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PROSTAGLANDINS AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS IN DYSMENORRHEA

W. Y. Chan

Department of Pharmacology, Cornell University Medical College, New York, New York 10021

INTRODUCTION

Dysmenorrhea, commonly known as menstrual pain or cramps, is classified into primary and secondary dysmenorrhea. Generally, primary dysmenorrhea has its inception at the onset of or soon after menarche and characteristically has no identifiable macroscopical pathology. In contrast, secondary dysmenorrhea usually has its onset in adulthood and is associated with specific pelvic pathology. Some of the causes of secondary dysmenorrhea are endometriosis, uterine polyps, pelvic inflammatory diseases, uterogenital anatomical anomaly, and intrauterine device. Primary dysmenorrhea is by far the more prevalent form.

The incidence and prevalence of primary dysmenorrhea have not been established, but it has been estimated that as many as 50% of women of reproductive age, particularly nulliparas, suffer from dysmenorrhea at one time or other. In approximately 10% of these dysmenorrheic subjects, the symptoms are disabling enough to cause incapacitation for one to two days a month (1–4). Primary dysmenorrhea is the most common gynecologic complaint. Because of its cyclic recurring nature, the medical and socioeconomic impact of dysmenorrhea is enormous. It is the greatest single cause of lost work hours and school days among women (5–8), with more than 140 million work hours estimated to be lost annually (4). With increasing numbers of women entering the work force, dysmenorrhea may cause an even greater economic loss to society.

Despite the prevalence of dysmenorrhea, until very recently, medicine has made very little headway either toward the understanding of the pathophysiology of dysmenorrhea or the discovery of a specific and effective therapy for this female malady. The introduction of oral contraceptives in the 1960s marked the advent of the first effective therapeutic agent for the treatment of primary dysmenorrhea. Oral contraceptives, however, are not specific agents for dysmenorrhea. Until that time, treatments for dysmenorrhea were primarily symptomatic, involving strong analgesics, antidepressants, alcohol, and a variety of home remedies. These therapeutic approaches have not been successful, because of either lack of efficacy or unacceptable side effects. The first rational therapy for dysmenorrhea appeared on the medical scene as late as the mid 1970s, when the relationship between prostaglandin (PG) and dysmenorrhea was recognized and the newer nonsteroidal anti-inflammatory drugs (NSAIDs) with PG synthetase inhibitory activity were being introduced to the general medical practice. This review focuses on the etiologic role of PG in primary dysmenorrhea and therapeutic suppression of uterine PG production as a specific therapy for dysmenorrhea.

PATHOPHYSIOLOGY OF PRIMARY DYSMENORRHEA

Many theories have been proposed for the cause of dysmenorrhea. These include such components as (*a*) psychological factors, (*b*) cervical-mechanical factor, (*c*) hormonal theory, (*d*) neuronal theory, and (*e*) PG theory (9–11). With the exception of the PG theory, none of these are generally applicable, nor do they have strong experimental support. Undoubtedly, primary dysmenorrhea may have a multifactorial etiology in some patients. Recent studies, however, have amassed substantial evidence that PG is a major causal factor in primary dysmenorrhea.

In the early 1960s, Pickles and his associates identified $PGF_{2\alpha}$ and PGE_2 in the menstrual blood and endometrium from normal and dysmenorrheic subjects and suggested a pathophysiological role of PG in primary dysmenorrhea (12, 13). Since then, the hypothesis that primary dysmenorrhea is related to an elevated level of menstrual $PGF_{2\alpha}$ or PGF/PGE ratio has received substantial corroboration from clinical and laboratory studies.

In the uterus, PGs are synthesized primarily by the endometrium (14, 15). Measurements of levels of $PGF_{2\alpha}$ and PGE_2 in the human endometrium during the menstrual cycle show that the levels for both PGs were low during the follicular phase and the early luteal phase, but rose sharply and reached their highest levels shortly before and during the onset of menses (16–18). The rise for $PGF_{2\alpha}$ was much greater than that for PGE_2. The PG theory of dysmenorrhea suggests the following course of events. The secre-

tory endometrium under the influence of estrogen and progesterone synthesizes PGs. As the endometrium breaks down, as a result of the withdrawal of estrogen and progesterone support, PGs are released and cause vasoconstriction and disruption of endometrial cells. Release of lysosomal enzymes causes further cellular dissolution, breakdown of membrane phospholipids, and stimulation of PG synthesis. The increased amount of $PGF_{2\alpha}$ causes uterine contractions, vasoconstrictive ischemia of the myometrium, and, consequently, uterine pain. When an excessive amount of $PGF_{2\alpha}$ gains entrance into the circulation, other systemic symptoms characteristically associated with dysmenorrhea occur. In fact, the common side effects of exogenous PG administration are essentially parallel to those symptoms of primary dysmenorrhea, namely headache, nausea, vomiting, diarrhea, and syncope.

