GENERAL GYNECOLOGY

Clinical efficacy and differential inhibition of menstrual fluid prostaglandin $F_{2\alpha}$ in a randomized, double-blind, crossover treatment with placebo, acetaminophen, and ibuprofen in primary dysmenorrhea

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OBJECTIVE: The purpose of this study was to compare acetaminophen with ibuprofen for pain relief and menstrual fluid prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) suppression in primary dysmenorrhea.

STUDY DESIGN: Twelve subjects were randomized to placebo, acetaminophen (1000 mg orally, 4 × daily for 3 days) or ibuprofen (400 mg orally, 4 × daily for 3 days), once during each cycle in a prospective, double-blinded, crossover study. Using preweighed super absorbent tampons, menstrual fluid was collected, extracted, and $PGF_{2\alpha}$ radioimmunoassayed.

RESULTS: Ten patients completed the study. Ibuprofen ($P = .002$) and acetaminophen ($P = .022$) were rated significantly better than placebo. Total menstrual fluid $PGF_{2\alpha}$ with placebo was 36.2 + 6.1 μg but were 14.8 + 3.0 μg with ibuprofen ($P = .001$) and 21.4 + 3.4 μg with acetaminophen ($P = .008$). $PGF_{2\alpha}$ concentrations with placebo were 0.34 + 0.054 μg/mL, with ibuprofen 0.16 + 0.026 μg/mL ($P = .001$), and with acetaminophen 0.23 + 0.029 μg/mL ($P = .016$).

CONCLUSION: Both ibuprofen and acetaminophen were superior to placebo for pain relief and menstrual fluid $PGF_{2\alpha}$ suppression, with ibuprofen being more potent.

Key words: acetaminophen, ibuprofen, menstrual fluid prostaglandin $F_{2\alpha}$, primary dysmenorrhea, prostaglandin synthethase

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Primary dysmenorrhea is a prevalent gynecologic disorder among postpubescent and young females.[1] A recent Cochrane analysis of nonsteroidal anti-inflammatory drugs (NSAIDs) indicates that they are effective for relief of pain in primary dysmenorrhea.[2] Current evidence points to excessive production and release of endometrial prostaglandins (PGs) at menstruation causing abnormal uterine hypercontractility, reduced uterine blood flow, uterine hypoxia and hypersensitization of pain fibers by PGs.[3-5] When NSAIDs such as ibuprofen[6-8] and naproxen[9] are given to patients with primary dysmenorrhea, there is a significant reduction in prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with concomitant relief of pain compared with placebo-treated cycles. At the same time, administration of these medications also causes attenuation of the uterine hypercontractility with restoration of uterine activity similar to that seen in eumenorrheic women.[10]

Acetaminophen exerts a highly selective pharmacologic effect with antipyretic[11] and moderate analgesic[12] properties but little or no anti-inflammatory action.[13] Its potent antipyretic effect is brought about through selective suppression of PGE_2 biosynthesis in the brain[14,15] mediated by inhibition of prostaglandin H synthase activity and hydroperoxide concentration contributes to its cellular selectivity.[16] The analgesic effect of acetaminophen is partly produced through a supraspinal activation of the descending serotonergic pathways[17-19] but its primary site of action may still be selective and variable inhibition of prostaglandin production.[19,20] In spite of considerable advances in our understanding of the pathogenesis of menstrual cramps in primary dysmenorrhea, there is still controversy about the ability of acetaminophen to inhibit endometrial PG production as well as its efficacy in relieving primary dysmenorrhea. In a small comparative but nonplacebo-controlled comparative study, acetaminophen and ibuprofen were found to be effective but there was a trend towards better relief with ibuprofen.[21] When a single dose of acetaminophen (500 mg) was compared with ibuprofen (400 mg) and naproxen sodium (250 mg), it did not significantly change intrauterine pressure or pain score over a 4 hour period.[22] Thus, it appears that the clinical efficacy of acetaminophen in primary dysmenorrhea remains to be fully

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TABLE
Mean + SEM of relevant clinical characteristics of 10 patients with primary dysmenorrhea

Age (y)	Menarche (y)	Parity	Cycle length (d)	Menstrual flow (d)	Dysmenorrhea (d)
31 + 1.5	12.5 + 0.4	1 + 0.3*	28.5 + 0.4	4.1 + 0.3	1.8 + 0.3

* Four patients were nulliparous, 6 were para 3.

evaluated and its ability to suppress menstrual PGs in vivo has not been examined. Therefore, we conducted a prospective randomized, double-blind, placebo-controlled, crossover study to determine the clinical efficacy as well as the suppression of menstrual fluid $PGF_{2\alpha}$ by ibuprofen (400 mg) versus acetaminophen (1000 mg) versus placebo in 3 different menstrual cycles in women with primary dysmenorrhea.

