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

M. Yusoff Dawood, MD; Firyal S. Khan-Dawood, PhD

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

Cite this article as: Dawood MY, Khan-Dawood FS. 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. Am J Obstet Gynecol 2007;196;35.e1-35.e5.

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

From the Departments of Obstetrics and Gynecology (Drs Dawood and Khan-Dawood), Physiology (Drs Dawood and Khan-Dawood), and Pathology (Dr Khan-Dawood), Robert C. Byrd Health Science Center, West Virginia University School of Medicine, Morgantown, WV.

Received February 20, 2006; revised June 13, 2006; accepted June 29, 2006.

Reprints: M. Yusoff Dawood, MD, Department of Obstetrics and Gynecology, West Virginia University School of Medicine, PO Box 9186, Morgantown, WV 26506-9186; ydawood@hsc.wvu.edu

This study was supported by a grant from Bristol-Myers, Inc.

0002-9378/$32.00

doi: 10.1016/j.ajog.2006.06.091

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-