CLINICAL TRIALS OF A NEW DRUG, IBUFENAC, IN THE TREATMENT OF RHEUMATOID ARTHRITIS

A PRELIMINARY REPORT

BY

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Since its introduction in 1899, aspirin has been widely prescribed for its anti-inflammatory and analgesic properties. Appreciation of its therapeutic imperfections, however, has led to the search for a compound of equal or greater effectiveness yet free from aspirin's troublesome side-effects. The purpose of this paper is to describe one such compound (Ibuprofen-4-isobutylphenyl-acetic acid), a substance possessing anti-inflammatory, analgesic and anti-pyretic properties in animal tests (Adams and Nicholson, 1961), and to report the results of the first clinical trials of this new drug.

Clinical assessment of Ibuprofen had been preceded by experience with two other substances which had shown promise of anti-inflammatory activity in preliminary biological tests. Of these, the first showed no suppression of the Trafton reaction (Truelove and Duthie, 1959), whereas the second did significantly modify it in a single oral dose of 30 gr. In clinical trials of these drugs, the first proved ineffective in controlling the symptoms of patients with rheumatoid arthritis, and the second, while controlling the symptoms adequately, was associated with the appearance of a purpuric rash in a high proportion of cases.

A placebo period was incorporated in the double-blind trials of these drugs. The use of placebo, however, was associated so constantly with exacerbations of symptoms that in subsequent trials the placebo period was omitted from the design.

Methods

Ibuprofen was given to in-patients in two short clinical trials, and these were followed by a longer trial of the drug in out-patients.

In-Patient Trials

Twelve patients, each with classical or definite rheumatoid arthritis as defined by the diagnostic criteria of the American Rheumatism Association (1959), were admitted to each of these trials. They were all receiving routine treatment of rest in bed, graduated physio-

therapy, conservative splinting, and salicylates before the period of trial.

The object of the first trial was to compare the effect of 60 gr. aspirin with that of 30 gr. Ibuprofen, when given daily for a period of one week. Each patient received each treatment for 7 days, the sequence being randomized.

In the second trial, the object was to assess the effect of doubling and of halving the dose of Ibuprofen used in the first trial. This trial ran for 3 consecutive weeks. During one week the patient received 60 gr. aspirin daily; during another he received 60 gr. Ibuprofen daily, and during a third he received 15 gr. Ibuprofen daily. Point of entry to the trial and sequence of treatments were randomly allocated.

In both trials the tablets employed were identical and patient and observer remained unaware of which preparation was being taken at any time. Assessments were carried out daily, beginning usually a few days before the commencement of the trial periods to accustom the patient to the methods used.

In the first trial assessment was restricted to daily estimations of strength of grip, using a mercury column dynamometer with the cuff initially inflated to 30 mm. Hg; three attempts were made with each hand, the average of the six readings being recorded.

In the second trial, in addition to estimations of strength of grip, estimations of joint tenderness (or pressure tolerance) were made daily. For this, the plunger of a 20-ml. syringe, padded with rubber, was pressed firmly three times over two selected joints in each hand, the hand and wrist being firmly supported. The syringe nozzle was connected to a small pressure gauge and pressure tolerance was expressed as the pressure at which the patient indicated experience of pain. The average of the twelve figures so observed was recorded as the pressure tolerance for the day.

In the second trial, weekly estimations of haemoglobin (as measured by the alkaline-haematin method) and of the erythrocyte sedimentation rate (modified Westergren method) were also noted.

Out-Patient Trial

After these two in-patient trials, a further trial was designed with the object of assessing the value of Ibuprofen for maintenance therapy in out-patients.

41 patients, of whom all but one were suffering from definite rheumatoid arthritis, were admitted to this trial in two groups. The first twelve patients (Group 1) were randomly given tablets containing either 5 gr. aspirin or 2½ gr. Ibufenac, and were asked to substitute these, tablet for tablet, for the anti-inflammatory/analgesic tablet they were currently taking, for a period of 4 weeks.

The 29 patients in Group 2 were given similar instructions, but after 4 weeks the tablets were interchanged and the trial continued for a further 4 weeks. By this double-blind cross-over technique, each patient in this group acted as his own control.

Each patient was encouraged to complete the trial period but was free at his own discretion to revert to his usual preparation should his symptoms become uncontrolled or serious side-effects develop.

Patients on steroid preparations were excluded from the trial. Assessments were made initially and at fortnightly intervals until the completion of the trial period. Most patients were seen again after a further 4 weeks. Functional capacity and disease activity were recorded, in addition to body weight, haemoglobin, erythrocyte sedimentation rate, total leucocyte count, platelet count, and sensitized sheep cell titre. Strength of grip was measured at each visit by the method previously described and as far as possible the patient was seen at the same time of day at each visit. The urine was tested for albumin and urobilinogen and examined microscopically. The patient was invited to comment on his progress, and any side-effects which had been noted were duly recorded.

