Br. J. clin. Pharmac. (1980), **9**, 605–608

FLURBIPROFEN IN THE TREATMENT OF PRIMARY DYSMENORRHOEA

U.R. KRISHNA, S. NAIK, A. MANDLEKAR, K.C. GUPTA, V.N. KULKARNI & U.K. SHETH

Clinical Pharmacology Unit,
Seth G. S. Medical College and K.E.M. Hospital,
Bombay 12, India

1 In a double-blind crossover study, flurbiprofen produced marked relief of pain which was significantly more than with aspirin and placebo in patients suffering from primary dysmenorrhoea. In contrast, there was no significant difference between the relief of pain obtained with aspirin and placebo.

2 The clinician's overall assessment of efficacy also indicated that flurbiprofen produced better response as compared to aspirin and placebo in these patients with dysmenorrhoea.

3 Both flurbiprofen and aspirin did not produce any apparent adverse effects on blood loss during the menstrual period.

4 In conclusion, the analgesic effect of flurbiprofen seen in this trial establishes the therapeutic usefulness of the drug in the treatment of primary dysmenorrhoea.

Introduction

Primary dysmenorrhoea is one of the commonest gynaecological complaints and is a major cause of loss of work in young women. No consistently effective treatment has yet been devised, other than the use of antiovulatory oral contraceptives, a choice that is not always acceptable for obvious reasons. The etiology of primary dysmenorrhoea is not known, although many theories for its cause have been advanced.

There is increasing evidence to suggest that prostaglandins of the E and F series may be involved in the pathogenesis of dysmenorrhoea (Pickles, Hall, Best & Smith, 1965; Willman, Collins & Clayton, 1976; Chan & Hill, 1978). Discharge of endometrial prostaglandins may contribute to the cramps of dysmenorrhoea, and possibly to 'menstrual diarrhoea' as well. Recent clinical reports indicate that non-steroidal anti-inflammatory drugs which inhibit the enzyme complex, prostaglandin synthetase, are of value in the treatment of primary dysmenorrhoea (Schwartz, Zor, Lindner & Naor, 1974; Anderson, Haynes, Fraser & Turnbull, 1978; Halbert, Demers, Fontanna & Darnell Hones, 1978; Kapadia & Elder, 1978).

Flurbiprofen is a new and one of the most powerful of the anti-inflammatory agents in inhibiting the action of prostaglandin synthetase in various tissue systems (Blackham & Owen, 1975; Crook, Collins, Bacon & Chan, 1976). This feature of flurbiprofen prompted us to evaluate its efficacy in comparison with aspirin and placebo in the treatment of primary dysmenorrhoea.

Methods

Resident staff and student nurses aged between 14–26 years and suffering from primary dysmenorrhoea for at least 3 months were selected for the study. Nurses who gave a history of dyspepsia or peptic ulceration and those who were taking oral contraceptives were excluded from the trial.

The severity of pain of dysmenorrhoea when untreated was categorised as: moderate- pain though bearable produces some inhibition of normal activities; severe- pain, very distressing, severely limiting normal activities at least for 1 day; very severe- pain, worse, producing complete cessation of normal activities and necessity for bed rest at least for 1 day. Patients who complained of mild pain during previous periods were not included in the study.

Each patient received all three drugs, one at each menstrual period, as per order of drug administration given in Table 1. The three drugs, flurbiprofen, aspirin and placebo were administered as capsules of

0306–5251/80/060605–04 $01.00

Table 1 Treatment administration

	Treatment	
1	*2*	*3*
Flurbiprofen	Aspirin	Placebo
Aspirin	Placebo	Flurbiprofen
Placebo	Flurbiprofen	Aspirin
Aspirin	Flurbiprofen	Placebo
Flurbiprofen	Placebo	Aspirin
Placebo	Aspirin	Flurbiprofen

identical appearance; neither the clinician nor the patient knew the code identifying the drugs. Each capsule contained either flurbiprofen 25 mg, aspirin 300 mg or placebo. Patients were given three containers, each containing 30 capsules of either flurbiprofen, aspirin or placebo, and were asked to return the unused capsules to the clinician. No other analgesic anti-inflammatory drug was allowed during the treatment period.

