Treatment of cyclical mastalgia with a solution containing a Vitex agnus castus extract: results of a placebo-controlled double-blind study

M. Halaška,* P. Beles,† C. Gorkow‡ and C. Sieder†
*Department of Gynecology and Obstetrics, Charles University of Prague, U Nemocnice 2, 128 00 Praha 2, Czech Republic; †Dr. Peithner KG, Trebohostická 12, 100 00 Prague 10, Czech Republic; ‡Bionorica Arzneimittel GmbH, Postfach 1851, 92308 Neumarkt/Opp., Germany

SUMMARY. In a placebo-controlled, randomized, double-blind study the efficacy of a Vitex agnus castus extract-containing solution* (VACS) was investigated in patients suffering from cyclical mastalgia. Patients had mastalgia on at least 5 days in the pre-treatment cycle. During this cycle and during treatment (3 cycles; 2 × 30 drops/day), the intensity of mastalgia was recorded once per cycle using a visual analogue scale (VAS).

After one/two treatment cycles, the mean decrease in pain intensity (mm, VAS) was 21.4 mm/33.7 mm in women taking VACS (n = 48) and 10.6 mm/20.3 mm with placebo (n = 49). The differences of the VAS-values for VACS were significantly greater than those with placebo (p = 0.018; p = 0.006). After three cycles, the mean VAS-score reduction for women taking VACS was 34.3 mm, a reduction of ‘borderline significance’ (p = 0.064) on statistical testing compared with placebo (25.7 mm). There was no difference in the frequency of adverse events between both groups (VACS: n = 5; placebo: n = 4). VACS appears effective and was well tolerated and further evaluation of this agent in the treatment of cyclical mastalgia is warranted. © 1999 Harcourt Publishers Ltd

INTRODUCTION

From sexual maturity to menopause, approximately 50% of the women suffer from premenstrual breast pain or mastalgia. Mastalgia has an age peak at 34 years.1 Although premenstrual mastalgia often appears as a single symptom, it is often associated with the premenstrual symptom complex (PMS) and thus is commonly considered as the principal sign of PMS. Mastalgia is considered to be related to latent and slightly increased basal prolactin serum levels.2–9 Among other hormones, increased serum levels of the hormone prolactin stimulate lactation and lobular-alveolar growth of mammary tissue. A latent hyperprolactinemia results in subchronic unphysiological stimulation of the mammary tissue and, thus, mastalgia. During the premenstrual week which is the phase of decreasing estradiol and progesterone levels, latent hyperprolactinemia often becomes manifest.3,7

*Mastrodynon®, manufactured by Bionorica Arzneimittel GmbH.

Address correspondence to: Christoph Gorkow, Bionorica Arzneimittel GmbH, Postfach 1851, 92308 Neumarkt/Opp., Germany. Tel.: +49-9191-231-217; Fax: +49-9191-231-146

Experimental studies have proven that Vitex agnus castus extract inhibits prolactin release which is caused by selective stimulation of pituitary dopamine receptors of the D2-type.10–13 In clinical investigations and double-blind trials with preparations containing Vitex agnus castus extract, a decrease of latent and pathologically increased prolactin levels and an influence on prolactin release in healthy subjects has been demonstrated.14–19 A significant decrease of mean basal prolactin level with VACS (Vitex agnus castus extract-containing solution) treatment, comparable to that demonstrated in patients with mastalgia treated with bromocriptine20 was shown in a double-blind study.14 Not only is there experimental-pharmacological evidence for a prolactin-inhibiting effect, but it is also confirmed by pharmacological studies on humans. Therefore, the dopaminergic principle of action is a plausible explanation for the view that VACS would be successful in the treatment of mastalgia.

