An attempt at real prophylaxis of primary dysmenorrhea: comparison between Meclofenamate sodium and Naproxen sodium

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Summary: Dysmenorrhea is a widespread phenomenon, affecting mainly young nulliparous women, often inducing difficulties in study or in work. Its pathogenesis involves a release of local vasoconstrictors like Prostaglandins and Leukotrienes. Modern therapy is based firstly on the administration of prostaglandin-Synthetase Inhibitors or Contraceptive Pills, with the aim of reducing the menstrual excess of pain inducing substances. In order to achieve more efficacy, on the basis of the already proven effectiveness of the Non Steroid Anti-Inflammatory Drugs (NSAID)s in this field, we recently set out to prevent dysmenorrhea in a double-blind randomized study with Meclofenamate Sorium and Naproxen Sodium. Through the observation of the drop in Basal Body Temperature which usually precedes menstrual flow, we were able to instruct our patients in the earlier recognition of impending menstrual onset, leading to earlier prevention of Prostaglandin and Leukotriene release. Meclofenamate Sodium in particular led to considerable pain reduction, with very good patient compliance and without significant complications, probably of its additional receptor effect.

Key words: Dysmenorrhea; Meclofenamate sodium; Naproxen sodium.

INTRODUCTION

The medico-social importance of dysmenorrhea is already well-known (1). A problem involving most women (up to 70% of adolescent girls), (2) it has represented for many years a regular obstacle to their health and social life. Today the main factor responsible for this symptomatology is considered to be the excess endometrial production of painful substances, like Prostaglandins (PGE2 and PGF2a), Leukotrienes (LT) and Platelet Activating Factor (PAF), which cause miometrial hypercontractility and ischemia (3, 4). Vasopressin and Gonadal Steroids (Estrogens and Progesterone) are mediators of this production (5, 6), although a genetic factor is thought to be directly responsible (because of the high incidence of this syndrome among mothers and daughters) (7). The role of psychological factors is still unclear (8) (Fig. 1).

Moreover we should not forget the situations of secondary dysmenorrhea, which are linked to important gynecological pathologies (endometriosis, pelvic inflammation, genital malformations, etc.). In the past various therapeutical approaches have been suggested, although mainly empirical and with poor results. Furthermore, the effectiveness of cervical dilata-

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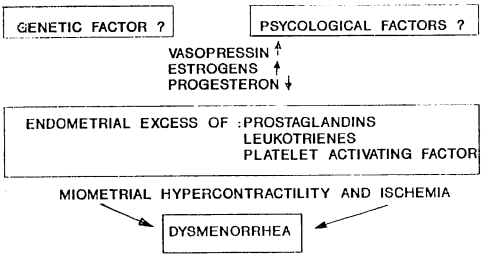

Fig. 1. — Outline of dysmenorrhea pathogenesis.

tion with surgery or vaginal delivery to eliminate dysmenorrhea has always been recognized; this effect is due to the interruption of adrenergic terminations of the cervix ([9]). Based on the latest physiopathological knowledge, modern therapy consists mainly of the administration of NSAIDs and Contraceptive Pills, with the aim of reducing the excess production of pain-inducing substances (Prostaglandins and Leukotrienes) ([10–13]). A lot of alternative therapies could be proposed, but these are either not very effective or are difficult to apply: oral Progestogens, GnRh Analogues, vaginal suppositories with Indometacin, Intrauterine Devices with Progesteron, Acupuncture, Transcutaneous Electrical Stimulations, Hypnosis, Biofeedback, Autogenous Training, etc. The effectiveness of the Vasopressin Inhibitors, of the Calcium Channel Blockers and of the Magnesium Salts has not been sufficiently proved. Estro-Progestogens, which employ long-term intake of hormonal substances, should be proposed when contraception is required: in these cases common rules and contra-indications must be respected. Nevertheless, today NSAIDs are thought to be the first-choice drugs for dysmenorrhea, because of their high efficacy and quick effect at low doses ([10, 11]). Through the inhibition of prostaglandin and Leukotriene synthesis, these drugs are most effective if administered before the onset of menstruation.