Of the 41 patients admitted to the trial, it was found that only 23 patients had actually taken Ibufenac for a 4-week period. Of the remaining eighteen patients, some, from Group 1, had not been allocated the drug, while others, from Group 2, had withdrawn from the trial either before the end of their 4-week period on Ibufenac or before changing over to the drug.

The results for the 23 patients receiving Ibufenac for 4 weeks (Group 3) are considered separately.

Results

In-Patient Trials

The results of the estimations of strength of grip recorded in the first in-patient trial are set out in Table I, expressed as weekly averages obtained from the daily recordings. It is seen that:

- (i) Where any numerical differences, however small, are taken into account, aspirin was superior in six patients, Ibufenac was superior in five, and in one patient no difference was recorded.
- (ii) Where only marked numerical differences are taken into account, aspirin was superior in four patients, Ibufenac in two, and in the remain-

ing six patients the differences were not appreciable.

TABLE I
FIRST IN-PATIENT CLINICAL TRIAL

ESTIMATIONS OF STRENGTH OF GRIP

Patient No.	Weekly Average Grip Strength (mm. Hg)	
	While on Ibufenac (30 gr./day)	While on Aspirin (60 gr./day)
1	97	113
2	89	95
3	95	79
4	219	253
5	107	105
6	72	78
7	117	134
8	281	301
9	139	136
10	246	228
11	88	86
12	174	174
Mean . . .	143.5	148.5

The results of estimations of strength of grip and joint tenderness obtained in the second in-patient trial are shown in Table II (overleaf).

With regard to strength of grip, it is seen that six patients recorded their highest weekly average while taking aspirin, three while taking 60 gr. Ibufenac and two while taking 15 gr. Ibufenac. One patient did equally well on aspirin and on 15 gr. Ibufenac, and better on either than when on 60 gr. Ibufenac. The pattern obtained for grip estimations does not suggest that the sequence of treatments affected performance.

The same could not, however, be said of joint tenderness as an index of anti-inflammatory activity. When weekly averages for joint tenderness are considered chronologically, it is apparent that there is a tendency to improvement unrelated to sequence of treatment. This trend had been noted in previous trials in which joint tenderness has been used as an index of effectiveness.

During the short periods of trial, no significant differences were observed in haemoglobin levels or erythrocyte sedimentation rates.

TABLE II
SECOND IN-PATIENT CLINICAL TRIAL
ESTIMATIONS OF STRENGTH OF GRIP AND JOINT TENDERNESS (PRESSURE TOLERANCE)

Patient No.	Medication					
	Aspirin 60 (gr./day)		Ibufenac (60 gr./day)		Ibufenac (15 gr./day)	
	Grip Strength (mm. Hg)	Pressure Tolerance (lb./sq. in.)	Grip Strength (mm. Hg)	Pressure Tolerance (lb./sq. in.)	Grip Strength (mm. Hg)	Pressure Tolerance (lb./sq. in.)
1	365	20	346	16	259	16
2	110	14	107	15	95	8
3	297	15	342	14	351	13
4	230	15	221	14	204	14
5	82	7	102	19	96	12
6	246	8	242	10	258	11
7	197	19	206	18	188	15
8	275	18	261	17	206	16
9	197	18	177	14	186	16
10	93	1	101	0	93	1
11	80	4	72	3	80	6
12	400	16	379	14	324	12
Mean	214.3	12.9	213	12.8	195	11.6

Out-Patient Trial (Table III, opposite)

These patients will be considered in three groups:

GROUP 1. *Twelve patients who had either aspirin or Ibufenac for a trial period of 4 weeks.*—Of these, three did not complete the period of trial, leaving nine for consideration, five of whom had aspirin and four Ibufenac. The results for these nine patients show that, with regard to strength of grip, more patients on aspirin showed some improvement than on Ibufenac, but equal numbers showed slight deterioration. The results for sedimentation rate and haemoglobin showed no advantage for either drug, and the subjective index, based on the patients' comments on progress, suggested slight superiority for Ibufenac. The numbers involved in this group were, however, small.

GROUP 2. *29 patients who entered the 8-week double-blind cross-over trial.*—Of these, fifteen actually completed the trial period taking aspirin for 4 weeks and Ibufenac for 4 weeks.

The figures obtained from estimations of grip and erythrocyte sedimentation rate suggest that more patients showed some improvement when taking Ibufenac than when taking aspirin, and fewer

showed actual deterioration. The mean changes in haemoglobin level were too small to be meaningful and the subjective index showed little superiority with either drug.

GROUP 3. *23 patients who completed a 4-week period on Ibufenac but who did not, for various reasons, have aspirin for a similar period.*—The results for this group suggest that with regard to strength of grip, erythrocyte sedimentation rate, and subjective index, twice as many patients showed improvement while on Ibufenac as showed deterioration. Mean changes in haemoglobin values were again very small.

