ABSTRACT

Cyclic mastalgia, by definition, occurs in premenopausal women and connotes breast pain that is clearly related to the menstrual cycle. Premenstrual mastalgia may be severe enough to interfere with usual daily activities, and its effect on quality of life is often underestimated. Hormonally active treatments are effective for patients with cyclic mastalgia. This book consists of five studies and presents effects of antiestrogen toremifene in mastalgia in premenopausal breast.

The aim of the first study was to evaluate the potential role of toremifene in the treatment of mastalgia, and to investigate its mechanism of action in this indication. The next aim was to evaluate if there are any measurable changes in luteal phase sex hormones attributable to toremifene in women with premenstrual mastalgia. The third aim was to find out if the effect of toremifene on breast would be detectable with dynamic magnetic resonance imaging (MRI). The fourth aim was to investigate the vascular and volume effects of toremifene on healthy premenopausal breast by 3D ultrasound.

In the first study a total of 62 premenopausal women suffering from cyclic mastalgia were randomized to receive toremifene 20 mg daily or placebo from day 15 of the menstrual cycle until menstruation for three consecutive cycles. After a wash-out cycle the women were crossed over to receive placebo or toremifene, respectively, for three additional cycles. In the second and third study the population was the same as previously described. However, only those participants, who had given blood samples at all measuring points, were included to the study. Forty-eight patients gave three blood samples during the luteal phase of the menstrual cycle: the first at baseline, the second during the third toremifene/placebo cycle and third during the third placebo/toremifene cycle, respectively. The investigated hormones were: follicle stimulating hormone, estradiol, progesterone, prolactin, androstenedione, total and free testosterone in the second and inhibin A/B in the third study.

In the fourth study ten women with a marked premenstrual mastalgia were randomized to receive either toremifene 20 mg or placebo from cycle day 15 until the next menstruation for three menstrual cycles. After a washout period, the treatment was crossed over for three additional cycles. The MRI evaluations were performed prior to menstruation at the end of each treatment phase. Breast pain and quality of life scores were collected from one baseline cycle and from all treatment cycles. Nine participants were included in the final analysis. In the fifth Study twenty healthy premenopausal women were recruited to the study. Following a single non-medicated baseline menstrual cycle, the participants received toremifene 20 mg/d from cycle day 15 until the second examination. The breast 3D ultrasound evaluations were performed within 5 days prior to menstruation. The both breast were assessed as four quadrants. The power Doppler setting was used and standardized with twenty degrees volume angle and maximum quality.

In Study I there was a 64 % reduction in median pain scores in the toremifene-treated cycles compared with a 26 % reduction in placebo-treated cycles. The median pain scores were 1.8 (during toremifene treatment), 3.7 (during placebo), and 5.0 (baseline). Although also the placebo effect was significant, toremifene reduced the pain significantly more than placebo. The adverse reactions turn out to be mild and infrequent during the treatment and were evenly distributed between the arms. The overall quality of life scores remained unchanged. In study IV the median VAS scores were during toremifene 1.83 and during placebo 6.33. Again toremifene alleviated breast pain, but the difference was only of borderline significance (P=0.078). However, the quality of life scores appeared to be slightly lower during toremifene as compared to placebo (P=0.047). This is likely to be coincidental result due to much smaller sample size in

Study IV than in Study I (nine vs. 56 patients, respectively). The median serum estradiol and progesterone levels were significantly higher in the toremifene-treated cycles. The median serum prolactin concentration was significantly higher during the toremifene treatment as compared to the baseline. There were no significant changes in other hormone concentrations evaluated. The concentrations of both inhibins were within normal range for the luteal phase and remained unchanged throughout the treatment cycles. The mechanism by which toremifene has a therapeutic effect in cyclic mastalgia does not seem to involve inhibition or stimulation of ovarian inhibin production.

Both the enhancement ratio and the maximum slope of enhancement tended to be lower during the toremifene cycles as compared to placebo. These findings indicate that the therapeutic effect of toremifene in alleviating premenstrual mastalgia may at least partly be mediated though diminished blood flow to breast. The 3D measured volumes and all vascular indices in healthy breasts remained unchanged during the treatment with toremifene as compared to the baseline.

The finding that toremifene significantly alleviated premenstrual breast pain over placebo with few mild adverse effects encourages its use for this indication. The short-term safety of 20 mg of toremifene administered daily during the luteal phase was addressed. The present results imply that the mechanism of action of toremifene in mastalgia is at least partly based on local effects, although the luteotropic effect was also evident.
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