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MEFENAMIC ACID IN RHEUMATOID ARTHRITIS*

BY

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During the past 3 years we have been studying the new anti-inflammatory drug mefenamic acid (N-(2,3-xylyl) anthranilic acid) in the treatment of painful musculo-skeletal conditions. Cahill, Hill, Jessop, and Kendall (1965) showed that it was effective in the treatment of osteo-arthritis. The object of this study was to determine whether mefenamic acid was of value in the treatment of rheumatoid arthritis. We made a preliminary assessment of mefenamic acid in comparison with indomethacin, a drug which has been well documented (Hart and Boardman, 1965; Smyth, 1965; Pitkeathly, Banerjee, Harris, and Sharp, 1966) and then compared mefenamic acid with placebo in a double-blind controlled trial.

Preliminary Assessment

The patients (Table I), who had classical or definite rheumatoid arthritis according to the 1958 A.R.A. criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), were attending a rheumatology outpatient clinic. They were already receiving standard treatment which included prednisolone, corticotrophin, aspirin, and phenylbutazone. If their pain was not adequately controlled on their current therapy they were given mefenamic acid 1·5 g. daily by mouth in addition. The results were compared with a similar group of patients who were given indomethacin for the same reason. The dose of indomethacin was 25 mg. daily, increasing by 25 mg. every third day until side-effects were produced or until a satisfactory effect had occurred, the usual daily dose being 75 mg. (maximum 150 mg.). The patients were assessed before and after 4 weeks' treatment, using grip strength and joint tenderness, and were asked to express an opinion about the effectiveness of the analgesia. If the patient thought the drug was effective and the clinician was able to confirm this by measuring a decrease in joint tenderness or an increase in grip strength, the result was classed as effective. If the patient thought the drug was effective but the clinician was unable to find any evidence of improvement, the result was classed as doubtful. The results are given in Table II.

TABLE I
PATIENTS IN PRELIMINARY ASSESSMENT

Drug..		Mefenamic Acid	Indomethacin
Number of Patients		44	27
Age (yrs)	Range Mean	21–72 53	27–68 49
Duration of Disease (yrs)	Range Mean	2–36 9·5	2–27 11
Sex	Female Male	32 12	23 4
No. on ACTH or Corticosteroids		32	18
D.A.T. Positive (>1:16)		41	18
Mean Erythrocyte Sedimentation Rate at Start of Trial (mm./hr)		46	38

TABLE II
ANALGESIC EFFECT

Drug	No. of Cases	Result		
		Effective	Doubtful	Ineffective
Mefenamic Acid ..	44	29	5	10
Indomethacin.. ..	27	10	3	14

The side-effects are listed in Table III (opposite). The commonest side-effect of mefenamic acid was diarrhoea, which usually developed after about 10 days. Some cases became symptom free when the dose was reduced, but usually the drug was stopped. Attempts to re-introduce mefenamic acid often led to the immediate recurrence of diarrhoea. There

*Based on a paper read to the Heberden Society on November 18, 1966.

TABLE III

SIDE-EFFECTS IN PRELIMINARY ASSESSMENT

Drug ..	Mefenamic Acid		Indomethacin	
No. of Cases		44		27
Side-Effects	Diarrhoea	10	*Central Nervous	16
	Dizziness	1	†Gastric	9
	Nausea	1	Malaise	2
	Malaise	1		
	Rash	2		
	Haemolytic Anaemia	1		
	None	28	None	7

Note: Some cases had more than one side-effect.
*Includes headache, vertigo, mental disturbance.
†Includes epigastric pain, nausea, vomiting.

were no effects which were definitely gastric in origin, although one patient complained of nausea. One patient who continued to take mefenamic acid developed a haemolytic anaemia and is described in detail, although the anaemia did not occur during the period of preliminary assessment.

A man aged 53 had had classical rheumatoid arthritis for 6 years. He had been treated with prednisolone 15 mg. daily for 5 years and mefenamic acid 1·5 g. daily for 12 months. He had felt unwell for 3 weeks with epigastric discomfort, diarrhoea, and breathlessness on exertion. He was pale and slightly jaundiced; the liver and spleen were not palpable.