Materials and Methods

Patients and study protocol

The study was approved by the Institutional Review Board at the University of Illinois College of Medicine and carried out there while the authors were faculty members. Twelve women age 22-35 years with a clinical diagnosis of primary dysmenorrhea, in good general health and not on any medication were recruited to the study. Based on our previous published studies, 10 patients will be more than sufficiently powered to detect the difference of 40-50% in menstrual fluid $PGF_{2\alpha}$ ibuprofen treatment.[6-8] To allow for some drop out or noncompliance, we erred on the side of enrolling 12 subjects. Each woman was studied for 3 ovulatory cycles. The onset of dysmenorrhea was within 1 year of their menarche. Their menarche, cycle length, cycle duration, and parity are outlined in Table 1. All subjects had to have a normal Pap smear and a negative pelvic examination. They were required to practice a medically approved method of contraception (either condom or diaphragm) other than oral contraceptives or intrauterine contraceptive device unless they are sexually inactive or had been surgically sterilized. Patients with known peptic ulcer, chronic alcohol and/or drug abuse, known allergies to nonsteroidal anti-inflammatory drugs, pregnancy, pelvic inflammatory disease, urinary tract infection, adnexal masses, endometriosis, adenomyosis, ovarian cysts and uterine fibroids, polyps, and adhesions were not eligible for the study.

Medications and dosing regimen

Since the ibuprofen (tablet) and extra-strength acetaminophen (caplet) were of different size, shape, and appearance, active medication (tablet or caplet) and matching placebo (caplet or tablet) for the other medication were provided. In the case of placebo, both the tablet and caplet were placebos. This preserved the double-blind design of the study. Each tablet of ibuprofen was 200 mg and each caplet of acetaminophen was 500 mg. Patients were randomly assigned to the treatment regimen as they enrolled. Each patient was crossed-over to receive study medication for 3 dysmenorrheic cycles. Midluteal phase serum progesterone indicative of an ovulatory cycle and a negative pregnancy test were needed for each cycle while in the study. The subjects took 2 tablets and 2 caplets dose of study medication when her menstrual flow began irrespective of her pain level. Patients were instructed to refrain from taking any analgesic, premenstrual syndrome, dysmenorrhea, anti-inflammatory, or muscle relaxant medication during the next 6 hours.

Patient visits, assessments, and instructions

Each patient was seen on day 20-23 of her cycle for serum progesterone and hCG. She was provided with preweighed super Tampax tampons and 2 ounce capacity specimen jars with screw caps containing 40 mL isotonic saline. Each specimen jar will contain only 1 used tampon from the patient. The time and date of tampon insertion and removal were noted for each tampon on the specimen jar. With the onset of menstrual flow, the patient inserted 1 of the investigator-provided tampons and took the first dose of study medication (regardless of the level of pain at the onset of menstrual flow). The medication time was recorded in the diary. The medication dose was 2 tablets/2 caplets every 4 hours 4 times a day for the first 3 days of menstrual flow. Thus, a total of 12 doses were taken for each cycle. The specimens were to be kept cool in a refrigerator until submitted to the laboratory. All specimens were turned in daily including over weekends. The patient diary and study medication for the ensuing menstruation were then given to the patient.

Each patient was seen on the third or fourth day of her menstruation to assess efficacy, review proper completion of her menstrual diary, and reconcile the medication taken and any left over. Relief of primary dysmenorrhea was assessed as global evaluations by both the patient and the investigator in addition to menstrual fluid PG determination. Patient ratings were on a 4-point scale of poor, fair, good, or very good. During the 72-hour study periods, use of concurrent analgesics, tranquillizers, and other drugs that may interfere or mask the pharmacologic effect of the study medications were not permitted. Use of any concurrent medications had to be documented.

Menstrual fluid PG extraction

Each specimen jar turned was reweighed and the amount of menstrual fluid present was calculated in grams. Tampons were allowed to equilibrate in the saline solution in the specimen jar for 24-32 hours at 5°C. The saline-menstrual fluid solution was then centrifuged. A measured volume of the supernatant was then extracted for PG by: a hexane wash at pH 7.5-8.0 to remove nonpolar lipids; extraction of the prosta-

glandin material into chloroform at pH 4.0; back extraction of PG material into aqueous phosphate buffer at pH 7.4; re-extraction of PG material into chloroform to dryness under nitrogen and reduced pressure. The residue was stored at 20°C until used for radioimmunoassay.