The efficacy of VACS in the treatment of mastalgia has been shown in a double-blind trial vs placebo performed in compliance with GCP guidelines.14 The objective of the present study was to confirm the efficacy and tolerability of VACS in the context of a study of similar design.
PATIENTS AND METHODS

Based on a randomization plan, n=100 women with cyclical mastalgia shall be included in a single centre, placebo-controlled, double-blind study with parallel groups. VACS or placebo was allocated at the baseline examination on day 3 or 4 of cycle 1. After 20 cases each, the frequency distribution of both preparations to be compared was balanced. The determination of sample size was based on an estimated difference of 15 mm in the visual analogue scale at a significance level of $p = 0.05$ and a power of 0.9 at an estimated standard deviation of 20 mm. The necessary sample size of $n = 35$ patients per group was increased to $n = 50$ patients per treatment group to compensate for drop-outs in the intention-to-treat analysis.

In the cycle before start of treatment, patients ranging from 18 to 45 years had to suffer from mastalgia on at least 5 days. The minimum cycle duration within the last 3 cycles before treatment had to be 25 days; the maximum duration had to be 35 days. Signs of fibrocystic mammatic tissue alterations were allowed. Hormonal contraceptives were admitted providing they had been taken for the last 6 months before treatment started and that they were to be continued during the study without alteration. Breast cancer, fibroadenoma, intraductal papilloma, galactorrhea, purulent or bloody nipple discharge, severe endocrinopathies, recent or impending breast surgery, concomitant therapy with analgesics or NSAIDs (non-steroid anti-inflammatory drugs) and successful alcohol detoxication were exclusion criteria. Pregnancy and lactation were also reasons for exclusion from the study.

Treatment was preceded by one cycle (cycle 0) without treatment in which patients were examined for inclusion and exclusion criteria. After the baseline examination on day 3/4 of cycle 1 patients were given their study medication sufficient for the period to the next assessment.

VACS (Vitex agnus castus extract-containing solution) is a drug with a complex composition administered as a solution. The daily dose of $2 \times 30$ drops (1.8 ml) is equivalent to 32.4 mg extract of the Vitex agnus castus drug. Ten grams of the solution contain 2 g of mother tincture of Vitex agnus castus, 1 g Caulophyllum thalictroides dil. D4, 1 g Cyclamen dil. D4, 1 g Ignatia dil. D6, 2 g Iris dil. D2, and 1 g Lilium tigrinum dil. D3. The preparation contains 53% (v/v) alcohol. The placebo solution was an ethanol–water mixture (55.4% [v/v] ethanol) with similar taste and optical appearance to the verum solution. For each treatment cycle, the patients received a 75 ml bottle.

Examinations were carried out on day 3 or 4 of the cycles 1, 2, 3, and 4. The target parameter for the assessment of efficacy was the visual analogue scale score. Using this scale, patients were asked to record the intensity of mastalgia during the premenstrual days on day 3 or 4 of the follow-
study and the risks involved, all patients gave their written informed consent to participate in this study.

RESULTS

A total of \( n=97 \) patients was included into the study. Distribution of sample size and of demographic data was well balanced in both groups (VACS: \( n=48 \), placebo: \( n=49 \)) (Table 1). To prevent a delay in completion of the study a total of 97 patients were recruited instead of the originally planned sample size (\( n=100 \)). There were no other deviations from the study protocol.

A total of 11 randomized patients dropped out prematurely: 5 from the VACS and 6 from the placebo group. The most frequent reason for discontinuation was lack of compliance. One patient, each from the placebo and from the VACS group, reported adverse events as the reason for discontinuation. It is remarkable that 3 of the 5 drop-outs from the VACS group already had a marked reduction in pain intensity at the time of discontinuation; therefore, the lack in continuing with the study did not seem to be due to an insufficient therapeutic effect. In the placebo group, 2 of 6 drop-outs reported a moderate therapeutic effect.

The quality of data in the case report forms (CRF) was extraordinarily high. No inconsistencies, contradictions, or questionable information was detected. Almost all data were complete, except for patients following drop-out. All entries in the CRFs were completed and all corrections were signed and dated. No violation of inclusion or exclusion criteria, no taking of non-permissible medication, and no wrong group allocation was detected. Due to an adverse event (permanent tiredness), the randomization code was revealed for one patient from the VACS group (patient no. 44). Afterwards, this patient dropped out of the study.

The pain intensity (mm VAS) before the start of treatment was comparable in both treatment groups (median: VACS: = 63.5, placebo = 58.0) (Fig. 1). The difference in the mean values between both patient groups was 3 mm.