Earlier efforts to demonstrate the presence of a higher serum level of $PGF_{2\alpha}$ in dysmenorrheic women were not successful (19, 20). The inability to demonstrate a difference in blood levels of $PGF_{2\alpha}$ between nondysmenorrheic and dysmenorrheic subjects is understandable since PGs are rapidly metabolized in the lungs. When the more stable PG metabolites in the serum or when PGs in the menstrual blood were measured, higher concentrations of PGs were found in dysmenorrheic subjects, compared to those of nondysmenorrheic subjects (21–26). The endometrium of dysmenorrheic subjects was also found to have a higher level of $PGF_{2\alpha}$ (21, 27). Perhaps the most compelling evidence in support of an etiologic role for PGs in dysmenorrrhea are the clinical observations that, with the exception of aspirin, all NSAIDs so far tested are effective in alleviating primary dysmenorrhea. Oral contraceptives are equally efficacious. In both cases, relief of dysmenorrhea is associated wth a suppression of uterine PG release (28–34). The mechanisms by which these two classes of drugs suppress PG production, however, are different.

HORMONES AND ORAL CONTRACEPTIVES IN DYSMENORRHEIC THERAPY

It is a well-known clinical observation that in dysmenorrheic subjects, anovulatory cycles are generally free of pain. The recognition that there is an association between dysmenorrhea and ovulation (35) led to the use of hormonal ovulation suppression therapy for the treatment of dysmenorrhea (36, 37). When oral contraceptives were introduced in the 1960s, the utility of this therapeutic modality in treating dysmenorrhea was immediately recognized and applied. The effectiveness of oral contraceptives in the treatment of dysmenorrhea is well established in clinical practice (38–42). It is generally accepted that oral contraceptive steroids relieve dysmenorr-

hea by inhibition of ovulation. However, there is no documental evidence that inhibition of ovulation is the primary mechanism of action of oral contraceptives in dysmenorrheic therapy. On the contrary, available evidence suggests that the salutary effect of oral contraceptives in dysmenorrhea may be related more to their action on the endometrium than to the inhibition of ovulation. Measurements of menstrual PGs in subjects taking combination oral contraceptives showed levels lower than that found in nondysmenorrheic non-users (23, 31). In dysmenorrheic subjects, oral contraceptive therapy suppressed both menstrual fluid volume and menstrual PG release, whereas ibuprofen, a PG synthetase inhibitor, reduced menstrual PG release without significantly affecting menstrual fluid volume. When dysmenorrheic subjects who were effectively treated by oral contraceptives were taken off of the therapy, their menstrual fluid volume and menstrual PG release increased 3 to 5-fold and symptoms of dysmenorrhea recurred (31). Oral contraceptive steroids are not known to have a direct PG synthesis inhibitory activity. The suppression of menstrual PG release could be explained by at least two direct effects of these steroids on the endometrium. 1. Oral contraceptive therapy causes hypoplasia of the endometrium (43–45). Since the endometrium is the principal site of PG synthesis in the uterus (14, 15), inhibition of endometrial growth leads to a reduction of menstrual PG production and menstrual fluid volume. 2. The altered hormonal milieu induced by oral contraceptive therapy produces an unfavorable condition for uterine PG synthesis. Uterine PG synthesis is under the influence of an orderly ovarian hormone dominance. The majority of laboratory studies showed that uterine PG synthesis was stimulated by estrogen. This stimulating effect of estrogen was reduced when progesterone was coadministered (46–49). In one study in sheep, only progesterone was found to stimulate $PGF_{2\alpha}$ production. This stimulating effect of progesterone was further enhanced when estrogen was given with the progesterone (50). Under oral contraceptive therapy, the secretory endometrium fails to develop fully and more closely resembles the proliferative state, which has a low PG synthesizing capacity (16–18).

Further evidence suggesting a local effect of oral contraceptives on the endometrium is the clinical observation that the combination type oral contraceptives are more effective than the sequential type in relieving dysmenorrhea (51) and the finding that dydrogesterone, an oral progestogen that does not possess antiovulation activity, is also effective in treating dysmenorrhea (52–57). Intrauterine progesterone (Progestasert) also reduces both menstrual fluid volume and menstrual $PGF_{2\alpha}$ and alleviates dysmenorrhea (58) as seen with oral contraceptives (31). In one study, it was found that the uterine response to $PGF_{2\alpha}$ of subjects on oral contraceptive therapy was reduced at all phases of the menstrual cycle (59).