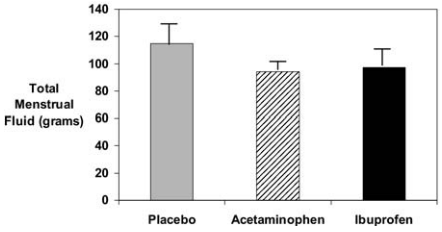
Radioimmunoassay of $PGF_{2\alpha}$

The stored residue was measured for $PGF_{2\alpha}$ by a specific and sensitive radioimmunoassay (RIA) using the Seragen $PGF_{2\alpha}$ ^3H RIA kit (Seragen, Inc, Boston, MA). The assay was validated in our laboratory before use for the stored samples. The antibody was raised in rabbits immunized against $PGF_{2\alpha}$-bovine serum albumin conjugate and was highly specific with minimal cross-reactivity against the following: PGE_1 1.1%, 6-keto-$PGF_{1\alpha}$ 1.1%, thromboxane B_2 0.5%, PGE_2 0.3%, and PGD_2, PGA_2, PGA_1, PGB_1, PGB_2 and 6-keto PGE_1 all $< 0.1\%$. Separation of bound from unbound ligand was achieved with dextran-coated charcoal suspension which contains 0.4% Norit in water with 0.4% dextran and 0.1% sodium azide. The stored residue from the specimen (see above) was suspended in glacial acetic and extracted with ethyl acetate. Extraction efficiency was monitored with tritiated $PGF_{2\alpha}$ and all results were corrected for extraction. The limit of detection for the assay significantly different from zero was 2.7 pg. The intrassay coefficient of variation was 5% or less and interassay coefficient of variation was 8-10%. All assays were carried out for the same patient's individual cycle within the same run and were completed within 6 months or less of sample collection. We have subsequently tested the samples up to 3 years after storage and the results were within the interassay coefficient of variability

Analysis of data

All results for a particular treatment group were expressed as mean + standard error of the mean (SEM). Relative treatment differences were evaluated for total PG and PG concentration. PG concentration is the amount of PG present per mL of the menstrual fluid while total menstrual PG is the total amount of PG secreted for that particular menstruation. The analysis of differences among treatments was conducted using a cross-over design analysis of variance model, which provides a within patient comparison of treatments adjusted for any differences among menstrual periods (that is cycle 1, 2, and 3). The analysis of relative differences among treatments utilized the same model applied to log transformed data, which is appropriate when relative differences are of interest. One way analysis of difference for repeated measures were employed. All analyses were conducted using the general linear models procedures in SAS (Cary, NC). A P value of $< .05$ was considered statistically significant.

FIGURE 1
Total menstrual fluid volumes with placebo, acetaminophen and ibuprofen treatments in women with primary dysmenorrhea



Mean + SEM (standard error of the mean) total menstrual fluid released and collected from 10 women who underwent treatment with placebo, ibuprofen (400 mg 4 times daily) and acetaminophen (1000 mg 4 times daily) for primary dysmenorrhea in a double-blinded, crossover study. The treatment was given for the first 3 days of menstruation. The menstrual fluid volume is expressed as grams based on weight. There was no significant difference in the menstrual fluid weight.

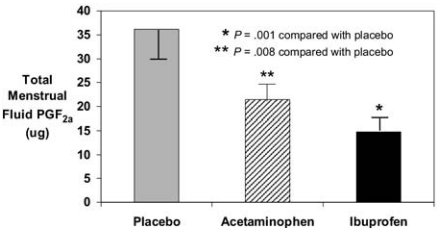
RESULTS

Two patients had to be excluded as 1 of them took naproxen during 1 of her menstrual cycles and the other completed only 2 of the 3 menstrual cycles. Thus, 10 patients who completed all 3 cycles each and who were compliant were available for analysis.

Total menstrual fluid weights or volume did not differ significantly among treatments (Figure 1). Both total $PGF_{2\alpha}$ (Figure 2) and $PGF_{2\alpha}$ concentration (Figure 3) were lowest with ibuprofen treatment and highest with placebo treatment. Patient and physician efficacy ratings were similar in all the cycles studied. Patient efficacy ratings were highest for ibuprofen and lowest for placebo. The ratings for ibuprofen were 3 very good, 6 good, and 1 poor, for acetaminophen 1 very good, 6 good, 2 fair, and 1 poor, and for placebo 0 very good, 3 good, 3 fair, and 4 poor. The differences in ibuprofen and acetaminophen ratings from placebo were statistically significant ($P = .002$ for ibuprofen vs placebo; $P = .022$ for acetaminophen vs placebo).