In fact the main production and delivery of Prostaglandins and Leukotrienes takes place during the first 48 hours of menstrual flow, thus explaining the intense pain of the first 2 days of menstruation ([14]). But the risks of this prophylactic outline are the excessive administration in women with irregular cycles or intake in an early unknown pregnancy. Therefore, the recent rules for dysmenorrhea treatment provide for NSAID administration every 8-12 hours on the first 2-3 days of menstrual flow. With the aim of reducing intake of the drugs, while at the same time achieving high efficacy, we tried to verify the possibility of obtaining an effective and safe dysmenorrhea prophylaxis by means of two strategies: the choice of the most effective drug and of the best time for intake. For the first goal we chose Sodium Meclofenamate, which can be considered as the "Ideal Drug" for dysmenorrhea, because of its unique capacity to inhibit Prostaglandin and Leukotriene synthesis together with receptor antagonism, thus also blocking already-formed products ([15–18]). For the second goal we asked our patients to record the pre-menstrual drop in their basal body temperature which usually indicates impending menstrual flow. In ovulatory cycles, in fact, the corresponding pre-menstrual fall in Progesteron levels triggers the biosynthetical chain of Prostaglandins and Leukotrienes ([19, 20]).

MATERIALS AND METHODS

In this study we compared the clinical effectiveness and the tolerability of Meclofenamate Sodium (Lenidolor, Menarini, 100 mg) against Naproxen Sodium (275 mg orally administered for 5 subsequent cycles after a basal control cycle. We admitted to our double-blind randomized study 30 patients aged 15-25, nulliparous, with regular menstrual cycles (28 ± 3 days), affected for at least 6 months by primary dysmenorrhea of medium-high gravity (2nd-3rd degree on Andersch and Milsom's Score) ([2]). Exclusion criteria were: light menstrual upsets, menstrual ir-

Table 1. — *Clinical features of the patients.*

	Average (+SD)
No. of patients	30 (15+15)
Age	23.8+2.6
Menarche age	12.1+1.0
Beginning of dysmenorrhea	12.8+1.3
Cycle length (days)	28.6+1.9
Menstruation length (days)	5.1+1.0
Menstrual flow amount:	
Slight	4/30 (13.3%)
Normal	21/30 (70%)
Abundant	5/30 (16.6%)

regularities, organic dysmenorrhea, gastro-duodenal ulcer, regional enteritis, ulcerative colitis, spastic colon, already known allergy to NSAIDS, IUDs or Oral Contraceptives. Informed consent was obtained prior to entry into the study. The patients' characteristics are presented in Table 1.

The patients were instructed on how to register their Basal Body Temperature daily, to mark its typical biphasic trend and, if possible, its pre-menstrual drop; this fall was shown in 136 cycles out of 180 (75%). After a first basal cycle (without treatment), for 5 subsequent cycles the patients took (on a full stomach) a capsule of the drug – assigned to them by randomization – as soon as they observed the fall in Basal Temperature (Fig. 2). If they were not able to observe this fall, they took the drug at the first appearance of menstrual flow. After 8 hours, they took a second capsule. Every evening of the first 3 days of menstruation, patients had to fill in the "Daily Diary of Dysmenorrhea Symptom Self-Evaluation", reporting their pain assessment on a "Visual Analogue Scale" [2]; besides, they had to report the extent of their symptoms by means of the "Sultan Score" (Table 2) [21]. Side effects or additional drugs also had to be reported. Statistical analysis was performed using the two-tailed Student's t-test and one-way Analysis of Variance.

Fig. 2. — Drug intake according to Basal Body Temperature Drop in Biphasic Cycles.

