Europ. J. Obstet. Gynec. reprod. Biol., 12 (1981) 189—194
Elsevier/North-Holland Biomedical Press

TREATMENT OF PRIMARY DYSMENORRHEA WITH DICLOFENAC SODIUM

P. RIIHILUOMA, E. WUOLIJOKI and M.O. PULKKINEN

Student Health Center, and Department of Obstetrics and Gynecology, University of Turku, Turku, Finland

Accepted for publication 7 May 1981

RIIHILUOMA, P., WUOLIJOKI, E. and PULKKINEN, M.O. (1981): Treatment of primary dysmenorrhea with diclofenac sodium. *Europ. J. Obstet. Gynec. reprod. Biol.*, *12/3*, 189—194.

The efficacy of diclofenac sodium was investigated in the painful symptoms of primary dysmenorrhea and in reducing menstrual bleeding. Thirty-five nulliparous women (17—28 yr of age) were included in a double-blind cross-over study for four menstrual periods, two periods with diclofenac sodium and two periods with placebo. The diclofenac sodium treatment (total of 58 periods) reduced the pain significantly in comparison with placebo (57 periods), as evaluated by subjective rating ($P < 0.001$) and by a 6-point scale of pain intensity ($P < 0.05$). Also the amount of menstrual bleeding was significantly reduced as measured by subjective rating ($P < 0.001$) and by counting the number of sanitary pads used ($P < 0.05$). The results indicate that diclofenac sodium in low doses (about 75 mg daily) is effective not only in reducing the pain at menstruation, but also the bleeding.

diclofenac sodium; dysmenorrhea; menstrual bleeding

INTRODUCTION

The efficacy of prostaglandin synthesis inhibitors in painful primary dysmenorrhea has been reported and discussed in several reviews (Ylikorkala and Dawood, 1978; Marx, 1979).

As menstrual pain is supposed to be closely connected with increased uterine activity and high concentrations of prostaglandins in the menstrual blood (Pulkkinen, 1979), inhibition of prostaglandin synthesis is one possibility for reducing menstrual pains.

Diclofenac sodium (the sodium salt of *o*-(2,6-dichloroanilino)phenylacetate (Fig. 1) is believed to be one of the most powerful inhibitors of prostaglandin synthesis (Mathies, 1979). It has antiinflammatory, antipyretic and analgesic effects, and it also exerts an inhibitory action on platelet aggregation.

Address for correspondence: Martti O. Pulkkinen, M.D., Naistenklinikka, Turun yliopistollinen keskussairaala, 20520 Turku 52, Finland.

0028-2243/81/0000—0000/$02.50

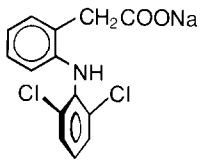

Fig. 1. Chemical structure of diclofenac sodium.

In addition, diclofenac sodium produces antipyretic and analgesic effects even in low doses as compared to other prostaglandin synthesis inhibitors (Krupp et al., 1976, Brogden et al., 1980). These properties prompted us to examine whether diclofenac sodium would have an effect on menstrual pain and the amount of menstrual bleeding.

MATERIAL AND METHODS

Thirty-five nulliparous women suffering from painful menstruation consented to participate in the trial. All medical histories were investigated and each woman was given a gynecological examination for the exclusion of secondary dysmenorrhea, desired pregnancy or contraindications to diclofenac sodium therapy. Basic information on the subjects is given in Table I. The subjects were students from the University of Turku, attending the Students' Health Center of the University.

Twenty-nine of the 35 patients completed the trial: a total of 58 periods on diclofenac sodium and 57 on placebo. Two pregnancies, one move from the district, two insufficient compliances and one exclusion due to oral contraceptive use were the causes for the six drop-outs. Twenty-four of the subjects had had to stay at home or in bed due to pain before the trial.