It therefore appears that, in dysmenorrheic therapy, oral contraceptive steroids act by disrupting the normal sequence of hormonal dominance in the endometrium, leading to an inhibition of endometrial growth and hence a reduction of both PG production and menstrual fluid volume during menstruation. By reducing menstrual PG production, oral contraceptives are effective for the treatment of primary dysmenorrhea. Oral contraceptive therapy, however, lacks specificity.
is unjustified to expose the subjects to the various endocrine and metabolic effects of oral contraceptive steroids by placing them on a 21-day medication regimen for the relief of pain that occurs, if at all, for only one to two days. However, until the introduction of NSAIDs in dysmenorrheic therapy, oral contraceptives were the only effective rational therapy for this disorder.

NSAIDs IN DYSMENORRHEIC THERAPY

The use of NSAIDs in dysmenorrhea started before PGs were known to be present in the menstrual blood and before the discovery of the PG synthetase inhibitory activity of this class of antiinflammatory
early 1950s, it was noted that when dysmenorrheic patients were treated with phenylbutazone for arthritis, their dysmenorrheic symptoms subsided (60, 61). This serendipitous observation led to the experimental use of phenylbutazone for the treatment of dysmenorrhea (62, 63). However, this treatment modality was not generally known, and except for the few experimental trials, it was rarely prescribed. The pharmacologic rationale for the use of NSAIDs in dysmenorrhea was not apparent until the 1970s when these agents were discovered to be PG synthetase inhibitors (64–68). The introduction of newer and safer NSAIDs, which soon followed, further encouraged the experimental trials of these newer agents in dysmenorrhea.

Flufenamic acid appears to be the first NSAID used specifically as a PG synthetase inhibitor for the treatment of dysmenorrhea (69). This report on the use of a PG synthetase inhibitor and PG antagonist for the treatment of dysmenorrhea was published in 1974. Since then, numerous clinical trials have been conducted on various NSAIDs for the treatment of dysmenorrhea, based on the belief that primary dysmenorrhea is associated with an elevated level of PG production in the endometrium. With the noted exception of aspirin, all these trials reported remarkable efficacies of these agents in dysmenorrhea.

The clinical trials of NSAIDs in dysmenorrhea have been reviewed recently in a number of papers (28, 29, 32, 33, 70) and, therefore, are not presented in detail here. To date, four groups of NSAIDs have been evalu-

ated. They are (*a*) indomethacin, (*b*) the fenamates, (*c*) the arylpropionic acids, and (*d*) aspirin (acetylsalicylic acid).

Indomethacin

Indomethacin, an indoleacetic acid derivative, was among the first NSAIDs extensively evaluated for the treatment of dysmenorrhea (71–78). Over 100 patients were treated in both open and placebo-controlled trials. Relief was obtained in 71% to 83% of the treated cycles.

Although the efficacy of indomethacin in dysmenorrhea has been clearly demonstrated in all the clinical trials reported so far, the compound is potentially toxic and has a high incidence of side effects. Gastrointestinal symptoms, headache, and drowsiness occur in 20% to 30% of the patients on a regimen of 25 mg three times a day, and may reach as high as 50% on a 50 mg regimen. Because of the high incidence of these dose-related side effects, indomethacin is not recommended for routine dysmenorrheic therapy.

The Fenamates

The fenamates are anthranilic acids. Flufenamic acid (69, 79, 80), mefenamic acid (79, 81, 82, 87), and tolfenamic acid (73) have been shown to be effective in dysmenorrhea. The fenamates have a PG-antagonistic property on smooth muscles (83–88) including the myometrium (86–88). One would expect the fenamates to be highly efficacious in dysmenorrhea, owing to their ability to suppress PG synthesis as well as to antagonize PG action. The available data show that the fenamates are equally as effective as the other NSAIDs that have been tested in dysmenorrhea. A direct comparative study between the fenamates and other members of the NSAIDs, however, is not available. Assessment of relative efficacy cannot be made with accuracy in the absence of direct comparisons.

Mefenamic acid is known to cause an allergic-type diarrhea. This limits its usefulness in susceptible patients.

The Arylpropionic Acids

The arylpropionic acids are the newer NSAIDs which were introduced in the mid 1970s. Ibuprofen and naproxen are two members of this family that have been extensively evaluated and are probably the most commonly used NSAIDs in dysmenorrhea.