Table 2. — *Evaluation score for dysmenorrhea symptoms (by Sultan Ch., 1986).*

	Very pronounced	Pronounced	Mild	
Pelvic pain	3	2	1	0
Lumbago	3	2	1	0
Vomiting, nausea	3	2	1	0
Diarrhoea, intestinal troubles	3	2	1	0
Asthenia	3	2	1	0
Irritability	3	2	1	0
Dizziness	3	2	1	0
Myalgia	3	2	1	0
Lipothymia	3	2	1	0
Absense from work	3	2	1	0
Total	30	20	10	0

RESULTS

The analysis of pain self-evaluation through the Visual Analogue Scale (VAS) shows a good analgesic effect on the part of the drugs, both of which are able to induce considerable pain reduction. For Meclofenamate Sodium this reduction is statistically significant at each treatment cycle, with a further improvement at the 5th and 6th cycle (Fig. 3).

Naproxen Sodium, instead, shows significant pain reduction only at the 4th and

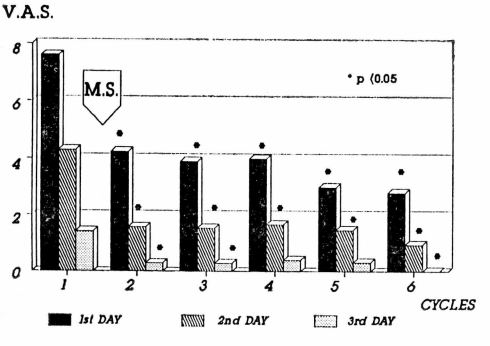

Fig. 3. — Menstrual pain self-evaluation (Visual Analogue Scale - V.A.S.) following administration of oral Meclofenamate Sodium. Statistical comparison (T-test) versus 1st Cycle.

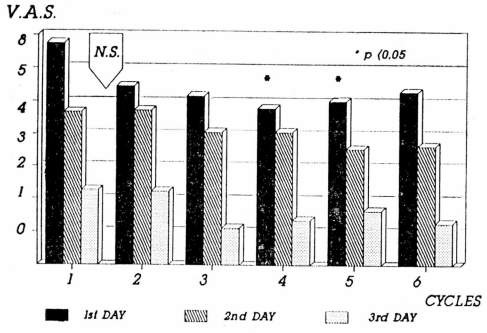

Fig. 4. — Menstrual pain self-evaluation (Visual Analogue Scale - V.A.S.) following administration of oral Naproxen Sodium. Statistical comparison (T-test) versus 1st cycle).

5th cycle (Fig. 4). In any case, a direct comparison between the two drugs emphasized a higher overall efficacy of Meclofenamate Sodium, with significant difference as against Naproxen Sodium (Fig. 5). Afterwards we analyzed Pain Relief, a percentage difference against basal cycle at each observation, following the formula:

$$\frac{\text{post-treatment value - baseline value}}{\text{baseline value}} \times 100$$

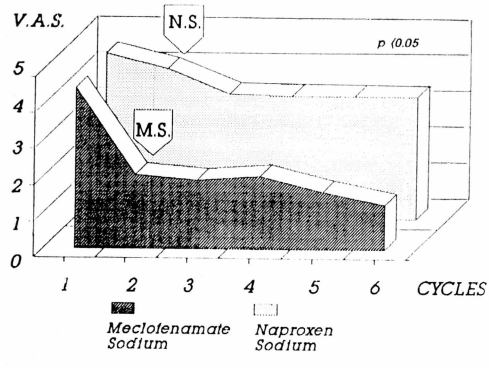

Fig. 5. — Menstrual pain self-evaluation (Visuau Analogue Scale - V.A.S.); comparison between Meclofenamate Sodium and Naproxen Sodium oral administration (T-test).

In this way Meclofenamate Sodium induced a pain reduction of up to 80%, against 29% for Naproxen (Table 4). Moreover, by examining drug effectiveness not only against pain, but also against the symptoms which make up the dysmenorrhea syndrome as a whole (Sultan's Score), we observed high efficacy of Meclofenamate Sodium against these symptoms also. This efficacy persisted for all the study cycles (Fig. 6), while Naproxen Sodium seems to be effective only at the 3rd cycle (Fig. 7). The comparison between the two drugs further underlines this difference, especially evident at the