The investigation was performed as a double-blind cross-over trial with two randomized patient groups. The first group took the medication for four menstrual periods in the following sequence: diclofenac sodium, placebo, diclofenac sodium, placebo. The other group had the same treatment in reverse order. Diclofenac was prescribed t.i.d. as a 25 mg Voltaren® tablet for 2 to 7 days after the first symptoms of menstruation. The patients were

TABLE I

BASIC DATA ON THE SUBJECTS

Parameter	Mean ± SD	Range
Age	21.7 ± 3.2 yr	17—28
Weight	57.0 ± 9.2 kg	45—80
Menstrual cycle	29.5 ± 3.5 days	24—42
Duration of menstruation	5.4 ± 0.9 days	4— 7
Pain score according to the six-point scale	4.9 ± 1.0	3— 6

told that the dose could be increased up to six tablets a day, if needed. In case of insufficient effect the patients had the possibility of taking rescue analgetics. The trial medication was stopped when the pain ceased. The subjects were seen five times (before the trial for exclusion of secondary dysmenorrhea and after each of the four menstruations) for providing new medication, filling in the case record forms and counting the tablets used.

The pain in the lower abdomen was assessed in two ways, as follows:

A. By a six-point scale of pain intensity:
   1. no pain
   2. mild pain
   3. moderate pain
   4. heavy pain, but patients able to work
   5. pain forcing confinement at home
   6. pain forcing confinement to bed.

B. By subjective scoring of pain, as compared to the previous menstruation:
   1. much worse
   2. worse
   3. equal
   4. less
   5. much less.

The amount of bleeding was also scored in two ways:

A. By subjective assessment of bleeding as compared to the previous menstruation:
   1. lighter
   2. normal
   3. heavier.

B. By counting the number of sanitary pads used.

The patients used a daily card covering the menstruation for recording the following variables: number of days of bleeding, edema, depression, nausea, diarrhea, pain in the upper abdomen, heartburn, headache, dizziness and other symptoms.

RESULTS

Menstrual pain

The six-point scale of pain intensity produced a mean score of 3.3 ± 0.2 (SE) for diclofenac sodium and 3.9 ± 0.2 for placebo ($P < 0.05$, analysis of variance). The mean pain in the lower abdomen as compared to the previous menstruation was subjectively scored at 3.8 ± 0.1 for diclofenac sodium and 3.0 ± 0.1 for placebo ($P < 0.001$, analysis of variance). The results are also given in Tables II and III.

The mean duration of pain in diclofenac sodium periods was 1.9 ± 0.1 days and in placebo periods 2.0 ± 0.1 days. The mean number of tablets taken during one menstrual period was 6.6 ± 0.5 for diclofenac sodium and 7.6 ± 0.6 for placebo. By all measurement methods diclofenac sodium had

TABLE II

INTENSITY OF MENSTRUAL PAIN AS SCORED WITH A SIX-POINT RATING SCALE

Pain score	Intensity of pain	No. of periods	
		Diclofenac sodium	Placebo
1	no pain	4	3
2	mild pain	20	10
3	moderate pain	13	11
4	heavy, but patients able to work	7	11
5	pain forcing confinement at home	6	8
6	pain forcing confinement to bed	8	14
Total		58	57

an analgesic effect compared with placebo. Pain forced patients to stay at home or in bed during fourteen menstrual periods in the diclofenac group and twenty-two in the placebo group.

Amount of bleeding

The mean subjective score as compared with the values of the previous menstruation, was 1.8 ± 0.1 (SE) for diclofenac sodium and 2.2 ± 0.1 for placebo ($P < 0.001$, chi-square test), see Table IV.

The number of sanitary pads was 15.9 ± 0.6 for diclofenac sodium and 18.3 ± 1.0 for placebo ($P < 0.05$, analysis of variance). The mean duration of bleeding was 5.5 ± 0.1 days for diclofenac sodium and 5.6 ± 0.2 days for placebo. The number of sanitary pads used during active treatment was reduced in 19 patients, increased in 5 patients, and remained unchanged in 6 patients, as compared to placebo ($P < 0.01$, sign test). Thus diclofenac

