = 0.196	NS
Patient's assessment of pain	55.30 $\pm$ 5.36	60.65 $\pm$ 4.21	t = 2.034	NS
Ritchie's articular index	30.00 $\pm$ 4.37	34.40 $\pm$ 5.10	t = 0.084	NS
Grip strength (mm)				
Right	118.11 $\pm$ 5.70	108.30 $\pm$ 10.69	t = 0.861	NS
Left	113.78 $\pm$ 9.59	107.60 $\pm$ 10.03	t = 0.799	NS
Duration of morning stiffness (h)	2.30 $\pm$ 0.43	2.25 $\pm$ 0.36	t = 0.193	NS
Walking time (s)	37.30 $\pm$ 2.06	47.33 $\pm$ 3.77	t = 1.515	NS
Average daily consumption of paracetamol	7.14 $\pm$ 0.72	7.40 $\pm$ 0.79	t = 0.182	NS
Body weight (kg)	59.42 $\pm$ 2.97	58.85 $\pm$ 2.96	t = 0.011	NS

Table II *Analysis of the assessments of the 20 patients completing the trial*

<i>Variables</i>	<i>Sequences</i>	<i>Improvement after 1st treatment period</i>	<i>Improvement after 2nd treatment period</i>	<i>Variation between treatments</i>
Patient's assessment of pain	ASP-FEP FEP-ASP	13.35 ± 7.00 47.65 ± 4.44	33.10 ± 4.14 24.10 ± 4.39	P < 0.001
Articular index	ASP-FEP FEP-ASP	6.30 ± 2.96 16.10 ± 3.53	11.40 ± 1.63 10.20 ± 2.70	P < 0.025
Grip strength (mm)				
Right	ASP-FEP FEP-ASP	19.10 ± 6.23 47.80 ± 5.08	30.90 ± 5.8 24.10 ± 3.80	P < 0.001
Left	ASP-FEP FEP-ASP	14.00 ± 6.49 44.50 ± 5.54	22.40 ± 7.38 25.70 ± 5.39	0.05 < P < 0.10
Morning stiffness (h)	ASP-FEP FEP-ASP	0.57 ± 0.29 1.82 ± 0.41	1.68 ± 0.58 0.90 ± 0.22	P < 0.05
Walking time (s)	ASP-FEP FEP-ASP	2.88 ± 2.02 11.89 ± 1.91	5.00 ± 1.51 5.88 ± 1.13	P < 0.025
Average daily consumption of paracetamol	ASP-FEP FEP-ASP	3.28 ± 1.24 6.28 ± 0.88	6.27 ± 0.76 4.85 ± 0.90	P < 0.025
Doctor's assessment of progress	ASP-FEP FEP-ASP	0.80 ± 0.36 2.50 ± 0.34	2.20 ± 0.29 2.40 ± 0.27	P < 0.025

Mean values ± SEM of improvement in variables observed at the end of each treatment period.

of the trial. During the aspirin treatment period there was a mean decrease in the haemoglobin level by 1.01 g/dl, contrasting with a mean increase during the feprazone treatment period by 1.58 g/dl—the difference being statistically significant ($P < 0.001$). Plasma levels of feprazone and salicylate were also monitored. The majority of feprazone blood levels were in the range 30 to 70 µg/ml but there was no correlation between blood levels and clinical improvement or the incidence of side effects.

(d) Patient's preference

At the end of the trial the patients were asked to express their preference for one or other treatment

Table III *Side effects seen in the 22 patients who entered the trial*

<i>Symptoms</i>	<i>Feprazone</i>	<i>Aspirin</i>
Gastrointestinal irritation (e.g. dyspepsia)	0	6
Rashes	3	0
Tinnitus & impaired hearing	0	2
Somnolence	1	0
Dizziness	0	1
Total	4	9

One of the patients who developed a skin rash with feprazone was withdrawn from the trial, and another defaulted while on aspirin. The others were able to continue.

period. Feprazone was preferred significantly more frequently than aspirin ($P = 0.012$, Binomial test) (Table IV). This preference for feprazone is independent of the order of administration of the two drugs ($\chi^2 = 0.013$; $P > 0.90$).

(2) GASTROINTESTINAL TOLERANCE STUDY

Two patients failed to complete the study, feprazone in the trial dosage failing to control joint pain adequately. Of the twenty patients who completed the trial, all reported an improvement in symptoms of gastrointestinal irritation and many lost all symptoms (Figure). Apart from gastrointestinal symptoms the following possible adverse reactions were seen: insomnia, dizziness, frontal headache, slight generalized pruritis, and urinary tract infection, each in one patient only and none severe enough to necessitate withdrawal of treatment. The Wilcoxon rank for paired observation test was carried out to compare

Table IV *Treatment period preferred by the 20 patients completing the trial*

<i>Sequences</i>	<i>Drug</i>		<i>Indifferent</i>	<i>Total</i>
	<i>ASP</i>	<i>FEP</i>		
ASP-FEP	1	7	2	10
FEP-ASP	2	7	1	10
Total	3	14	3	20

FIGURE Histogram representing the frequency distribution of the patients' assessment of severity. The vertical axis gives the number of subjects in each class interval

the values recorded initially and those at the 28th day. The values for severity of gastrointestinal irritation were significantly different ($Z = 3.91$; $P < 0.0001$). The Figure shows the frequency distribution of the patients in each class interval at the different times. For statistical analysis a 2×4 contingency table was considered and tested for independence of response from time of observation by a χ^2 test. The χ^2 value for the null hypothesis of no association between scores of patient's assessment of severity of gastrointestinal intolerance and days of observation (initial assessment versus 28th day) is $\chi^2 = 36.80$, highly significant at the 1% level.

Discussion

The results of the present study show that feprazone, in a dose 600 mg daily, has greater anti-inflammatory

and analgesic action in patients with rheumatoid arthritis than does aspirin in a dose of 3.6 g/day. Feprazone has previously been shown to possess an anti-inflammatory and analgesic activity similar to that of phenylbutazone (Lignière, Colombo, Carrabba, Ferrari, and Robotti, 1972; Pasotti, Barbieri, Buniva, and Chierichetti, 1972; Ghiringelli, Mazzi, and Chierichetti, 1972) and indomethacin (Dotti, Ongari, Carazzi, and Chierichetti, 1972; Rooney, Watkins, Ahola, Gray, and Dick, 1974). These studies showed that feprazone possesses a much reduced tendency to cause symptoms of gastrointestinal irritation compared to these and other nonsteroidal anti-inflammatory drugs.

The incidence of other side effects, such as rashes, somnolence, headache, and dizziness, is similar to that occurring with phenylbutazone therapy (Graham, 1958; Denko, Ruml, and Begenstal, 1955; Mason, and Steinberg, 1959). Three patients out of the 44 in these studies developed a rash, an incidence of 6.5%, the rash clearing with discontinuation of therapy. It seems likely, therefore, that feprazone will prove a useful drug in the clinical management of patients suffering from inflammatory or degenerative joint disease.

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