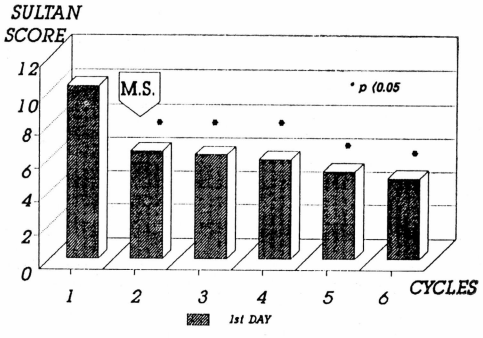

Fig. 6. — Dysmenorrhea symptoms (Sultan Score) following Meclofenamate Sodium oral administration. Statistical comparison (T-test) of each therapy cycle versus basal cycle (1st day).

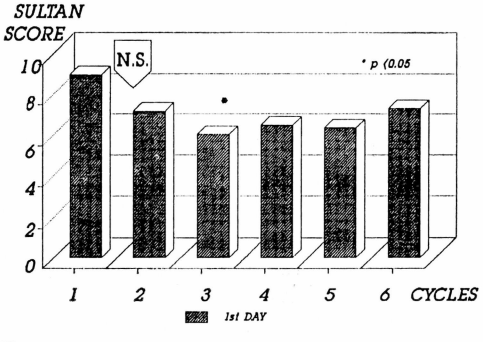

Fig. 7. — Dysmenorrhea symptoms (Sultan Score) following Naproxen Sodium oral administration. Statistical comparison (T-test) of each therapy cycle versus basal cycle (1st day).

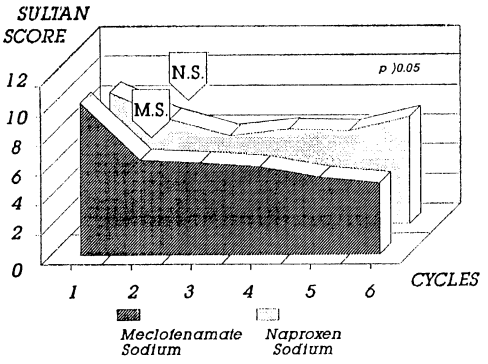

Fig. 8. — Dysmenorrhea symptoms (Sultan Score); comparison between Meclofenamate Sodium and Naproxen Sodium oral administration (T-test).

5th and 6th cycle (Fig. 8). With the aim of knowing if our suggestion of taking the drugs at BBT drop had been useful, we subsequently examined, apart, the cycles in which this drop was not seen (24.5%). In these cases the effect of both the drugs is not so evident: Pain Relief as a whole is inferior for both the drugs, with irregular and undecipherable trends (Table 4). Tolerability is better for Meclofenamate Sodium than for Naproxen Sodium: only one patient complained of side-effects with the first drug (epigastralgia), against 3 patients with the second drug (2 epigastralgia - 1 headache). All the patients reported good compliance with this guideline for drug intake.

DISCUSSION

In our trial, the comparison between Meclofenamate Sodium and Naproxen Sodium – up to now the most effective drug for primary dysmenorrhea – showed Meclofenamate Sodium to be superior in reducing menstrual discomfort, with good patient tolerability. This further confirms recent physiopathologic findings on mechanisms responsible for dysmenorrhea symptoms, stressing the importance of of the choice of the most useful drug (able to inhibit both Prostaglandins and Leukotrienes and to act also on already-formed substances) ([16, 22, 23]). The attempt at making an effective prophylaxis of primary dysmenorrhea by recording premenstraul drop in Basal Body Temperature was useful in cycles in which this signal was recognized. In this way it was possible to obtain a good dysmenorrhea control with only two administrations of the drug; this is very important in evaluating the cost-benefit ratio of a therapy which has a long-term influence on the life of many patients, often young. In the other cycles, probably anovulatory, the NSAID effect was not so marked, suggesting the possibility that other factors, psychological or otherwise, could play preponderant roles. In these cases other therapeutical solutions could be suggested ([1, 10, 24]).

Thus the recognition of different clinical situations among dysmenorrhea patients enables us to apply to each case the most effective therapeutical approach.

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