Numerous clinical trials of ibuprofen (24, 26, 74, 89–93) and of naproxen or naproxen sodium (25, 29, 30, 76, 94–99) by different investigators have demonstrated the remarkable effect of these two arylpropionic acids in relieving menstrual cramps and other associated dysmenorrheic symptoms. Naproxen sodium was the first NSAID to be approved by the FDA specifi-

cally for the treatment of dysmenorrhea. Therapeutically, no distinction can be made between the acid, naproxen, and its sodium salt, naproxen sodium, as, in the blood, naproxen with a pK_a of 4.2 is 99.9% dissociated (100) and hence forms a salt with sodium, the predominant cation in the blood.

Two other arylpropionic acids have also been evaluated in dysmenorrhea. One of these, ketoprofen, proved as effective as indomethacin (78). The other, flurbiprofen, was highly effective in one study (101), while no more so than aspirin in another (102). In a recent study flurbiprofen was found to be as effective as other NSAIDs, but produced a higher incidence of side effects (102a).

The popularity of ibuprofen and naproxen in dysmenorrheic therapy will undoubtedly increase with time because they are well tolerated by most patients. There has been no direct comparison of efficacy among various members of the arylpropionic acid family. The few studies that compared ibuprofen (74), naproxen (76), or ketoprofen (78) against indomethacin did not reveal a significant difference between the arylpropionic acid and indomethacin in their clinical effectiveness. In comparison with aspirin, ibuprofen and naproxen were clearly superior to the salicylate (34, 90). In addition, ibuprofen was also found to be superior to acetaminophen (89) and to propoxyphene (92, 103).

Aspirin

Aspirin (acetylsalicylic acid), the prototype of NSAIDs, is not effective in dysmenorrhea, at least when conventional analgesic doses are employed. A number of placebo-controlled trials have demonstrated that aspirin, given at a dose of 500 to 650 mg four to six times a day, was no more effective than the placebo (34, 90, 101, 102, 104). One study conducted exclusively on adolescent dysmenorrheic subjects, however, found aspirin moderately superior to the placebo in pain relief (105). In this study, aspirin was given prophylactically. It should also be noted that in this study, aspirin did not improve the other systemic symptoms of dysmenorrhea, whereas other NSAIDs relieved both the uterine and extrauterine symptoms.

The poor efficacy of aspirin in dysmenorrhea may be related to its weak PG synthetase inhibitory activity in the uterus. In one double-blind, crossover study (34), the effects of naproxen sodium, aspirin, and placebo on pain relief and plasma PGF metabolite (15-keto,-13,14-dihydro-$PGF_{2\alpha}$) were determined. Naproxen sodium afforded excellent pain relief and reduced the blood concentration of PGF metabolite by 73.5%. Aspirin, 650 mg four times a day, was not superior to the placebo in affording pain relief. The blood concentration of PGF metabolite was reduced by only 31.2%. It was not studied whether higher doses of aspirin would have a greater suppressing effect on uterine PG synthesis and would thus afford higher levels of

pain relief. However, with higher doses of aspirin, gastrointestinal toxicities may preclude its use in many patients.

PHARMACOLOGY OF NSAIDs IN DYSMENORRHEA

Mechanism of Action of NSAIDs in Dysmenorrhea

Although the clinical effectiveness of NSAIDs in dysmenorrhea is well established, there is surprisingly little information on the pharmacology of this class of drugs in dysmenorrhea. The general belief that the NSAIDs relieve dysmenorrhea by suppression of PG synthesis is based primarily on circumstantial evidence. This includes the clinical observation that various NSAIDs tested so far are all effective in the treatment of dysmenorrhea. The clinical response is ascribed to their common pharmacologic property, which is the inhibition of PG synthetase activity. Measurements of blood concentration of PGF metabolites (21, 34) or menstrual blood PG concentrations (22, 25, 26) in dysmenorrheic patients indeed showed decreased concentrations during treatment cycles. Although these findings are consistent with a PG role in dysmenorrhea, they do not directly demonstrate a correlation between PG suppression and clinical response. Studies in animals have shown that the release of PGs from the uterus, as sampled from the uterine and peripheral venous blood, occurs in spikes (50, 106, 107). Therefore, PG values obtained from isolated single samples may show large differences due to spontaneous oscillations. More critically, PG values obtained from isolated discontinuous samples cannot quantitatively relate PG levels to clinical or therapeutic responses.

When our laboratory developed the tampon method for the measurement of menstrual PGs (23), it became possible to monitor menstrual PG release continuously and to determine the total amount of PGs released per menstruation. Measurements of menstrual PG release by this method indeed showed that there were large fluctuations in PG concentrations from sample to sample and from cycle to cycle (Figure 1). The total amount of menstrual fluid and the total amount of PG released per menstruation, however, were fairly constant for a given subject. Generally, about 95% of the total menstrual PGs are released during the first 48 hours and by 72 hours about 99% of the total menstrual PGs have been released.

