Efficacy of ketoprofen in treating primary dysmenorrhea

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A 6-month double-blind crossover trial compared ketoprofen with placebo in the treatment of primary dysmenorrhea in 27 women who satisfied explicit inclusion and exclusion criteria. The response to treatment was assessed with a pain scale and a disability scale and by noting amelioration of associated symptoms, such as nausea, vomiting, diarrhea, fatigue, dizziness and headache. Ketoprofen was significantly superior to placebo in relieving the pain ($p < 0.001$), disability ($p < 0.001$) and headache ($p < 0.01$) associated with menstruation. No order effect of treatment was observed. Adverse effects were few and minimal.

Une étude à double insu en chassé-croisé d'une durée de 6 mois a comparé le kétoprofène au placebo dans le traitement de la dysménorrhée primaire chez 27 femmes qui répondaient à des critères formels d'inclusion et d'exclusion. La réponse au traitement fut évaluée sur des échelles de la douleur et d'incapacité physique, de même qu'en observant l'amélioration de symptômes associés, tels que nausée, vomissement, diarrhée, fatigue, étourdissement et céphalée. Le kétoprofène s'est montré significativement supérieur au placebo pour soulager la douleur ($p < 0.001$), l'incapacité ($p < 0.001$) et la céphalée ($p < 0.01$) reliées aux menstruations. Aucun effet de la séquence des traitements ne fut observé. Les effets secondaires furent triviaux et peu nombreux.

Dysmenorrhea may affect over 50% of women at some time in their lives.[1] Primary dysmenorrhea, which occurs in the absence of pelvic disease, incapacitates about 10% of women suffering from it;[1] associated symptoms may include nausea, vomiting, diarrhea, fatigue, dizziness and headache.[2]

For years the cause of primary dysmenorrhea was poorly understood, but research has recently implicated the prostaglandins, particularly $PGF_{2\alpha}$.[3,4] PGE_2 and $PGF_{2\alpha}$ are normally secreted by the endometrium, but it appears that women with dysmenorrhea secrete $PGF_{2\alpha}$ during menstruation in concentrations approximately four times those of matched controls.[5,6] $PGF_{2\alpha}$ has been shown to promote strong contractions of the uterine muscle, thus causing pain.[3,4]

Nonsteroidal anti-inflammatory drugs produce their analgesic effect by inhibiting prostaglandin synthesis.[7,8] Long known to be effective against arthritis, several of these drugs, including mefenamic acid, naproxen sodium and ibuprofen, have recently been shown to relieve dysmenorrhea in most women.[2,8,9] Ketoprofen, an arylpropionic acid derivative similar to naproxen and ibuprofen, has been shown in vitro to be a potent inhibitor of prostaglandin synthetase.[10,11] It is currently approved in Canada for the treatment of arthritis, but not yet for the treatment of dysmenorrhea.

There is a strong placebo effect when one is treating any type of pain with a medication. In a double-blind crossover trial comparing placebo with naproxen sodium, Lundström[2] found that 34% of women with dysmenorrhea experienced moderate to marked relief while taking placebo. We compared the efficacy of ketoprofen and placebo in the treatment of primary dysmenorrhea using a double-blind crossover design.

Methods

We recruited 31 women between the ages of 16 and 31 years from the practices of family physicians in Kingston, Ont. The women had regular menstrual periods, suffered from primary dysmenorrhea severely enough to require analgesics and did not use an intrauterine contraceptive device or oral contraceptives. They were in good physical health and showed no evidence of asthma or hepatic or renal disease. Each woman was interviewed at the initial visit by one of the investigators and asked to rate the severity of the pain associated with most of her menstrual periods using a scale of 1 to 10, with a score of 1 indicating mild pain and 10 representing severe pain. Likewise, she was asked to rate the usual disability associated with her periods, with a score of 1 indicating little, if any, interference with normal activities and 10 representing complete incapacity for at least half a day. The women were also questioned about the presence of associated symptoms and asked to rate their severity on a scale of 0 to 4.

Each woman received 3 consecutive months' treatment with ketoprofen and 3 consecutive months' treatment with lactose as a placebo, the order being determined by the use of a random numbers table. The capsules of ketoprofen and placebo were identical in appearance. Each month the women received 12 capsules and were instructed to start using these either at the onset of menstruation or at the onset of symptoms of dysmenorrhea after menstruation began. They were told to take the capsules at intervals of 4 to 6 hours, to take no more than four capsules per day for no more than 3 days, and to discontinue the capsules whenever their symptoms subsided.

Following each menstrual period the women filled out

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a questionnaire in which they graded the severity of their pain after starting to take the medication, using the 1 to 10 scale described earlier. They also graded the degree of disability experienced and the severity of any associated symptoms and noted any adverse effects. The pain scores recorded by each woman were summed for the three placebo cycles and for the three ketoprofen cycles, then the total score for the ketoprofen cycles was subtracted from the total for the placebo cycles. Laboratory tests were performed on each woman to evaluate hematologic parameters and hepatic and renal function at the initial visit, after the first 3 months of treatment and after completion of the trial.