Investigations:
Haemoglobin 7·9 g. per cent. W.B.C. 11,000 per cu. mm. Normal differential. Howell Jolly bodies present. Reticulocytes 37 per cent. Erythrocyte sedimentation rate 136 mm./hr. Differential agglutination test, 1:512. Antinuclear factor, negative. Serum bilirubin 2 mg. per cent. Mean red cell life 9 days (measured by ^{51}Cr). Glucose-6-phosphate dehydrogenase screening test normal.
The National Blood Transfusion Service reported:
"The direct Coombs' test is strongly positive. The (antibody) globulin coating the patient's cells is mainly of the 'warm' or gamma variety. There is also evidence of a cold autoantibody. Serum contains autoantibodies which appear to have anti-e specificity. There is also a weak non-specific autoantibody present".

Mefenamic acid was stopped. In view of the possibility of side-effects, an increase in the corticosteroid dose was thought to be undesirable. He was treated with azathioprine 200 mg. daily for 4 weeks and made an uneventful recovery, the haemoglobin rising to normal although the direct Coombs' test remained positive. No other cause for the haemolytic anaemia was discovered and it is possible that it was related to mefenamic acid although autoimmune haemolytic anaemia is a known complication of rheumatoid arthritis.

A similar haemolytic anaemia had been reported in patients taking α-methyl dopa (Worlledge, Carstairs, and Dacie, 1966). They found that the direct Coombs' test was a useful screening procedure in those cases. We are now performing direct Coombs' tests routinely on all patients having long-term mefenamic acid. The 25 cases examined to date have been negative.

Double-Blind Controlled Trial

On the basis of the results in Tables I and II, it appeared that mefenamic acid might be a superior analgesic with fewer side-effects than indomethacin. We therefore decided to study mefenamic acid further and a double-blind controlled trial against a placebo was conducted.

Methods.—26 patients with classical or definite rheumatoid arthritis were admitted to the trial who were already on standard treatment (Table IV). None had been given mefenamic acid previously and all were thought to need further analgesia than that provided by their current treatment, which was left unchanged. Thirteen were given mefenamic acid 500 mg. 8 hourly for 2 weeks followed by the placebo in identical capsules for 2 weeks; thirteen received the placebo first. Patients were assessed before and after each course of capsules; grip strength, walking time, erythrocyte sedimentation rate, duration of early morning stiffness, and patient's preference were used as criteria.

TABLE IV

PATIENTS IN DOUBLE-BLIND TRIAL

No. of Cases		24
Duration of Disease (yrs)	Mean ..	6·5
	Range ..	2–13
Sex	Female	20
	Male ..	4
No. on ACTH or corticosteroids		13
DAT Positive (>1:16)		18

Results.—Two patients were excluded from the assessment because they had not taken the capsules according to instructions, and the remaining 24 were evaluated. Twelve had taken the placebo first and twelve mefenamic acid first. Subsequent analysis showed that these two groups were comparable in terms of age, sex, and severity of disease. Fifteen patients preferred mefenamic acid, four preferred the placebo, and five were unable to express an opinion.

The mean values of grip strength, erythrocyte sedimentation rate, and walking time are given in Tables V and VI. The patients taking mefenamic acid showed a significant improvement in grip strength ($0{\cdot}01 < P < 0{\cdot}025$) and in walking time ($0{\cdot}001 < P < 0{\cdot}005$). Both placebo and mefenamic acid were more effective in reducing the walking time when taken first, but the differences remained significantly in favour of mefenamic acid whether taken first or second. There was no significant difference in the duration of early morning stiffness, but there was an inexplicable difference in the way the erythrocyte sedimentation rate behaved in the two groups. Those who received placebo first improved slightly on both treatments, but the other deteriorated on both treatments. This difference was statistically significant ($0{\cdot}025 < P < 0{\cdot}05$).

Side-effects.—There were no serious complications. The side-effects are shown in Table VII. Five patients had side-effects with both mefenamic

TABLE VII

INCIDENCE OF SIDE-EFFECTS

Some cases had more than one side-effect. Figures in brackets represent actual number of cases.