We studied the effects of ibuprofen (24, 93) and naproxen sodium (108) on menstrual PG levels and on the symptomatic relief of dysmenorrhea in two double-blind, placebo-controlled, crossover trials. The results of these two studies provided the most compelling evidence to date for an etiologic role of PG in dysmenorrhea and demonstrated PG suppression as the principal mechanism of action of NSAIDs in dysmenorrheic therapy.

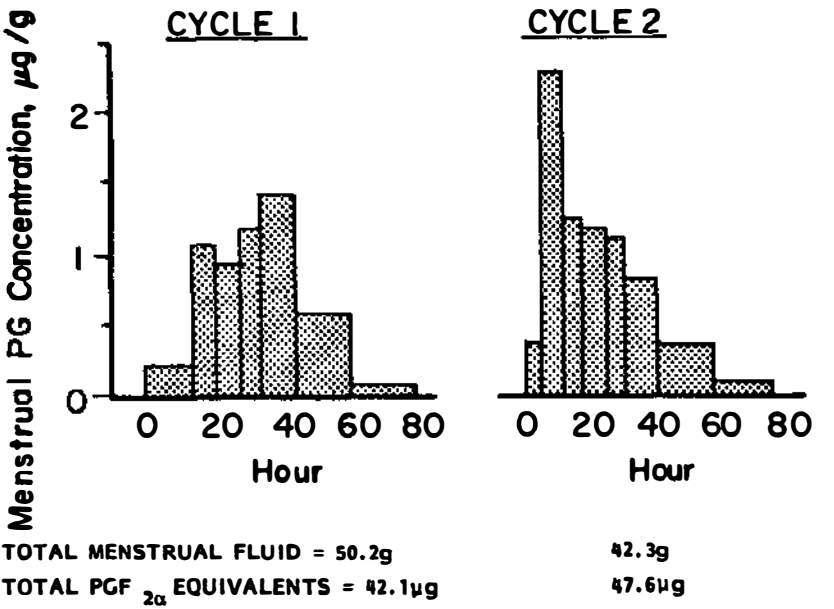

Figure 1 Menstrual fluid prostaglandin concentration measured throughout menstruation in two different cycles from the same dysmenorrheic subject. Note the fluctuations in menstrual fluid prostaglandin concentration at different time intervals but the similarity in both total menstrual fluid and total prostaglandin released during menstruation in the two cycles.

Ibuprofen or naproxen sodium therapy markedly suppressed menstrual PG release, while placebo therapy had no significant effect on menstrual PG release (Table 1). Reduction of menstrual PG release by ibuprofen or naproxen sodium brought good to excellent relief in 80% of the treatment cycles, in contrast to the placebo treatment which afforded little or no relief. Furthermore, in individual subjects, there was a positive correlation between the severity of dysmenorrhea and the levels of menstrual PG released during the corresponding period (Figure 2).

A causal relationship between uterine contractions and dysmenorrheic pain has been demonstrated by a number of investigators (9, 109–112). The spasmodic pain may be compounded by ischemic pain as sustained uterine contractions compromise uterine blood flow. NSAIDs, by inhibiting PG synthesis in the uterus, diminish uterine hypercontractility. Indeed, in all cases where uterine contractility was monitored when NSAIDs were administered, significant reduction of uterine contractility was observed (81, 91, 110, 113, 114). Although it cannot be excluded from the available data

Table 1 Effects of ibuprofen, naproxen sodium, or placebo treatment on menstral PG release[a]

	Total menstrual PG release per cycle in μg (mean ± S.E.)		Percent inhibition relative to control	
	$PGF_{2\alpha}$	PGE_2	$PGF_{2\alpha}$	PGE_2
Ibuprofen study				
Control cycles	27.3 ± 7.1	7.4 ± 3.1		
Placebo-treated cycles	24.5 ± 4.5	5.1 ± 0.8	N.S.	N.S.
Ibuprofen-treated cycles	9.1 ± 2.6	4.9 ± 2.2	66.6	33.8
Naproxen sodium study				
Control cycles	23.2 ± 4.8	5.3 ± 1.1		
Placebo-treated cycles	20.1 ± 2.4	4.6 ± 0.7	N.S.	N.S.
Naproxen-treated cycles	5.1 ± 1.3	1.1 ± 0.3	78.0	79.2