TABLE III

EVALUATION OF PAIN AS COMPARED WITH THE PREVIOUS MENSTRUATION

Pain score	Intensity of pain	No. of periods	
		Diclofenac sodium	Placebo
1	much worse	2	5
2	worse	5	17
3	equal	11	15
4	less	26	15
5	much less	14	5
Total		58	57

TABLE IV

AMOUNT OF MENSTRUAL BLEEDING AS COMPARED WITH THE PREVIOUS MENSTRUATION

Amount of bleeding	No. of periods	
	Diclofenac sodium	Placebo
Lighter	15	3
Normal	40	41
Heavier	2	13
Total	57 [a]	57

[a] Missing data in one case.

sodium treatment reduced the amount of bleeding as compared with placebo. This was seen both in subjective rating scores and in the numbers of sanitary pads used. The incidence of other symptoms recorded is presented in Table V.

Diclofenac sodium exerted a beneficial effect on five of the symptoms,

TABLE V

SYMPTOMS RECORDED IN THE SUBJECTS' DAILY DIARY

Symptom		No. of days during the trial	No. of menstruations the symptom was present
Oedema	DS [a]	37	20
	P [b]	37	18
Depression	DS	35	18
	P	35	18
Nausea	DS	29	17
	P	39	22
Diarrhea	DS	21	15
	P	24	19
Pain in upper abdomen	DS	29	17
	P	23	14
Heartburn	DS	10	4
	P	10	6
Headache	DS	38	21
	P	46	20
Dizziness	DS	24	15
	P	32	21
Others [c]	DS	39	17
	P	51	22

[a] Diclofenac sodium.
[b] Placebo.
[c] Mainly backpain and tiredness.

only pain in the upper abdomen being more prevalent in the diclofenac sodium group ($P > 0.05$). None of the patients were withdrawn from the trial due to intolerance to the medication. Rescue analgesic (tolfenamic acid) was prescribed in four cases: three on placebo and one on diclofenac sodium.

DISCUSSION

The efficacy of diclofenac in painful dysmenorrhea and as a bleeding reduction agent became evident in the trial. Menorrhagia can be treated with a prostaglandin synthetase inhibitor (Anderson et al., 1976). Even the relatively low dosage (typical for long-term treatment in rheumatology) tended to improve the patients disability to work. As lower average scores for nausea, diarrhea, headache and dizziness also occurred during low-dose diclofenac sodium treatment, larger dosages may reduce these dysmenorrheic symptoms even more clearly.

There was more difference in the sixpoint pain scale between basic data and placebo than between diclofenac sodium and placebo. This stresses how important a proper study design is (double-blind, randomized) when dealing with subjective parameters like pain.

ACKNOWLEDGEMENTS

The authors are indebted to Ms. Marja-Liisa Harju for her technical assistance, and to CIBA-GEIGY Medical Department, Helsinki, for the drug supply.

REFERENCES

Anderson, A.B.M., Haynes, P.J., Guilleband, J. and Turnbull, A.C. (1976): Reduction of menstrual blood-loss by prostaglandin synthetase inhibitors. Lancet, 1, 774—776.

Brogden, R.N., Heel, R.C., Pakes, G.E., Speight, T.M. and Avery, G.S. (1980): Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic disease and pain of varying origin. Drugs, 20, 24—28.

Krupp, P., Menasse, R. and Ziel, R. (1976): Chemistry and pharmacology of diclofenac in Voltaren. In: Proceedings of a Symposium held during the VIIIth European Rheumatology Congress, Helsinki 1975, pp. 13—18. Hans Huber Publishers, Bern.

Marx, J. (1979): Dysmenorrhea: basic research leads to rational therapy. Science, 205, 175—176.

Mathies, H. (1979): The mechanism of action of antirheumatic agents. Triangle (En.), 130, 65.

Pulkkinen, M. (1979): Suppression of uterine activity by prostaglandin synthetase inhibitors. Acta Obstet. Gynec. Scand. Suppl., 87, 39—43.

Ylikorkala, O. and Dawood, Y. (1978): New concepts in dysmenorrhea. Amer. J. Obstet. Gynec., 120, 833—847.