The nature of the trial was explained to all patients after an initial interview during which a full medical and gynaecological history was noted. The patients were instructed to take two capsules of trial medication at the onset of dysmenorrhoea and continue taking two capsules at 8 hourly intervals until the symptoms disappeared. Aspirin was administered 8 hourly to maintain double-blind nature of the trial. Each patient was asked to fill up a self-assessment card which was provided to her during the menstrual period under study, and was asked to see the same clinician after each menstrual period.

The degree of pain relief obtained during treatment was graded as: 4-complete relief, when there was no pain at all; 3-marked relief, when pain was dull and there was no restriction of activities; 2-moderate relief, when pain was mild and there was some restriction of normal activities; 1-slight relief, when there was some relief and restriction of normal activities; 0-no relief. Each patient was instructed to assess the degree of pain relief obtained with each trial drug treatment, based on her previous experience of dysmenorrhoea, when untreated.

Blood loss, whether more, or less or same as compared to pre-trial menstrual blood loss was also recorded.

Any symptoms which may be related to the treatment were also noted down. The clinician's overall assessment of the efficacy of treatment was based on an interview with the patients regarding symptomatic relief obtained during each drug treatment. Efficacy of trial medication was graded as: 3-excellent; 2-good; 1-fair and 0-poor.

Results

Out of the 48 patients enrolled in the trial, nine patients did not complete the study. Three patients refused to participate subsequent to their initial enrolment in the trial. Six patients proceeded on leave after completion of one or two drug treatments and did not return to the clinic, and have not been included in the analysis. No patient dropped out due to occurrence of side-effects, and there was no bias in the drugs taken in the treatment cycles before patients dropped out.

Table 2 Patient characteristics

Number of patients	: 39		
Age (years) range	: 14–26	Mean	: 20
		±s.d.	: ±2.51
Duration of dysmenorrhoea (years)		Range	: 1–13
		Mean	: 4.3
		±s.d.	: ±3.39
Severity of dysmenorrhoea (Number of patients)	*Moderate*	*Severe*	*Very severe*
	1	29	9
Duration of pain during cycle (days)		Range	: 1–5
		Mean	: 1.4
		±s.d.	: ±0.749
Length of the menstrual cycle (days)		Range	: 21–45
		Mean	: 30.3
		±s.d.	: ±3.916
Blood loss during period (Number of patients)	*Average*	*Slight*	*Heavy*
	29	2	8

Table 3 Pain relief score

	Treatment		
	Placebo	*Aspirin*	*Flurbiprofen*
Mean pain relief score ± s.e. mean	1.8 ±0.28	2.5* ±0.27	3.4** ±0.18

*No significant difference compared to placebo ($P > 0.05$)
**Significant difference compared to placebo ($P < 0.001$) and aspirin ($P < 0.02$)

Thirty-nine patients completed the trial. The profile of these patients is shown in Table 2. The various symptoms reported by the patients included abdominal pain, backache, vomiting, leg pain, headache, giddiness and constipation. The only symptoms recorded by all patients in each menstrual cycle were abdominal pain and backache, the other symptoms being less constant.

Mean pain relief score for each drug is shown in Table 3. Both aspirin and flurbiprofen produced greater relief than placebo. Statistical analysis was carried out applying Wilcoxon's matched-pairs

signed-ranks test, to compare the efficacy of trial treatments. Flurbiprofen was significantly superior to aspirin and placebo in relieving pain during the menstrual period. Although aspirin produced greater relief of pain than placebo, the difference between the two drugs did not reach a level of statistical significance.

Since out of the 48 patients enrolled, only 39 patients completed all three trial treatments, the sequences of drug administration were not balanced. Flurbiprofen was received by 15 patients, aspirin by 11 and placebo by 13 as the first trial drug. Therefore, further analysis was carried out to see the effect of order on administration of drugs. Table 4 shows mean pain relief score obtained in all three trial treatments, irrespective of drugs received by patients. Statistical analysis of this data applying Friedman's two-way analysis of variance test indicates that there is no influence of order of drug administration on the results of this study.

