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Prostaglandin Inhibitors: Rational Therapy for Dysmenorrhea

SUMMARY

Dysmenorrhea affects at least 50% of women at some time in their lives. Painful contractions of the uterine muscle (similar to labor pains) are triggered by increased endometrial synthesis of prostaglandins, which appear in elevated amounts in the plasma and menstrual fluid of women with dysmenorrhea. Non-steroidal anti-inflammatory drugs, which have been used for years in arthritis, are effective prostaglandin inhibitors. Taken by mouth at the onset of menstruation, they can relieve dysmenorrhea in the majority of cases. This is a major advantage for women in whom oral contraceptives are not indicated. (Can Fam Physician 1982; 28:91-94).

SOMMAIRE

Au moins 50% des femmes souffrent de dysménorrhée à un moment ou à un autre de leur vie. De fortes contractions (analogues aux douleurs du travail) des muscles utérins sont déclenchées par une augmentation de la synthèse endométriale de prostaglandines, qui apparaissent en quantités élevées dans le plasma et le liquide menstruel des femmes souffrant de dysménorrhée. Les médicaments anti-inflammatoires sans stéroïdes, utilisés depuis des années pour traiter l'arthrite, sont de puissants inhibiteurs des prostaglandines. Pris oralement au début des règles, ils peuvent soulager la dysménorrhée dans la majorité des cas. Un avantage important lorsque les contraceptifs oraux ne sont pas indiqués.

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A SURVEY of dysmenorrhea in a family practice population found that at least 50% of women had experienced menstrual pain at some time and 30% had experienced it within the preceding two months.[1] Very few had sought medical attention for this disorder and the records showed that dysmenorrhea was listed as a diagnosis in only 1% of female patients. Dysmenorrhea has been estimated to cause 140 million lost work hours annually,[2] and at least one day's absence from school each year for 20% of high school girls.[3]

Dysmenorrhea may be primary or secondary. Primary dysmenorrhea occurs in the absence of pelvic disease and secondary dysmenorrhea is related to such conditions as endometriosis, fibroids, pelvic inflammatory disease and the presence of an intrauterine contraceptive device.[4]

Historical Perspective

A review of the methods which have been used through the ages for treating dysmenorrhea makes intriguing, and sometimes chilling, reading.[5] Hippocrates recommended fumigation with vapors of sweet wine, fennel and rose oil. Chinese physicians of the Ching dynasty used acupuncture and moxibustion, which involved burning wormwood chips on the abdomen of the supine victim. A zealous 19th century American surgeon, Robert Batty, removed the normal ovaries of young women afflicted by dysmenorrhea, and many others followed his example. Later, lumbar sympathectomy became the surgical treatment of choice for severe dysmenorrhea. The drugs in favor at the turn of the century were morphine, Cannabis indica and nitroglycerine. One American physician, Chauncey Palmer, advocated a different approach: "Experience has taught us that drugs used in chronic rheumatism may be admirably adapted to dysmenorrhea".[6] He noted that the use of salicylates made the menstrual flow "more free and less painful". To this day, aspirin probably remains the commonest over-the-counter remedy for mild dysmenorrhea.

Scientific research during the 1930s led to the observation that estrogens suppressed ovulation, thereby relieving dysmenorrhea.[7] It was more than 20 years later that oral contraceptives came on the market and it was recognized that relief of dysmenorrhea was an added benefit. Combined oral contraceptives have been widely used for this purpose during the past two decades and they are still the logical choice for those needing contraception.

The use of prostaglandin inhibitors for the treatment of dysmenorrhea has developed over the past ten years, although observations were made much earlier that phenylbutazone had a beneficial effect.[8-10] In 1957 Pickles reported that he had found a substance in

the menstrual fluid which could stimulate smooth muscle. He suggested that it might promote contractions of the myometrium, leading to primary dysmenorrhea.[11] He later demonstrated that the menstrual fluid of patients with dysmenorrhea contained prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in a higher concentration than that of patients without dysmenorrhea.[12] Vane reported in 1971 that aspirin-like drugs act through inhibition of prostaglandin synthesis.[13] The next step was to try prostaglandin inhibitors in the treatment of dysmenorrhea.

Prostaglandins Cause Dysmenorrhea

Prostaglandins are derived from polyunsaturated fatty acids. Those of the 2 series are synthesized from arachidonic acid by the action of the enzyme prostaglandin synthetase.[14] This enzyme is inhibited by non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, phenylbutazone and others. Prostaglandin biosynthesis occurs everywhere in the body and little is understood about the factors regulating it. It is known that prostaglandins E_2 and $F_2\alpha$ (PGE_2 and $PGF_2\alpha$) are produced by the endometrium in small amounts throughout the menstrual cycle and that there is an increase in $PGF_2\alpha$ concentration at the start of menstruation.