The pain diaries demonstrated that on average the patients were without pain on about 50% of the days of the cycle. On 30% of the days of the cycle, pain was moderate, and on almost 20% of the days, mastalgia was severe. Pain intensity and frequency was comparable in both groups.

The reduction in the intensity of mastalgia was quicker in the VACS group. Even after the first treatment cycle, the mean pain reduction on VACS treatment was 21.4 mm VAS (corresponding to 30%), while on placebo it was 10.6 mm (corresponding to 11%). After the second treatment cycle, the mean reduction in pain intensity on VACS treatment was 33.7 mm VAS (corresponding to 53%), and on placebo it was 20.3 mm (corresponding to 25%). At the end of the first two cycles, the differences in the reductions in the visual analogue scale values differed significantly between VACS and placebo group (\( t \)-test: \( p = 0.018; p = 0.006 \)). In the third therapy cycle, only a slight decrease in
pain intensity was achieved in the VACS group. In total, pain reduction during VACS treatment was 54% VAS (corresponding to 34.3 mm), while under placebo the total reduction at study completion was 40% VAS (corresponding to 25.7 mm). At the completion of therapy, only borderline significance between VACS and placebo group was obtained in the statistical analysis ($p = 0.064$) (Fig. 2). Following two treatment cycles, the visual analogue scale values during VACS treatment fell below 35 mm VAS in 71.4% of the cases. This means that for the majority of patients the pain scale level was so low that a further reduction was either no longer (corresponding to relief from complaints) or hardly (corresponding to intensive amelioration) possible. Correspondingly, the VAS values on continued VACS treatment were only slightly reduced. On the other hand, after two treatment cycles of placebo treatment, sufficient potential for pain reduction still existed. For an exact assessment of the therapeutic effect, the mean differences in mastalgia reduction (mm VAS) and 95% confidence intervals were calculated and graphically represented (Fig. 3). At cycles 2 and 3, zero was not included in the confidence intervals, i.e. at these times the therapeutic effect of VACS treatment was significantly better.

Before therapy, the relative proportion of days with severe pain was almost equal in both groups. During therapy, the relative proportion of the days of the cycle with severe pain was distinctly reduced in both treatment groups, although with VACS treatment the effect was quicker and more pronounced. After two cycles, the median of the VACS group was already 0, this means that 50% of patients had no days with severe pain. Another 25% of the patients still had severe pain on up to 4.3% of the days of the cycle. In contrast, the median of the placebo group at the same time was 3.9%. The 75% percentile (i.e. the point with 75% of the values falling below and 25% lying above) was 13.8. After three cycles, also of placebo treatment, the median had fallen to 0, while the 75% percentile remained unchanged (13.8, see Fig. 4). For cycles 3 and 4, the differences between the treatment groups were significant ($p = 0.007; p = 0.014$, Wilcoxon test). The differences between both treatment groups were even more pronounced in patients who reported severe pain on more than 15% of the days of the cycle (VACS: $n = 25$, placebo: $n = 30$). After one cycle, the number of days with severe pain was first reduced in both groups. From the second cycle, median and percentiles remained at the same level with placebo treatment, while in the VACS group the relative proportion of days with severe pain continued to reduce in the following cycles. From the second cycle, half of the patients were free from severe pain. After the third cycle, 75% of the VACS patients had severe pain on less than 10% of the days of the cycle (Fig. 5). For cycles 3 and 4, significant differences were seen in favour of the VACS group ($p = 0.021; p = 0.015$, Wilcoxon test). Correspondingly, the proportion of pain-free days increased.

With regard to the frequency of adverse events (AE), no difference existed between treatment groups (VACS: $n = 5$, placebo: $n = 4$). As far as a relationship to the test medication was considered as possible or probable, AE were only slight. The most frequent AE in both treatment groups were cycle anomalies, which were reported by three patients.
Fig. 4  Decrease in the number of days with severe pain (box plots). Due to variations in cycle duration, the number of days with severe pain was expressed as a proportion of the total cycle.