All patients complied with the instruction to take two tablets at a time. The trial drugs, flurbiprofen, aspirin and placebo were taken for 1.4 ± 0.105; 1.6 ± 0.152 and 1.5 ± 0.142 mean number of days respectively, during menstrual period. These figures did not differ significantly from one another ($P > 0.05$).

Menstrual blood loss during treatment with flurbiprofen, aspirin and placebo was compared with pre-trial menstrual blood loss (Table 5). Most of the patients had no change in menstrual blood loss compared to their pre-trial blood loss. Some apparent increase/decrease was seen in some patients during trial treatment. On comparison of changes produced in menstrual blood loss, no significant differences were seen between the trial drugs ($P > 0.05$).

The clinician's overall assessment of efficacy was based on an interview with the patients after completion of each trial treatment. Analysis of data indicates that better response was seen with flurbiprofen as compared to aspirin and placebo (Table 6). No side-effects were reported in this trial.

Table 4 Mean pain relief score: Effect of order of drug administration

	Treatment 1	*Treatment 2*	*Treatment 3*
Mean pain relief score ±s.e. mean	2.7 ±0.25	2.4* ±0.26	2.5* ±0.27

*No significant difference compared to treatment 1 ($P > 0.05$)
**No significant difference compared to treatment 1 ($P > 0.05$) and treatment 2 ($P > 0.05$)

Table 5 Menstrual blood loss during treatment with placebo, aspirin and flurbiprofen

Menstrual blood loss compared to pre-trial blood loss	*Number of patients*		
	Placebo	*Aspirin*	*Flurbiprofen*
No change	30	29	26
More	6	5	5
Less	3	5	8

Discussion

Methodologically, the trial design as implemented was able to discriminate with clarity between the analgesic potencies of the three trial drugs, flurbiprofen, aspirin and placebo.

It is well recognized that psychogenic factors may play a part in the development of this syndrome (Novak, Jones & Jones, 1970), and Henzl, Buttram, Segre & Bessler (1977) have reported some relief in dysmenorrhoea with placebo therapy. Although relief of pain was seen with placebo in some patients in this study, flurbiprofen was significantly more effective in relieving pain compared to placebo ($P < 0.001$), indicating specific analgesic action of the drug.

Since prostaglandins are suggested to be involved in the pathogenesis of dysmenorrhoea, flurbiprofen was also compared with aspirin, a commonly used analgesic and also a prostaglandin synthetase inhibitor (Vane, 1971). The results show that flurbiprofen is also significantly more effective in relieving pain which is the most common symptom of dysmenorrhoea, than aspirin. As per another clinical report available, aspirin did not differ significantly compared to placebo (Rogers & Grace Reese, 1967).

Recently published studies with other prostaglandin synthetase inhibitors are in general agreement with our results. One study reported indomethacin to be effective in the treatment of dysmenorrhoea (Elder & Kapadia, 1979). Another study established the efficacy of naproxen sodium compared to placebo (Henzl *et al.*, 1977). Mefenamic acid and flufenamic acid, both prostaglandin synthetase inhibitors have been shown to be more effective in the treatment of primary dysmenorrhoea than analgesics such as dextropropoxyphene/paracetamol (Anderson *et al.*, 1978).

Although all these non-streoidal anti-inflammatory drugs inhibit prostaglandin synthesis, their therapeutic efficacy parallels their ability to inhibit prostaglandin synthetase to a remarkable extent (Goodman & Gilman, 1975). Flurbiprofen has been shown to be a potent inhibitor of prostaglandin synthesis as compared to aspirin and other non-steroidal anti-inflammatory drugs (Blackham & Owen, 1975; Crook *et al.*, 1976). It is conceivable,

Table 6 Clinician's overall assessment

	Placebo	*Aspirin*	*Flurbiprofen*
Number of observations	39	39	39
Mean grade	1.4	1.7*	2.2**
±s.e. mean	±0.19	±0.18	±0.14

*No significant difference compared to placebo ($P > 0.05$)
**Significant difference compared to placebo ($P < 0.01$), and no significant difference compared to aspirin ($P > 0.05$)

however, that the pain relieving effect of non-stroidal anti-inflammatory drugs is also mediated at other levels.