Drug		Mefenamic Acid	Placebo
Side-Effect	Diarrhoea	4	1
	Nausea	0	2
	Vomiting	1	1
	Abdominal Discomfort	6	2
	Constipation	2	2
	Night cramp	1	0
	Drowsiness	0	1
	Total	14 (11)	9 (9)

TABLE V

MEAN VALUES AND 95 PER CENT. CONFIDENCE LIMITS OF GRIP STRENGTH, ERYTHROCYTE SEDIMENTATION RATE, AND WALKING TIME

Group	Mean Value	Week 0	Week 2	Week 4
		←*Placebo*→	←*Mefenamic acid*→	
Placebo First	Grip Strength (mean of both hands)	127·3 (90·9–163·6)	120·6 (86·8–154·5)	129·8 (90·7–168·8)
	ESR (Westergren)	49·6 (27·2–72·0)	48·9 (30·0– 67·9)	47·6 (29·1– 66·0)
	Walking Time 50 ft (sec.)	14·7 (11·5– 17·9)	14·0 (11·2– 16·9)	13·5 (10·8– 16·1)
		←*Mefenamic Acid*→		←*Placebo*→
Mefenamic Acid First	Grip Strength	134·8 (111·4–158·2)	140·8 (111·4–163·3)	125·8 (102·7–148·9)
	ESR (Westergren)	43·9 (25·3– 62·6)	48·7 (29·0– 68·3)	55·2 (35·2– 75·2)
	Walking Time 50 ft	15·6	13·3	14·8

TABLE VI

MEAN CHANGES AND 95 PER CENT. CONFIDENCE LIMITS

Group	Mean Value	Week 2–Week 0	Week 4–Week 2
Placebo First	Grip Strength	*Placebo* −6·67 (−18·1) (+ 4·7)	*Mefenamic Acid* +9·17 (− 4·9) (+23·2)
	ESR	−0·67 (−5·6) (+4·3)	−1·33 (−6·5) (+3·8)
	Walking Time 50 ft	−0·625 (−1·40) (+0·15)	−0·583 (−1·47) (+0·30)
Mefenamic Acid First	Grip Strength	*Mefenamic Acid* +6·04 (− 5·6) (+17·7)	*Placebo* −15.00 (−31.4) (+ 1·4)
	ESR	+4·75 (− 5·4) (+14·9)	+6·58 (− 0·4) (+13·5)
	Walking Time 50 ft	−2·292 (−3·85) (−0·73)	+1·417 (+0·54) (+2·29)

acid and placebo. Abdominal discomfort was the most common symptom and was usually associated with diarrhoea.

Discussion

The preliminary assessment indicated that mefenamic acid was a superior analgesic to indomethacin and showed fewer side-effects. Barnardo, Currey, Mason, Fox, and Weatherall (1966) showed that mefenamic acid was a comparable analgesic to aspirin and phenylbutazone. Young (1963) showed that mefenamic acid was comparable to oxyphenbutazone. We decided to assess mefenamic acid in a formal trial against a placebo rather than against a standard drug because most of the patients were already receiving standard therapy and any alteration would introduce a second variable which would complicate the analysis. Since all were receiving near optimal analgesic therapy at the start of the trial, it was unlikely that any additional drug would produce striking changes. In view of this we think that the improvement in grip strength and walking time, together with the patient preference for mefenamic acid, indicate that it is an effective drug in rheumatoid arthritis. The action of mefenamic acid, judged by the absence of any effect on early morning stiffness or on the erythrocyte sedimentation rate, is probably mainly analgesic rather than anti-inflammatory, although animal studies have shown it to have anti-inflammatory properties greater than those of aspirin (Winder, Wax, Scotti, Scherrer, Jones, and Short, 1962).

The dose of indomethacin which we used is smaller than that used by some physicians, but since most of our patients had either developed side-effects of gained satisfactory benefit when they were taking 75 mg. daily it is unlikely that a higher dose would have improved these results.

The incidence of side-effects in this trial was not large, and this confirms our experience with the long-term administration of mefenamic acid. Apart from the one case of haemolytic anaemia which may have been associated with the underlying disease rather than with the drug, the only serious effect was diarrhoea. Since this is not generally dose-related and usually occurs early, it may be a hypersensitivity effect. We have regarded it as an indication for stopping the drug until further knowledge of the mechanism is available. The incidence of other side-effects has been very small. In particular, unlike almost all other anti-inflammatory analgesic drugs, there is no evidence of gastric irritation.

