

# Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis

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Preliminary studies of flurbiprofen, a newly introduced anti-inflammatory agent, have shown that it exerts some anti-inflammatory and analgesic effects in man when compared with placebo and is relatively well tolerated (Chalmers, Cathcart, Kumar, Dick and Buchanan, 1972). The purpose of this paper is to compare the effects of flurbiprofen, indomethacin, and placebo under double-blind conditions in a group of patients with ankylosing spondylitis.

## Material and methods

The patient group studied consisted of 24 subjects, three females and 21 males. All had a negative sheep cell agglutination test and fulfilled the criteria for the diagnosis of ankylosing spondylitis (Bennett and Wood, 1968). Exclusions from the trial were made on the basis of a history of peptic ulceration, intolerance to Indomethacin, and concurrent steroid therapy. Details of the patient group are shown in Table I.

**Table I** *Clinical particulars of patients*

Total number	24	Female 3 Male 21
Mean age (yrs)	43.2	
Mean duration of disease (yrs)	16.5	
Mean spondylometry (total range)	34.7°	
Mean chest expansion (cm.)	4.3	

## TREATMENT ALLOCATION

Patients were randomly allocated to one of six treatment sequences. Indomethacin in a dose of 25 mg. three times a day was compared with flurbiprofen 50 mg. three times a day, and a placebo capsule containing lactose. The capsules were of identical size, shape, and colouring. A return capsule count was made at the end of each treatment period. The use of paracetamol tablets was allowed during the course of the trial and the number taken daily

was recorded on a pain diary. The trial period consisted of three 2-week treatment intervals.

## WITHDRAWALS

Four patients were withdrawn from the trial: two on indomethacin for indigestion and nausea, one on flurbiprofen for vertigo, and one during the placebo period because of a severe exacerbation of pain and stiffness.

## ASSESSMENTS

These were made before entry to the trial and at fortnightly intervals.

## Subjective

Each patient was provided with a diary on which he recorded daily pain values graded: 0 absent, + mild, ++ moderate, +++ severe, ++++ very severe. The duration of morning stiffness (limbering-up time) was also recorded in minutes. The overall degree of pain during each treatment period was recorded on a 10-cm. visual analogue scale—the magnitude of each score being the distance from the zero pain end of the scale to the position marked by the patient.

## Objective

A preliminary assessment was made and further assessments taken at the end of each 2-week treatment period. The range of spinal movement was measured on the Dunham spondylometer (Dunham, 1949), the coefficient of intra-observer variation for this instrument being 3.5 per cent. and the inter-observer error acceptable (Sturrock, Wojtulewski, and Hart, 1973). Chest expansion in cm. was measured at the nipple line in men and at the sub-mammary line in the female patients. Details of any side-effects during the trial were noted at each visit.

## LABORATORY INVESTIGATIONS

A full blood count, including platelet count, the erythrocyte sedimentation rate, standard liver function tests, blood urea, and urine analysis, were done before entry to the trial and at the end of each 2-week treatment period.

## Results

Twenty patients completed the trial and the results are summarized in Table II (overleaf). Three of the variables assessed the analgesic properties

**Table II** *Relative effectiveness of three forms of treatment*

Parameters compared	Comparison	Indomethacin	Placebo	Flurbiprofen	Difference	S.E.	No. of cases	t	Probability	
Subjective impression of pain (visual analogue scale)	Plac. v. Ind.	1.30	1.77		0.47	± 0.23	19	2.08	P ≈ 0.05	
	Plac. v. Flur.		1.77	1.16	0.61	± 0.20	19	2.98	P < 0.01	
	Ind. v. Flur.	1.30		1.16	0.14	± 0.17	19	0.79	P > 0.02	
Paracetamol count	Plac. v. Ind.	2.97	3.50		0.54	± 0.59	19	0.91	P > 0.2	
	Plac. v. Flur.		3.50	1.77	1.73	± 0.55	19	3.12	0.01 > P > 0.001	
	Ind. v. Flur.	2.97		1.77	1.19	± 0.39	19	3.09	0.01 > P > 0.001	
Limbering-up time (min.)	Plac. v. Ind.	34.1	96.7		62.6	± 41.1	18	1.51	0.1 < P < 0.2	
	Plac. v. Flur.		96.7	46.0	50.7	± 40.7	18	1.24	P > 0.2	
	Ind. v. Flur.	34.1		46.0	11.9	± 14.0	18	0.85	P > 0.2	
Spondylometry (range in degrees)	Plac. v. Ind.	39.0	35.9		3.1	± 1.2	20	2.62	0.02 > P > 0.01	
	Plac. v. Flur.		35.9	40.1	4.2	± 1.7	20	2.51	P ≈ 0.02	
	Ind. v. Flur.	39.0		40.1	1.1	± 1.7	20	0.67	P > 0.2	
Chest expansion (cm.)	Males	Plac. v. Ind.	5.4	4.9		0.5	0.2	17	2.22	0.05 > P > 0.02
		Plac. v. Flur.		4.9	5.1	0.2	0.2	17	0.62	P > 0.2
		Ind. v. Flur.	5.4		5.1	0.3	0.2	17	1.80	0.1 > P > 0.05
	Females	Plac. v. Ind.	2.8	2.7		0.2	0.4	3	0.38	P > 0.2
		Plac. v. Flur.		2.7	2.3	0.3	0.9	3	0.38	P > 0.2
		Ind. v. Flur.	2.8		2.3	0.5	0.8	3	0.66	P > 0.2
Mean daily pain scores	Comparison	Wilcoxon's T	No. of cases	Critical 5 per cent. Value of T	Probability					
	Plac. v. Ind.	77	19	53	P > 0.1				Favours indomethacin	
	Plac. v. Flur.	32	17	34	0.05 > P > 0.02				Favours flurbiprofen	
	Ind. v. Flur.	51.5	19	53	0.05 > P > 0.02				Favours flurbiprofen	