[a] There were 7 cycles in each treatment group in the ibuprofen study and 12 cycles in the naproxen sodium study. Placebo values were not significantly different from their respective control values. Ibuprofen or naproxen values were significantly different from their respective control values, with $P < 0.01$ by the paired "t" test.

that NSAIDs, particularly the fenamates, may also antagonize PG actions (83–88), the suppression of uterine contractions by NSAIDs is primarily the result of inhibition of PG biosynthesis. By diminishing uterine contractility, uterine perfusion is improved. Both spasmodic pain and ischemic pain are relieved. Suppression of PG synthesis by NSAIDs blocks or attenuates PG-induced hyperalgesia (115). It also reduces the amount of PG entering the systemic circulation. Thus, treatment with NSAIDs in dysmenorrhea not only alleviates uterine cramps but also ameliorates many of the systemic symptoms caused by PGs, such as headache, nausea, vomiting, and diarrhea.

General Pharmacologic Considerations

Insofar as dysmenorrhea is related to an elevated or altered PG production of the endometrium, drugs such as the NSAIDs that inhibit PG synthesis may be regarded as specific therapy for this gynecologic disorder. However, it cannot be said that the NSAIDs are selective dysmenorrheic agents. There is no reason to believe that these agents, as they are currently employed, affect primarily PG metabolism in the uterus, since the dosages used are in the same dose range recommended for antiarthritic therapy. Unless there is evidence indicating otherwise, one must assume that therapeutic doses of NSAIDs affect PG synthesis in all body tissues. NSAIDs also inhibit PG synthesis indiscriminately. They inhibit the enzyme cyclooxygenase at the initial step of the arachidonic acid metabolic pathway, prevent-

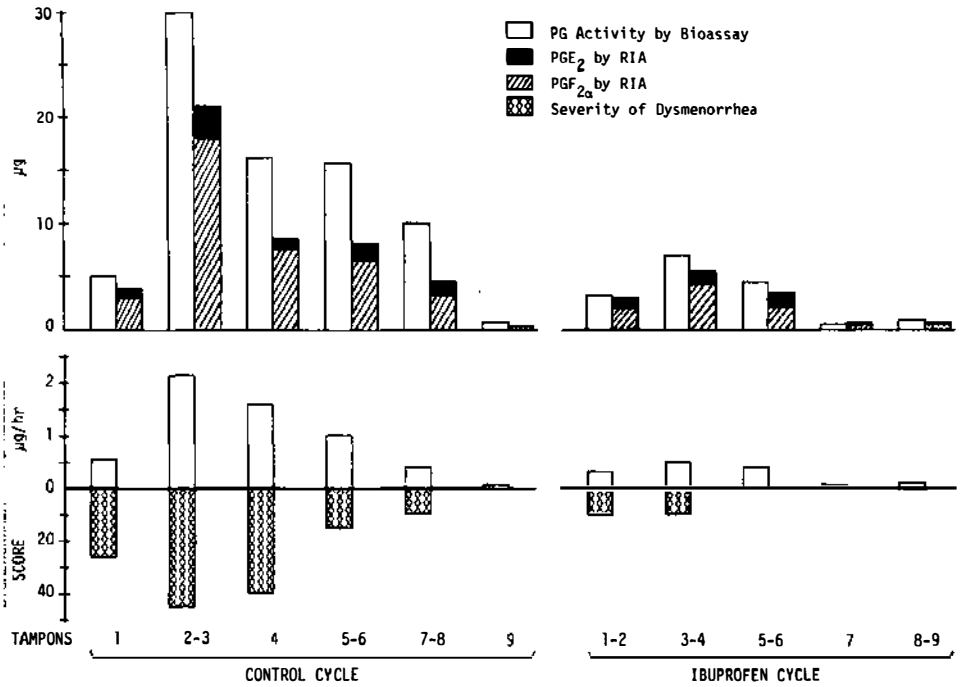

Figure 2 Menstrual prostaglandin activity measured by bioassay and by radioimmunoassay, and its relationship to dysmenorrhea. Consecutive tampons from a patient were measured for prostaglandin content and rate of release in a control cycle and in an ibuprofen-treated cycle. When tampons were pooled, the pooled specimens had similar dysmenorrheic score. The upper panel shows the prostaglandin content in the tampon measured by bioassay and by radioimmunoassay. In nearly all samples, the prostaglandin activity measured by bioassay was greater than the sum total of PGE_2 and $PGF_{2\alpha}$ determined by radioimmunoassay. Both assays, however, show similar changes. The lower panel shows the correlation between the severity of dysmenorrhea and the rate of prostaglandin release for the corresponding period. Reprinted from Chan et al (93) by permission of the *American Journal of Medicine.*