We have shown that mefenamic acid is a superior analgesic to both indomethacin and placebo. We think that mefenamic acid is an analgesic of about the same potency as aspirin and phenylbutazone and that it is a useful alternative in rheumatoid arthritis, especially in patients with gastric intolerance.

Summary

In an initial study, mefenamic acid appeared to be a superior analgesic to indomethacin in the treatment of rheumatoid arthritis, with fewer side-effects. In a double-blind controlled trial, mefenamic acid was a significantly superior analgesic to a placebo.

We are indebted to Dr. G. A. L. Gorringe of Park, Davis & Company, for his assistance and for supplying the mefenamic acid (Ponstan) and the placebo capsules.

DISCUSSION

DR. F. DUDLEY HART (*London*): I wonder if you have any evidence that the effect was anti-inflammatory or only analgesic?

DR. BACON: In this trial no effect was seen on early morning stiffness or erythrocytic sedimentation rate, but the trial lasted for only 2 weeks. One cannot say that the effect is anti-inflammatory, but there is evidence from animal trials that this is so.

DR. V. WRIGHT (*Leeds*): I wonder if you would agree that in fact it is dangerous to draw the conclusion that this drug is equivalent to phenylbutazone, since the evidence is purely circumstantial. The trial has shown that it is superior to placebo. If you wish to draw the conclusion that it is superior to phenylbutazone or indomethacin, you must set up the trial to show this. I wonder if it should be tested against placebo, rather than with the drug to which you think it may be superior or equivalent?

DR. BACON: I agree that it should be tested against other drugs as a further study, but we thought as a first stage it was useful to do it against placebo.

PROF. E. G. L. BYWATERS (*Taplow*): Do the authors think their dosage of Indomethacin high enough to show the effect required? I should have put it a little higher.

DR. BACON: By the time we reached this dose, most patients were either finding some beneficial effect or suffering side-effects.

DR. W. S. C. COPEMAN (*London*): Do you not think that when we do clinical trials with these new drugs which come on the market from time to time, we are a little uncertain what we are trying to find? Many of them have side-effects, and this one may or may not have an anti-inflammatory as well as an analgesic effect. I think Dr. Bacon was only talking about the analgesia. This may be the direct result of an anti-inflammatory effect, in which case, it is not primarily an analgesic drug. This argument applies equally to corticosteroids, where it is well known that we must not use them purely as analgesics and increase the dose because pain is not being suppressed adequately, even though joint swelling is being reduced, in which case we reinforce with a pure

analgesic. I think this proves that we ought to distinguish a little more clearly between the analgesic action as such and anti-inflammatory action as such, as the latter may not include the former.

DR. C. E. QUIN (*Lewes*): I have had 100 cases under treatment with mefenamic acid and I should like to say a word about side-effects. Eighteen of our 100 patients had diarrhoea, and although it is alleged that this only occurs with high dosage, we found it occurred on doses as low as 750 mg./day. I should be interested to know if anyone else has observed this. About twelve patients complained of frequency of micturition, which occurred in the first week in about three cases and later in others. Have you observed any cases with disturbances of micturition?

DR. BACON: We did not notice this at all. We did not ask patients, but we got no complaints.

DR. R. M. MASON (*London*): In case Dr. Bacon is led into doing a controlled trial with phenylbutazone, we carried one out and have published the results.* If I remember correctly, 1·7 g. mefenamic acid was equivalent to 330 mg. phenylbutazone. I think it is important in these trials to allow the physician to vary the dose, and we built this variation into ours, allowing an alteration in the number of capsules prescribed. I think this is always worth doing in any controlled study.

* Barnardo and others (1966).

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L'acide méfénamique dans l'arthrite rhumatismale

RÉSUMÉ

A une première étude, l'action antalgique de l'acide méfénamique apparût supérieure à celle de l'indométhacine, avec des effets secondaires moindres, dans le traitement de l'arthrite rhumatismale. Après une épreuve en *double-blind* l'action antalgique de l'acide méfénamique s'est avérée significativement supérieure à celle d'un placebo.

El ácido mefenámico en la artritis reumatoide

SUMARIO

En el primer estudio la acción analgésica del ácido mefenámico pareció superior a la de la indometacina, con menos efectos secundarios, en el tratamiento de la artritis reumatoide. En la segunda investigación, conducida por el método de *double-blind* la acción analgésica del ácido mefenámico fué significativamente superior a la de un placebo.