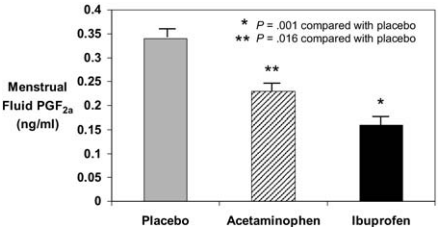
Analysis of relative differences in $PGF_{2\alpha}$ concentration among treatments showed ibuprofen was significantly lower than acetaminophen and placebo while acetaminophen was significantly

FIGURE 2
Menstrual fluid prostaglandin $F_{2\alpha}$ with placebo, acetaminophen and ibuprofen treatments in women with primary dysmenorrhea



Mean + SEM (standard error of the mean) total menstrual fluid $PGF_{2\alpha}$ from 10 women who were treated with placebo, ibuprofen (400 mg 4 times daily) and acetaminophen (1000 mg 4 times daily) for primary dysmenorrhea in a double-blinded, cross-over study. The treatment was given for the first 3 days of menstruation. There was significant reduction of menstrual fluid $PGF_{2\alpha}$ with ibuprofen ($P = .001$) and acetaminophen ($P = .008$) over placebo treated cycles. $PGF_{2\alpha}$ was reduced by 40 percent with acetaminophen compared to placebo. Ibuprofen further suppressed $PGF_{2\alpha}$ by another 35 percent below that of acetaminophen inhibition and almost reached statistical difference ($P = .063$).

FIGURE 3
Concentrations of prostaglandin $F_{2\alpha}$ in menstrual fluid with placebo, acetaminophen, and ibuprofen treatments in women with primary dysmenorrhea



Mean + SEM (standard error of the mean) concentration of $PGF_{2\alpha}$ in menstrual fluid from 10 women who underwent treatment with placebo, ibuprofen (400 mg 4 times daily) and acetaminophen (1000 mg 4 times daily) for primary dysmenorrhea in a double-blinded, cross-over study. The treatment was given for the first 3 days of menstruation. There was a significant reduction with ibuprofen treatment compared with placebo ($P = .001$) and with acetaminophen compared with placebo ($P = .016$). Reduction of menstrual fluid $PGF_{2\alpha}$ was greater with ibuprofen than with acetaminophen but the difference was not significant.

lower than placebo (Figure 3). The mean + SEM $PGF_{2\alpha}$ concentration during treatment with placebo was 0.34 + 0.054 μg/mL and declined significantly to 0.16 + 0.026 μg/mL with ibuprofen treatment ($P = .001$ vs placebo) and 0.23 + 0.029 μg/mL with acetaminophen ($P = .016$ compared with placebo).

Similar findings also apply to relative differences in total menstrual fluid prostaglandin. The total menstrual fluid $PGF_{2\alpha}$ (mean + SEM) during ibuprofen treatment was 14.8 + 3.0 μg and was 40% of the total menstrual fluid $PGF_{2\alpha}$ during placebo treatment (36.2 + 6.1 μg, $P = .001$; Figure 2). During acetaminophen treatment, total $PGF_{2\alpha}$ was 21.4 + 3.4 μg and averaged 61% of the total $PGF_{2\alpha}$ during placebo ($P = .008$). With ibuprofen treatment, total $PGF_{2\alpha}$ averaged 65% of the level found during treatment with acetaminophen. This 35% reduction almost approached statistical significance ($P = .063$).

COMMENT

This study shows that both ibuprofen and acetaminophen were clinically more effective and preferable over placebo for the relief of menstrual cramps in primary dysmenorrhea. Ibuprofen was better preferred than acetaminophen, albeit not significantly different. An earlier nonplacebo-controlled, double-blind, 2-cycle crossover study comparing ibuprofen with acetaminophen found both compounds gave similar clinical pain relief in primary dysmenorrhea, with ibuprofen favored over acetaminophen, although the difference was also not statistically significant.[21] This is similar to our study, which is placebo-controlled and supported with a concomitant reduction in menstrual fluid $PGF_{2\alpha}$ levels. In another study, clinical efficacy and failure to restore normal uterine activity could not be accomplished[22] with a single dose of 500 mg acetaminophen compared with ibuprofen 400 mg. The dose of 500 mg acetaminophen may be suboptimal, whereas in the present study we administered the usual dose of 1000 mg acetaminophen and for 4 times a day. Further, our assessment was global evaluation by the patient and investigator, which is similar to the earlier clinical report[18] and medication was given for 3 days during menstruation.

