Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain

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LETTERS TO THE EDITOR—CORRESPONDENCE

Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain

Dear Editor,

With great interest we read the paper by Cobellis et al. in your journal (2011, doi:10.1016/j.ejogrb.2011.04.011) [1], comparing the effectiveness and safety of the association of micronized N-palmitoylethanolamine (PEA) – transpolydatin (400 mg + 40 mg twice a day for 3 months) to that of Celecoxib (200 mg twice a day for 7 consecutive days) in the treatment of chronic pelvic pain related to endometriosis.

We were quite impressed by the positive results obtained with both treatment regimens. Actually, we gained similar findings with the use of the compound Pelvilen (Epitech Group, Italy) containing PEA and transpolydatin at the same dosage to that used by Cobellis et al. [1]. Particularly, in our clinic we often use this combination for pain due to endometriosis, as well as to interstitial cystitis and in various neuropathic pain states. In our hands, the onset of action is mostly at week 1, and may take up to 5 weeks in more complicated cases. The therapeutic response, as measured on a VAS score within 1–4 weeks, is at least 50% decrease compared to baseline measurements, without finding any side effects. At our website as well as on Youtube (channel Neuropathyinfo4u) we documented a great many cases of patients suffering from intractable neuropathic pain, as well as a complicated case of severe pain in lichen planus treated with Pelvilen.

However, to our experience, patients treated for about a week with Coxib NSAIDs do not usually report long-lasting beneficial effects on chronic pelvic pain, differently from what observed by Cobellis et al. [1]. In our opinion, the treatment duration adopted in their study (i.e., Celecoxib for 7 days) and more particularly the time lag between the end of treatment (day 7) and the final examination (day 90) rises a quite thorny issue. It is known that Coxib NSAIDs are fast-acting drugs; however they are not known to be long-acting after treatment discontinuation. Moreover, the usual treatment time for controlling pelvic pain is about 2–6-fold longer than reported in the study by Cobellis et al. [2]. A few years ago, Cobellis published in your journal a placebo controlled study, evaluating the effect of a different Coxib NSAID (i.e., rofecoxib) for controlling pelvic pain related to endometriosis [3]. Surprisingly, in this paper, a 6-month treatment was reported to significantly benefit pelvic pain, i.e., a treatment duration 24-fold longer than reported in the 2011 paper from the same journal [1].

Endometriosis-associated pelvic pain is a visceral pain and a challenge for gynecologists and those engaged in the management of pain. There is evidence that in the pathogenesis of pelvic pain at least three different mechanisms play a role (i.e., nociceptive, inflammatory, and neuropathic pathways), variably contributing to the dysmenorrhea, dyspareunia and non-cyclic pelvic pain. The involvement of mast cells (of both endometrial and endoneural location) in all the three pain mechanisms has been repeatedly confirmed. Thus, the possibility to use novel and safe therapeutic approaches targeting mast cells appears very attractive. Palmitoylethanolamide (PEA) is one of the compounds that best fits into this strategy. It is a safe and naturally occurring compound, able to down-modulate mast cell activation and consequently reduce pain [4].

Is it our opinion that data reported by Cobellis et al. [1] shed new light on the potential health benefits of PEA in patients with chronic pelvic pain, strengthening the findings previously published in your journal [5]. In the same time, their findings also raise new issues on the length (and consequently cost-effective) therapy with Coxib NSAIDs that call for a further and careful deepening.

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Reply to "Letter to Editor" by Keppel Hesselink JM "Effectiveness of the association micronized N-palmitoylethanolamine (PEA)–transpolydatin in the treatment of chronic pelvic pain"

Dear Editor,

We very much appreciate Prof. Keppel Hesselink's feedback on our work [1], to underline the need of a more comprehensive

understanding of new therapies of pelvic pain related to endometriosis (EMS), and we thank him for his contribution to the discussion on such an important topic.

Although pain related to EMS is difficult to alleviate without resorting to hormones or surgery, which often produce intolerable side effects or fail to help, recent findings suggest that the use of different drugs (i.e. micronized N-palmitoylethanolamine (PEA)–transpolydatin or Coxib NSAIDs) significantly benefit pelvic pain [1]. Therefore Prof. Keppel Hesselink's experience with the use of PEA–transpolydatin [2], together with our data [1], enforces the concept that the endocannabinoid system contributes to mechanisms underlying both the peripheral innervation of the abnormal growths and the pain associated with EMS [1,2]. Indeed, recent studies in a rat model and in women showed that sensory and sympathetic nerve fibers sprout branches to innervate the abnormal growths, and CB1 cannabinoid receptors are expressed on both the somata and fibers of such neurons [3]. Moreover, CB1 receptor agonists decrease, whereas CB1 receptor antagonists increase, endometriosis-associated hyperalgesia [3].

On the other hand, the international experience in the treatment of chronic pelvic pain related to EMS with Coxib NSAIDs is not consistent. Besides, Coxib NSAIDs are approved for the relief of symptoms related either to chronic inflammatory conditions such as osteoarthritis and rheumatoid arthritis, or to acute conditions, such as perioperative and postoperative pain [1].

In our 2004 study [4] we used a low dosage of rofecoxib (25 mg/day for 6 months) with good results; however studies on the use of Coxibs in the treatment of different conditions at high dosage (200 mg, 400 mg, or 500 mg) suggested the concrete possibility to use Celecoxib at high dosage reducing the length of therapy [1].

Indeed, Celecoxib is known to exert a direct effect on reduction of endometrial growth, with pro-apoptotic and anti-proliferative properties on different in vivo and in vitro models [5]. Furthermore, Seo et al. [5] evaluated the expression of non-steroidal anti-inflammatory drug (NSAID)-activated gene-1 (NAG-1), a gene involved in cellular processes such as inflammation, apoptosis and tumorigenesis, in the endometrium and in the absence or presence of endometriosis. They also investigated the effect of Celecoxib on NAG-1 mRNA levels and apoptosis in human endometrial stromal cells (HESCs). They showed that NAG-1 mRNA and protein levels were significantly lower in patients with endometriosis compared with the control group. Moreover, treatment with Celecoxib significantly increased both NAG-1 mRNA levels and HESC apoptosis, and both of these effects depended on Celecoxib concentration [5]. In addition, NAG-1 mRNA levels and apoptosis also increased with the duration of treatment [5].

In the light of these results [5], the long-term efficacy shown by Celecoxib is probably due to the high dosage of our protocol [1] (16-fold higher than reported in the 2004 study [4]). Definitely, our data perfectly match with these findings: we had good results either with long-term therapy at low-dosage [4], as well as with short-term therapy at high dosage [1].

Our data show that both Coxib NSAIDs and micronized N-palmitoylethanolamine (PEA)–transpolydatin are effective in the treatment of pelvic pain related to EMS, thus resulting in the clinical translation of recent laboratory findings that shed new light on our understanding of the mechanism underlying the origin and development of pelvic pain related to EMS [1,5]. Further studies are needed to better clarify these important findings and to improve and develop innovative first-line therapeutic modalities in EMS related pain.

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