In those with dysmenorrhea, there is a fourfold increase in $PGF_2\alpha$ in the endometrium and a significant rise in $PGF_2\alpha$ in plasma compared with normal subjects.[15] In addition there is greatly increased activity of the myometrium, raised intrauterine pressure and accompanying uterine ischemia in dysmenorrhea.[16] The logical conclusion is that prostaglandin $F_2\alpha$, a potent smooth muscle stimulant and vasoconstrictor, must be responsible. To prove this, $PGF_2\alpha$ was administered to normal women during menstruation and it invariably stimulated uterine activity.[17] Conversely, administration of PGE_2 relaxed the uterine muscle during menstruation in both normal and dysmenorrheic women. It appears that the degree of uterine activity at the time of menses depends on the relative amounts of $PGF_2\alpha$ and PGE_2 produced by the endometrium, and that the abnormal contractility pattern seen during dysmenorrhea is a product of an increased ratio of $PGF_2\alpha$ to PGE_2.[17] In addition, escape of prostaglandins from the uterus into the systemic circulation may be responsible for other unpleasant symptoms of dysmenorrhea such as faintness, dizziness, headaches, nausea, vomiting and diarrhea.[4]

What causes the increased synthesis of prostaglandins in certain women? Some investigators have suggested that high circulating levels of estradiol in the second part of the menstrual cycle may be responsible.[18] Prostaglandins, by triggering uterine contractions, play an important role in initiating both normal menstruation and labor. During pregnancy and the second half of the menstrual cycle their action is prevented by high concentrations of progesterone.[19] Once progesterone levels fall, prostaglandins can exert their effects on the uterine muscle. Thus prostaglandins can be used to induce labor and therapeutic abortion.

Estrogen and progesterone must play a role in the etiology of dysmenorrhea because women with anovulatory cycles seldom suffer menstrual pain. This is the rationale behind the use of oral contraceptives for dysmenorrhea. Oral contraceptives inhibit ovulation and cyclic endometrial development. They also decrease menstrual flow, menstrual prostaglandin release and plasma prostaglandin levels.[15, 20] Ovulation is not always a prerequisite for dysmenorrhea: in a study of adolescent girls in Finland 67.5% of those with dysmenorrhea reported pain during their earliest cycles, which were probably the anovulatory type.[21] I have observed in my own practice that many older women experience a return of dysmenorrhea in the perimenopausal period when menstruation may be irregular and often anovulatory.

Trials of Prostaglandin Inhibitors

Many trials of prostaglandin synthetase inhibitors have taken place during the last decade: the most reliable ones are double-blind crossover studies of the test drug versus placebo. One of the earliest trials found that ibuprofen (Motrin) gave moderate to complete pain relief in 73% of patients.[22] Later studies proved that the drug reduced uterine activity and intrauterine pressure[23] and lowered prostaglandin levels in the menstrual fluid.[24] Mefenamic acid (Ponstan) is both a prostaglandin synthetase inhibitor and a direct prostaglandin inhibitor. Two early studies demonstrated excellent relief of dysmenorrhea with mefenamic acid, but the doses used were high.[25, 26] A double-blind crossover trial using mefenamic acid in lower doses (250 mg qid) showed it to be significantly superior to placebo in relieving pain, nausea and dizziness accompanying dysmenorrhea.[27]

Naproxen sodium (Anaprox) gave marked or moderate relief of pain in 85% of those tested, whereas placebo relieved 34% in one double blind crossover trial.[28] In another study, 17 of 22 women who usually had to remain at home or in bed during dysmenorrheic episodes no longer had to do so while taking naproxen sodium.[29] Naproxen (Naprosyn) gave relief to 67% of dysmenorrheic women in an open trial[28] and to 80% of patients in a double-blind trial.[30] In an early study, naproxen was shown to relieve pain following insertion of an intrauterine device.[31]

Weaker prostaglandin synthetase inhibitors such as acetyl salicylic acid and acetaminophen were not effective against severe dysmenorrhea.[32] Stronger non-steroidal anti-inflammatory drugs such as indomethacin were found to be effective,[28, 33, 34] but side-effects were relatively frequent. Other prostaglandin synthetase inhibitors have been used successfully in Europe for dysmenorrhea: flufenamic acid (Arlef)[26] and ketoprofen (Orudis).[35]

All the prostaglandin synthetase inhibitors mentioned above are non-steroidal anti-inflammatory drugs that have been used for many years in treating arthritis. They do not cause tolerance or addiction, and those now approved for use as analgesics are ibuprofen, mefenamic acid, naproxen, naproxen sodium, fenoprofen and zomepirac.[36] No information is available for the last two concerning dysmenorrhea.

Side Effects

The side-effects of prostaglandin synthetase inhibitors can be divided into those common to the whole group and those characteristic of the individual drugs.[37] For dysmenorrhea, these drugs are given for only one to three days each month, which means that side-effects are generally less common or severe than they are during long-term treatment for arthritis. Potential

side-effects common to the group are mainly in the gastrointestinal and central nervous systems.

Gastrointestinal symptoms may include one or more of the following: anorexia, nausea, vomiting, diarrhea and constipation. Vane proposed that mechanical stimulation of the gastrointestinal tract during peristalsis leads to intramural synthesis of prostaglandins which in some way protect the mucosa from damage.[13] This protective action is removed when prostaglandin inhibitors are administered. Peptic ulceration has occurred in a number of patients treated for arthritis with acetylsalicylic acid, phenylbutazone and indomethacin. The aryl propionic acids such as ibuprofen and naproxen cause gastrointestinal side-effects less frequently.