ing the formation of endoperoxides, which are the intermediates for the formation not only of the primary PGs, but also of prostacyclin and thromboxane A_2. This nonselective inhibition of PG metabolism is probably responsible for the apparent equal efficacy among the NSAIDs tested so far in the treatment of dysmenorrhea. The blanket action on PG synthesis ensures their effectiveness in dysmenorrhea. Such a shotgun therapeutic approach is not desirable. It lacks selectivity and produces a wide range of side effects unnecessarily. Drug toxicity in dysmenorrheic therapy with NSAIDs, however, has been minimal. One of the reasons for their good safety is the short duration of therapy, which generally lasts for only one or two days. The effect of chronic use of NSAIDs in young females of

reproductive age is not known. Effort should and can be made to improve safety of NSAIDs in dysmenorrheic therapy.

Experimental and clinical experience show that there are substantial differences in pharmacologic profiles of these drugs. The PG generating enzyme system exists in multiple molecular forms within the organism (116). The synthetase enzymes from different tissue types exhibit different sensitivity to inhibition by PG synthetase inhibitors (117, 118). The relative inhibitory potencies of the various NSAIDs in the uterine PG system have not been determined. Undoubtedly, the relative potency and the uterine selectivity among these agents vary. Optimal dose regimen for dysmenorrhea should be determined. Since many of the side effects of the NSAIDs are related to the inhibition of PG biosynthesis in various target tissues, a more uterine-selective agent can be expected to produce fewer side effects than a less uterine-selective agent. The profile of PG inhibition in the uterus may differ among the various NSAIDs. The effects of ibuprofen and naproxen on menstrual PG release are dissimilar. Ibuprofen suppresses menstrual $PGF_{2\alpha}$ release far more than PGE_2, whereas naproxen suppresses menstrual $PGF_{2\alpha}$ and PGE_2 release equally (Table 1). This apparent preferential effect of ibuprofen on $PGF_{2\alpha}$ synthesis has far reaching pharmacologic and clinical implications. Pharmacologically, it suggests that in the uterus, ibuprofen and certain NSAIDs may, in addition to inhibiting cyclooxygenase, also inhibit enzyme(s) or factor(s) that direct the metabolism of $PGF_{2\alpha}$ or the distribution between $PGF_{2\alpha}$ and PGE_2 synthesis. Clinically, it suggests the possibility of developing a selective $PGF_{2\alpha}$ synthesis inhibitor, with reduced risk of causing closure of the fetal ductus arteriosus, for the treatment of premature labor.

We have begun a systematic comparative study of the $PGF_{2\alpha}$ and PGE_2 inhibitory potencies of NSAIDs in the uterus. Among the NSAIDs tested so far, only ibuprofen exhibits a high preference for $PGF_{2\alpha}$ (Figure 3). These agents also vary greatly in their relative potencies (119). Additional NSAIDs are being investigated. It is a reasonable expectation that more selective $PGF_{2\alpha}$ synthesis inhibitors may be uncovered.

In addition to their potential as tocolytic agents, selective $PGF_{2\alpha}$ inhibitors may prove to be the more effective and safer drugs for the treatment of dysmenorrhea. Although there is now substantial evidence supporting a causal role of PGs in primary dysmenorrhea, the precise nature of PG's involvement in the etiology of dysmenorrhea is far from being understood. PG concentrations in the menstrual blood of dysmenorrheic subjects vary greatly (24–26, 93, 108), and not all dysmenorrheic subjects show elevated levels of menstrual PGs (24, 108). This may simply indicate that not all subjects suffering from primary dysmenorrhea have elevated PG levels as the underlying cause. An interesting finding emerging from

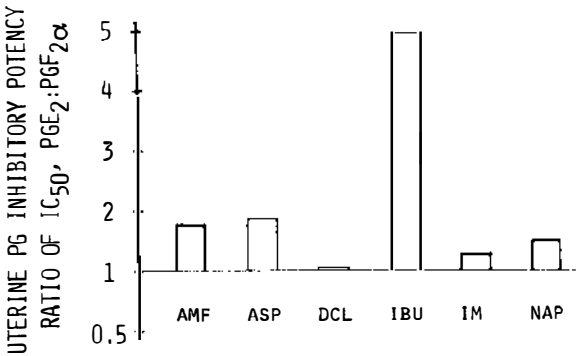

Figure 3 Differential inhibition of PGE_2 and $PGF_{2\alpha}$ in rat uterine homogenates by NSAIDs. The IC_{50} PGE_2:IC_{50} $PGF_{2\alpha}$ ratio expresses the PGE_2 inhibitory potency relative to the $PGF_{2\alpha}$ inhibitory potency of the drug. The NSAIDs tested were: AMF = amfenac sodium, ASP = aspirin, DCL = diclofenac sodium, IBU = ibuprofen, IM = indomethacin, and NAP = naproxen sodium. Note the high preference of ibuprofen for $PGF_{2\alpha}$ inhibition. Its molar concentration required for a 50% inhibition of PGE_2 synthesis was 5 times greater than the molar concentration required for a 50% inhibition of $PGF_{2\alpha}$ synthesis.