No changes were observed during the period of trial in the total leucocyte count, platelet count, or sensitized sheep cell titre, and no urinary abnormalities were noted.

Side-Effects.—During the two in-patient trials, no side-effects were observed. The side-effects recorded during the out-patient trial are shown in Table IV (opposite), which shows that Ibufenac was associated with gastro-intestinal upset in far fewer instances than aspirin.

TABLE III
RESULTS OF OUT-PATIENT CLINICAL TRIAL

Group	Index	Drug	Improvement		Patients Showing No Change	Deterioration	
			No. of Patients	Mean Improvement		No. of Patients	Mean Deterioration
1	Grip Strength (mm. Hg) ..	Aspirin	3	29	0	2	8.5
		Ibufenac	1	31	1	2	6.5
	E.S.R. (mm./1 hr) ..	Aspirin	3	2.3	0	2	22
		Ibufenac	2	7	1	1	1
	Haemoglobin (per cent.) ..	Aspirin	1	2	1	3	4.7
		Ibufenac	1	2	0	3	5
	Subjective Index ..	Aspirin	2		3	0	
		Ibufenac	3		1	0	
2	Grip Strength (mm. Hg) ..	Aspirin	8	31	1	6	17
		Ibufenac	11	24	1	3	17
	E.S.R. (mm./1 hr) ..	Aspirin	7	9	0	8	6
		Ibufenac	9	8	1	5	12
	Haemoglobin (per cent.) ..	Aspirin	9	2	0	6	2
		Ibufenac	8	3	2	5	5
	Subjective Index ..	Aspirin	5		9	1	
		Ibufenac	5		7	3	
3	Grip Strength (mm. Hg) ..	Ibufenac	14	23	2	7	10
	E.S.R. (mm./1 hr) ..	Ibufenac	14	7	2	7	7
	Haemoglobin (per cent.) ..	Ibufenac	10	4.3	3	10	5
	Subjective Index ..	Ibufenac	9		10	4	

TABLE IV
SIDE-EFFECTS NOTED IN OUT-PATIENT CLINICAL TRIAL

Side-Effect	While taking Usual Preparation before Trial Period	While taking Aspirin during Trial Period (a)	While taking Ibufenac during Trial Period (b)
Tinnitus ..	6	7	2
Deafness ..	3	2	1
Gastro-intestinal Symptoms ..	8	13	5
Skin ..	0	0	1
Other* ..	0	2	6

* Under "other" were included:

(a) With aspirin—giddiness; urinary frequency.

(b) With Ibufenac—palpitations; depression; giddiness; urinary frequency; sleep disturbance with nightmares.

Discussion

The results of these clinical trials would appear to indicate that Ibufenac is an acceptable drug for the treatment of the symptoms of rheumatoid arthritis. Of perhaps greater significance than any minor superiority or inferiority demonstrated by the

indices employed is the fact that no patient has shown any marked exacerbation of symptoms while taking the drug. In the out-patient trial, withdrawal at the patient's own discretion resulted in a relatively high loss of results for subsequent consideration, but it is of interest to record that an analysis of the reasons given for withdrawal revealed that as many patients had reverted to their usual anti-inflammatory/analgesic preparation while taking aspirin as reverted while taking Ibufenac.

It is concluded that Ibufenac is effective in the control of symptoms in rheumatoid arthritis, although no superiority over aspirin is apparent in this respect. The drug's usefulness would appear to be inherent in its potential for providing comparable symptomatic relief without comparable side-effects.

Summary

The results of three clinical trials of a new anti-inflammatory/analgesic substance (4-isobutylphenyl-acetic acid: Ibufenac) in patients with rheumatoid arthritis are presented and discussed.

It is concluded that Ibufenac is a useful drug in the treatment of the symptoms of rheumatoid arthritis. It appears to be as effective as aspirin in this respect at the dosage levels employed and its use was associated with considerably fewer side-effects.

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Essais cliniques d'un nouveau médicament, Ibufenac, dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

On présente et on discute les résultats de trois essais cliniques d'une nouvelle substance analgésique et anti-inflammatoire (acide 4-isobutylphénylacétique: Ibufenac) chez des malades atteints d'arthrite rhumatismale. On conclut que Ibufenac est un produit utile dans le traitement symptomatique de cette maladie. A cet effet en doses employées il semble être aussi efficace que l'aspirine avec des effets secondaires considérablement moins nombreux.

Ensayos clinicos de un nuevo fármaco, Ibufenac, en el tratamiento de la artritis reumatoide

SUMARIO

Se presentan y se discuten los resultados de tres ensayos clínicos de una nueva substancia analgésica y anti-inflamatoria (ácido 4-isobutilfenilacético: Ibufenac) en enfermos con artritis reumatoide. Se concluye que Ibufenac es un producto útil en el tratamiento sintomático de esta enfermedad. En este respecto, en dosis empleadas, parece ser tan eficaz como aspirina, con mucho menos efectos secundarios.