Headache is a common symptom in those taking high doses of acetylsalicylic acid and occurs in 20-40% of patients on indomethacin, but it is not a conspicuous side-effect of treatment with ibuprofen, naproxen or mefanamic acid. Other potential central nervous system effects, which are dose related, are dizziness, visual and hearing disturbances, irritability, depression, drowsiness and insomnia. These are unlikely to occur if the nonsteroidal anti-inflammatory drug is taken in moderate dosage for three days or less. In one study of dysmenorrhea, patients taking placebo complained of more 'side effects' than those taking naproxen and naproxen sodium,[28] presumably because the symptoms were a feature of the dysmenorrhea, not the treatment.

The side-effects characteristic of individual drugs are variable. Rashes and other allergic reactions can complicate treatment with phenylbutazone and indomethacin. Bronchospasm is precipitated by administration of aspirin in sensitive individuals. There is a cross-reaction between acetylsalicylic acid and other prostaglandin synthetase inhibitors in their ability to cause bronchospasm. All patients should therefore be questioned about sensitivity to aspirin and history of asthma before prescribing prostaglandin synthetase inhibitors.

Hematological disorders such as agranulocytosis and aplastic anemia are the most serious side-effects of phenylbutazone and indomethacin. Because of this, they are not acceptable in the treatment of dysmenorrhea. Mefenamic acid therapy for rheumatic diseases has occasionally caused autoimmune hemolytic anemia and acute renal insufficiency.

Which Drug to Choose?

Primary dysmenorrhea. I have discussed the side-effects of prostaglandin synthetase inhibitors in some detail because I think this knowledge is helpful in choosing appropriate therapy for dysmenorrhea. Phenylbutazone and indomethacin are contraindicated. Mefenamic acid (Ponstan 250 mg) and naproxen sodium (Anaprox 275 mg) appear to be more effective than ibuprofen (Motrin 200 mg) or naproxen (Naprosyn 250 mg), but all are acceptable in the treatment of primary dysmenorrhea when given up to qid for one to three days. No serious side effects have been reported during drug trials for this purpose.[22-30] The advantage of using a prostaglandin inhibitor is that it can be given prn at the first sign of dysmenorrhea. There is no need to take it prophylactically—its action is very rapid.[20, 28] In an open trial of 60 patients in my practice, I found that many women needed to take only one or two pills per month to relieve the symptoms of dysmenorrhea completely.

Prostaglandin synthetase inhibitors are the rational choice for treating primary dysmenorrhea in young women who are not sexually active. It makes sense to take as few pills a month as necessary, rather than take an estrogen-progestagen combination for 21 days out of 28.

For those who are sexually active and under age 30, low-dose combined oral contraceptives are a logical alternative. A recent review of oral contraceptives and cardiovascular disease reminds us that women taking oral contraceptives are at increased risk for thromboembolic disease, myocardial infarction and stroke.[38] The risk of myocardial infarction is three to four times greater among current users of oral contraceptives aged 25-49 than among women in that age group who have never used oral contraceptives. The increased risk continues for up to ten years after the drugs have been discontinued and is highest in women over 35 who smoke. This rather disturbing information may partly explain the decline in oral contraceptive use during the past ten years. There is little justification in giving oral contraceptives for dysmenorrhea alone.

Secondary dysmenorrhea. Many women who have completed their families, and some nulliparous women, are asking for tubal ligation and are disappointed to find that they experience a return of dysmenorrhea afterwards, having been free of it during their years on the birth control pill. Prostaglandin inhibitors may be useful for them. Others who use an intrauterine device (IUD) for contraception find that their menstrual cramps become more severe. This is almost certainly due to increased prostaglandin synthesis[13] and the use of prostaglandin inhibitors is reasonable. These drugs are also helpful in alleviating cramps during and after insertion of the IUD.[31, 39] Another secondary cause of dysmenorrhea is endometriosis; it has been shown that prostaglandin inhibitors may be beneficial in some cases.[40] Mefenamic acid and naproxen sodium have been reported in several studies to reduce menstrual flow,[28, 41, 42] but their efficacy in menorrhagia has not been determined.

Conclusion

We now have a rational therapy for dysmenorrhea in the form of medium strength prostaglandin synthetase inhibitors. These drugs, when used in low doses for one to three days, appear to be relatively free from harmful side-effects. Sensitivity to aspirin and a history of asthma are contraindications. Therapy should begin at the onset of menstrual bleeding or typical menstrual cramps and not before. Prostaglandin synthetase inhibitors have received wide medical acceptance in the treatment of dysmenorrhea.[43-45]

Personal experience in practice has confirmed patient acceptance and gratitude. Menstruation has been labeled 'the curse' by generations of women. Now that we can relieve the pain of menstruation for the majority, perhaps that epithet will be discarded. ◉

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