There was also a significant concomitant decrease in total menstrual fluid $PGF_{2\alpha}$ as well as concentration of menstrual fluid $PGF_{2\alpha}$ during acetaminophen treatment, with an average decline of 39% in total menstrual fluid $PGF_{2\alpha}$ compared with placebo treatment. However, ibuprofen was even more potent than acetaminophen in suppressing menstrual fluid $PGF_{2\alpha}$ with a further reduction of 35 percent compared with acetaminophen. This almost approached significance ($P = .063$).

Acetaminophen is generally considered to be a weak inhibitor of PG synthesis but its cellular specificity and inhibition of human endometrial PG biosynthesis has never been previously documented. In broken cell systems, acetaminophen is a weak inhibitor of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) but in therapeutic concentrations acetaminophen will inhibit PG synthesis in intact cells in vitro when arachidonic acid levels are low.[19] However, the weak effect of acetaminophen on PG synthesis is incorrect. Acetaminophen has clinical effects similar to those of COX-2 inhibitors such as celecoxib and rofecoxib,[23,24] which are clinically effective in relief of primary dysmenorrhea. While acetaminophen may not suppress the inflammation of rheumatoid arthritis, it does decrease the tissue swelling following oral surgery in humans similar to that seen with ibuprofen.[25] In normal as well as hypertensive women during the third trimester of pregnancy, acetaminophen inhibits prostacyclin production in vitro and in vivo, but not thromboxane, to the same extent.[26] Overall, the pharmacologic effects of acetaminophen are those of a selective COX-2 inhibitor[15,27] but will vary from tissue to tissue. In menstrual fluid there is a soup of broken and intact endometrial and blood cells. Thus, in the broken cells, acetaminophen may act as a weak inhibitor of COX-1 and COX-2 but in the intact endometrial cells as well as the shedding endometrium it could inhibit PG synthesis. Thus, there is reduction in menstrual fluid $PGF_{2\alpha}$, albeit somewhat less than that of ibuprofen. Additionally, some of the analgesic effect of acetaminophen may be partially mediated through supraspinal activation of the descending serotonergic pathways,[17-19] which may partially explain the lack of restoration of abnormal uterine contractions to normal in women with primary dysmenorrhea.[22]

Ibuprofen is significantly more effective in relieving menstrual pain and more potent in inhibiting endometrial $PGF_{2\alpha}$ biosynthesis with reduction of menstrual fluid $PGF_{2\alpha}$ than placebo. This finding reaffirms earlier work by our group showing relief of pain and suppression of menstrual $PGF_{2\alpha}$ in primary dysmenorrhea by ibuprofen.[6-8] In the present study, menstrual fluid $PGF_{2\alpha}$ is reduced to almost two thirds or about 40% of the levels found during placebo treatment without significantly affecting menstrual fluid volume. Compared with 1000 mg of acetaminophen, 400 mg ibuprofen is a more potent inhibitor of en-

dometrial $PGF_{2\alpha}$ with menstrual fluid levels further reduced by another 35% and this almost reached statistical significance ($P = .063$). Ibuprofen acts at the COX-1 and COX-2 levels and blocks the biosynthesis of cyclic endoperoxides.

We also found no significant difference in the weight or volume of menstrual fluid with either ibuprofen or acetaminophen treatment compared with placebo. This further indirectly confirms that both medications were inhibiting the enzymatic pathway for the biosynthesis of prostaglandins. Therefore, both ibuprofen and acetaminophen do not appear to have any significant effect on the endometrial development and thickness unlike the oral contraceptives, which not only reduce the menstrual fluid $PGF_{2\alpha}$ but also significantly decrease the menstrual fluid volume.[7,8] Acetaminophen has been shown to be ineffective in reducing menstrual blood loss,[28] which is consistent with the finding in our study. In women with menorrhagia where there is an imbalance between thromboxane and prostacyclin, there may be partially selective inhibition of these 2 prostanoids relative to 1 another as shown in some studies to restore the menstrual blood loss or menstrual fluid volume to normal.[29,30]

Our data show that both ibuprofen and acetaminophen are effective compared with placebo for relief of pain in women with primary dysmenorrhea with a preference for ibuprofen. Both ibuprofen and acetaminophen showed significant suppression in menstrual fluid $PGF_{2\alpha}$ with greater suppression by ibuprofen. Both medications did not affect menstrual fluid loss. Thus, our findings demonstrate for the first time that given over 3 days during menstruation, acetaminophen can significantly inhibit menstrual fluid $PGF_{2\alpha}$ but to a lesser extent than ibuprofen. ■

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