of the drugs—subjective impression of pain (visual analogue), mean daily pain scores, and the number of paracetamol tablets taken. All these three variables showed flurbiprofen to be significantly better than placebo at the 5 per cent. level of probability, and two of them showed flurbiprofen to be significantly better than indomethacin ( $P < 0.05$ ). The average limbering-up time was less than half that of placebo for both flurbiprofen and indomethacin, although these differences did not reach any level of significance because of the high variation inherent in this sort of data. Both flurbiprofen and indomethacin significantly increased the range of back movement as measured by the spondylometer, and indomethacin significantly increased male chest expansion compared with placebo.

#### Laboratory investigations

Of the laboratory variables measured, there were no changes in the haemoglobin, white cell count, platelets, or serum uric acid. The erythrocyte sedimentation rate was significantly reduced by flurbiprofen when compared with both placebo ( $0.05 > P > 0.02$ ) and indomethacin ( $0.02 > P > 0.01$ ).

#### Side-effects (Table III)

Fewer side-effects were reported in the flurbiprofen period than in the indomethacin period, although five patients complained of indigestion whilst on flurbiprofen.

#### Discussion

In this double-blind study, flurbiprofen has been shown to be superior to placebo and equipotent with indomethacin in improving the range of back movement in a group of patients with ankylosing spondylitis. Various measures of pain relief demonstrated flurbiprofen to be an effective analgesic and superior in this respect to both indomethacin and placebo under the trial conditions. The incidence of side-effects was low, when they did occur indigestion was the commonest symptom reported.

Various methods for the measurement of spinal movement in ankylosing spondylitis have been described (Moll and Wright, 1971; Loebel, 1967), although their use in monitoring changes occurring during the course of a drug trial has not been reported as far as we are aware. The Dunham spondylometer has been shown in this study to be capable of reflecting change in spinal mobility occurring during the various treatment periods of the trial and would seem to be a useful device for producing an objective quantitative measurement of spinal movement in ankylosing spondylitis.

#### Summary

The results of a double-blind cross-over trial of flurbiprofen in ankylosing spondylitis are presented. flurbiprofen was found to be superior to placebo in all of the assessment indices used and equipotent with

**Table III** Side-effects

System	Side-Effect	Drug		
		Indomethacin	Flurbiprofen	Placebo
Gastro-intestinal tract	Indigestion	3	5	1
	Nausea	1	1	1
	Diarrhoea	1		
	Wind	2	1	1
	Vomiting	1		
	Heart burn	1		
	Bad taste in mouth		1	
Central nervous system	Blurred vision			1
	Dizziness	1		
	Headache	3		1
Other	Skin eruption		1	
	Sweating			1
	Tiredness		1	
Total		13	10	6
Total patients with side-effects on each drug		11	6	5

indomethacin in improving spinal mobility. The analgesic properties of flurbiprofen were found to be significantly greater than those of indomethacin and placebo. The use of the Dunham spondylometer, as a measure of spinal mobility, during the trial period is described.

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## References

- BENNETT, P. H., AND WOOD, P. H. N. (1968) 'Population Studies of the Rheumatic Diseases', p. 456. Excerpta Medica, Amsterdam
- CHALMERS, I. M., CATHCART, B. J., KUMAR, E. B., DICK, W. C., AND BUCHANAN, W. W. (1972) *Ann. rheum. Dis.*, **31**, 319 (Clinico-pharmacological studies and clinical evaluation of flurbiprofen)
- DUNHAM, W. F. (1949) *Brit. J. phys. Med.*, **12**, 126 (Ankylosing spondylitis: measurement of hip and spine movements)
- LOEBL, W. Y. (1967) *Ann. phys. Med.*, **9**, 103 (Measurement of spinal posture and range of spinal movement)
- MOLL, J. M. H., AND WRIGHT, V. (1971) *Ann. rheum. Dis.*, **30**, 381 (Normal range of spinal mobility—an objective clinical study)
- STURROCK, R. D., WOJTULEWSKI, J. A., AND HART, F. DUDLEY (1973) *Brit. J. Rheum. Rehab.*, **12**, 135 (Spondylometry in a normal population and in ankylosing spondylitis)