our work-in-progress is the observation that the severity of dysmenorrhea is better correlated to the ratios of menstrual $PGF_{2\alpha}$:PGE_2 than to the concentrations of menstrual $PGF_{2\alpha}$. This suggests that the balance between endometrial $PGF_{2\alpha}$ and PGE_2 production may be important to the manifestation of dysmenorrhea. Conceivably, dysmenorrhea may be caused by either an elevated $PGF_{2\alpha}$ production or a relative deficit of PGE_2. $PGF_{2\alpha}$ is invariably a myometrial stimulant. The action of PGE_2 in the uterus is variable. In nonpregnant uterus, PGE_2 may cause relaxation. In dysmenorrheic subjects, PGE_2 has been shown to decrease myometrial activity and relieve pain (120). If a high $PGF_{2\alpha}$:PGE_2 ratio is an important determinant of dysmenorrhea, then PG synthetase inhibitors that have a preferential effect on $PGF_{2\alpha}$ synthesis would be superior to those that do not exhibit this preferential action as therapeutic agents for dysmenorrhea. The experience with ibuprofen gives confidence that more such selective $PGF_{2\alpha}$ synthesis inhibitors may be found.

CONCLUDING REMARKS

The recognition that primary dysmenorrhea is related to an excessive endometrial PG production is, perhaps, the most singular advance in the pathophysiology and treatment of this common gynecological disorder. This identification of a physical cause for dysmenorrhea has laid to rest many myths of menstrual pain and has dispelled the belief, once popular among medical practitioners, that primary dysmenorrhea was principally a psychosomatic disease. The introduction of the NSAIDs to dys-

menorrheic therapy is a major triumph in the treatment of this common cyclic recurring pain. The impact of this new therapy in the treatment of dysmenorrhea has yet to be felt, since the discovery was made only within the last few years and has not yet been widely disseminated to the medical community.

NSAIDs are also effective in relieving dysmenorrhea due to intrauterine device and certain other forms of secondary dysmenorrhea in which PG levels are elevated (121–125). The success rate in treating primary dysmenorrhea with NSAIDs has been between 75% and 90%. Because of this high efficacy of the NSAIDs, patients who do not respond to therapy with these drugs may well have missed diagnosed secondary dysmenorrhea and should be given more thorough workup to find the underlying cause.

Although a causal relationship between PGs and dysmenorrhea seems beyond dispute, much remains unknown. So far, it has been assumed that the PGs of importance in dysmenorrhea are $PGF_{2\alpha}$ and PGE_2. The role of active PG metabolites and other endoperoxide products, such as prostacyclin and thromboxane A_2, has not been investigated. More fundamentally, little is known about the regulatory mechanism of endometrial PG production and release during menstruation and the factors that separate the nondysmenorrheic from the dysmenorrheic subjects. Premenstrual syndrome is still a medical mystery. This symptom complex is not amended by NSAIDs.

The currently available NSAIDs, though highly efficacious, all suffer from a lack of selectivity that is responsible for many of their side effects, and may pose danger in chronic therapy. These agents suppress PG synthesis indiscriminately in all body tissues and inhibit all product formations arising from the PG endoperoxides in the arachidonate cascade. However, until the question is answered as to which of the arachidonate metabolites are relevant to the pathophysiology of dysmenorrhea, the broad and nonselective action of NSAIDs is a therapeutic advantage. This blanket action ensures the effectiveness of NSAIDs in the treatment of dysmenorrhea.

Our new knowledge of the biochemical basis of dysmenorrhea has led to a surge of interest in the research of this field and to the successful introduction, just within the last few years, of the first rational therapeutic agents, the NSAIDs, for the treatment of dysmenorrhea. The bridge between basic research and the application of basic discovery to clinical medicine is often frustratingly long. The success story of PG synthetase inhibitors in dysmenorrhea is a rare exception. It is hoped that the momentum will sustain and stimulate research to further our understanding of the etiology of dysmenorrhea and the development of a new generation of more selective and safer PG synthetase inhibitors for the treatment of this common disease.

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