In conclusion, the analgesic effect of flurbiprofen seen in this study establishes the therapeutic usefulness of the drug in the symptomatic treatment of primary dysmenorrhoea.

The authors express their gratitude to the Medical Department, The Boots Company (India) Limited, for the design of the protocol and for supply of drugs used in this study.

References

ANDERSON, A.B.M. HAYNES, P.J., FRASER, I.S. & TURNBULL, A.C. (1978) Trial of prostaglandin synthetase inhibitors in primary dysmenorrhoea, *Lancet*, **i**, 345–348

BLACKHAM, A. & OWEN, R.T. (1975). Prostaglandin synthetase inhibitors and leucocytic migration, *J. Pharm. Pharmac.*, **27**, 201–203.

CHAN, W.Y. & HILL, J.C. (1978). Determination of menstrual prostaglandin levels in non-dysmenorrheic and dysmenorrheic subjects, *Prostaglandins*, **15**, 365–375

CROOK, D., COLLINS, A.J., BACON, P.A. & CHAN, R. (1976). Prostaglandin synthetase activity from human rheumatoid synovial microsomes-effect of aspirin-like drug therapy, *Ann. Rheum. Dis.*, **35**, 327–332.

ELDER, M.G. & KAPADIA, L. (1979). Indomethacin in the treatment of primary dysmenorrhoea, *Br. J. Obstet. Gynaec.*, **86**, 645–647.

GOODMAN, L.S. & GILMAN, A. (1975). *The Pharmacological Basis of Therapeutics*, Fifth edition, pp. 640–647. London: Macmillan Publishing Company.

HALBERT, D.R., DEMERS, L.M., FONTANA, J. & DARNELL JONES, D.E. (1975). Prostaglandin levels in endometrial jet wash specimens in patients with dysmenorrhoea before and after indomethacin therapy, *Prostaglandins*, **10**, 1047–1056.

HENZL, M.R., BUTTRAM, V., SEGRE, E.J. & BESSLER, S (1977). The treatment of dysmenorrhoea with naproxen-sodium-a report on two independent double-blind trials, *Am. J. Obstet. Gynaec.*, **127**, 818–823.

KAPADIA, L. & ELDER, M.G. (1978). Flufenamic acid in the treatment of primary spasmodic dysmenorrhoea, *Lancet*, **i**, 348–350.

NOVAK, E.R., JONES, G.S. & JONES, H.W. (1970). *Novak's Textbook of Gynaecology*, Eighth edition, pp. 635–643. Baltimore: Williams & Wilkins Company.

PICKLES, V.R., HALL, W.J., BEST, F.A. & SMITH, G.N. (1965). Prostaglandins in endometrium and menstrual fluid from normal and dysmenorrheic subjects, *J. Obstet. Gynaec. Br. Commonw.*, **72**, 185–192.

ROGERS, K.D. & GRACE REESE, R.N. (1967). Aspirin for treatment of minor illness in adolescents, *Am. J. Dis. Child*, **114**, 55–63.

SCHWARTZ, A., ZOR, U., LINDNER, H.R. & NAOR, S. (1974). Primary dysmenorrhoea alleviation by an inhibitor of prostaglandin synthesis and action, *Obstet. Gynaec.*, **44**, 709–712.

VANE, J.R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs, *Nature New Biol.*, **231**, 232–235.

WILLMAN, E.A., COLLINS, W.P. & CLAYTON, S.C. (1976). Studies in the involvement of prostaglandins in uterine symptomatology and pathology, *Br. J. Obstet. Gynaec.*, **83**, 337–341.

(*Received September 28, 1979*)