Data were analysed by the Wilcoxon signed rank test[12] to determine differences between the drug and placebo cycles in the control of pain, disability and associated symptoms. A p value of less than 0.05 was considered statistically significant. For each of these parameters the group that received ketoprofen first was compared with the group that received placebo first to determine if the order of treatment influenced its effectiveness. This was done by means of the Wilcoxon rank sum test.[12]

Table I—Pain severity scores* for each of 27 women while taking placebo or ketoprofen and the differences between the two scores

Placebo score	Ketoprofen score	Placebo score minus ketoprofen score
11	4	7
12	4	8
18	24	−6
24	7	17
17	13	4
18	15	3
11	3	8
7	12	−5
15	12	3
16	21	−5
7	4	3
17	16	1
13	5	8
4	11	−7
15	8	7
19	17	2
9	5	4
12	3	9
10	12	−2
18	12	6
19	8	11
23	4	19
24	9	15
15	6	9
18	11	7
8	3	5
20	7	13

*Summed for three cycles of treatment.

Table II—Adverse effects of ketoprofen and placebo in the 27 women

Adverse effect	No. of patients	
	Ketoprofen	Placebo
Tinnitus	2	3
Easily bruised	–	3
Heartburn	2	3
Pruritus	3	4
Rash	–	1
Total	7	14

Results

Of the 31 women 27 completed the trial; 3 women wished to start using oral contraceptives and 1 became pregnant. The mean age of the women was 21.7 years. The mean age at menarche was 11.9 years, and the mean age at the onset of dysmenorrhea was 14.4 years.

As Table I shows, ketoprofen was significantly more effective than the placebo ($p < 0.001$) in relieving pain and in reducing disability during menstruation. Of the 27 women 22 (81%) had less pain and 20 (74%) less disability during the ketoprofen cycles compared with the placebo cycles. Only one of the associated symptoms, headache, was significantly diminished ($p < 0.01$) during ketoprofen treatment. No significant effect was observed for the order in which ketoprofen and placebo were administered.

Although 7 women experienced adverse effects while taking ketoprofen, 14 experienced adverse effects while taking the placebo (Table II). Only one woman experienced a side effect that she did not also experience while taking the placebo. No one left the trial because of adverse effects.

The results of the laboratory tests were all within normal limits.

Discussion

In our study ketoprofen was superior to placebo in relieving the pain and disability associated with menstruation. Only one other trial of ketoprofen treatment for primary dysmenorrhea has been carried out, but a placebo was not used. Kauppila and associates[13] compared ketoprofen with indomethacin using a double-blind crossover design. Good or moderate relief of pain was obtained in 88% of the ketoprofen-treated cycles and 90% of the indomethacin-treated cycles, and the proportion of women who lost working days was reduced from 78% before treatment to 4% with ketoprofen and 9% with indomethacin.

Indomethacin, although effective in the treatment of primary dysmenorrhea, is contraindicated because of the frequent occurrence of unpleasant and serious adverse effects, including headache (in 20% to 60% of individuals) and, more rarely, agranulocytosis and aplastic anemia.[14-16] Ketoprofen, on the other hand, has been associated with a low frequency of adverse effects, none of which are serious or irreversible.[17] In our study only one patient experienced an adverse effect that was not also experienced during the placebo treatment, and in no case were hematologic parameters altered by treatment with ketoprofen.

Ketoprofen was significantly superior to placebo in relieving headache in this study. Recently several studies have been published on the efficacy of prostaglandin synthetase inhibitors in the treatment of headache. Zomepirac sodium was reported to be superior to placebo in the treatment of muscle contraction head-

ache,[18] and naproxen was found to be superior to placebo in reducing the severity of migraine headache.[19] Although prostaglandin synthetase inhibitors may be useful in the treatment of headache, the mechanism of action is as yet poorly understood.

Medications containing codeine have been used in the treatment of primary dysmenorrhea; however, these can cause tolerance and addiction. Oral contraceptives are usually effective in relieving dysmenorrhea, but their use should be reserved for those requiring contraception since long-term use increases the risk of thromboembolic disease, myocardial infarction and stroke.[20] Nonsteroidal anti-inflammatory drugs, on the other hand, do not cause tolerance or addiction, can be taken just during the days the woman experiences dysmenorrhea and do not seem to be associated with cardiovascular side effects. Thus, prostaglandin synthetase inhibitors appear to be the rational first choice for treating primary dysmenorrhea in young women, especially those who are not sexually active.[16]

Mefenamic acid, naproxen sodium and ibuprofen have been approved for the treatment of dysmenorrhea. Ketoprofen is another nonsteroidal anti-inflammatory drug that may be used safely and effectively to relieve primary dysmenorrhea.

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