Fig. 5  Decrease in the number of days with severe pain (box plots) in patients who at a minimum of 15% of the days of the cycle had severe pain. Due to variations in cycle duration, the number of days with severe pain was expressed as a proportion of the total cycle.

each. One patient taking VACS discontinued due to permanent tiredness. On placebo, treatment was discontinued in 2 cases (1 × irregular menstrual bleeding, 1 × coxarthritis). For concomitant diseases occurring during the study and listed as adverse events (like tonsillitis, sinusitis, coxarthritis, and distortion of the knee), any connection with the medication was excluded (Table 2). The compliance of patients was good to excellent.
**Table 2** Adverse events (AE)

<table>
<thead>
<tr>
<th>VACS group</th>
<th>Pat. no.</th>
<th>Cycle</th>
<th>AE type</th>
<th>Severity</th>
<th>Connection to study medication</th>
<th>AE duration</th>
<th>AE frequency</th>
<th>Continuation of treatment</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>3</td>
<td></td>
<td>Tonsillitis</td>
<td>slight</td>
<td>none</td>
<td>whole day</td>
<td>occasional</td>
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<tr>
<td>44</td>
<td>3</td>
<td></td>
<td>Tiredness like in hypothyrosis</td>
<td>slight</td>
<td>probable</td>
<td>several days</td>
<td>permanent</td>
<td>discontinued</td>
</tr>
<tr>
<td>46</td>
<td>3</td>
<td></td>
<td>Distortion of the right knee</td>
<td>slight</td>
<td>none</td>
<td>once</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>3</td>
<td></td>
<td>Prolonged cycle</td>
<td>slight</td>
<td>possible</td>
<td>occasional</td>
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<td></td>
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<tr>
<td>65</td>
<td>4</td>
<td></td>
<td>Shortened cycle</td>
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<td>possible</td>
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<td></td>
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<tr>
<td>74</td>
<td>4</td>
<td></td>
<td>Irregular cycle</td>
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<td>occasional</td>
<td>yes</td>
<td></td>
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<table>
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<tr>
<th>Placebo group</th>
<th>Pat. no.</th>
<th>Cycle</th>
<th>AE type</th>
<th>Severity</th>
<th>Connection to study medication</th>
<th>AE duration</th>
<th>AE frequency</th>
<th>Continuation of treatment</th>
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<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>Metrorrhagia</td>
<td>slight</td>
<td>possible</td>
<td>several days</td>
<td>occasional</td>
<td>yes</td>
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<tr>
<td>1</td>
<td>3</td>
<td></td>
<td>Metrorrhagia</td>
<td>slight</td>
<td>possible</td>
<td>several days</td>
<td>intermittent</td>
<td>yes</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td></td>
<td>Nausea</td>
<td>slight</td>
<td>none</td>
<td>several days</td>
<td>intermittent</td>
<td>yes</td>
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<tr>
<td>1</td>
<td>4</td>
<td></td>
<td>Intermenstrual bleeding</td>
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<td>none</td>
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<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td></td>
<td>Intermenstrual bleeding</td>
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<td>several days</td>
<td>intermittent</td>
<td>yes</td>
</tr>
<tr>
<td>66</td>
<td>3</td>
<td></td>
<td>Coxarthrosis</td>
<td>severe</td>
<td>none</td>
<td>several days</td>
<td>intermittent</td>
<td>discontinued</td>
</tr>
<tr>
<td>68</td>
<td>2</td>
<td></td>
<td>Irregular period</td>
<td>slight</td>
<td>possible</td>
<td>several days</td>
<td>intermittent</td>
<td>discontinued</td>
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</table>

**DISCUSSION**

At least half of all women in child-bearing age have mastalgia within the last few days before menstrual bleeding. Any therapy should have been demonstrated to be effective in clinical double-blind studies. Mastalgia is a subjective symptom which, therefore, cannot be objectively assessed. In a recent double-blind study which investigated the effect of VACS, mastalgia was converted to measurable units using a visual analogue scale (VAS), and, therefore, efficacy of VACS in comparison to placebo could be shown. The objective of the present study was to confirm the efficacy of VACS with an almost identical study design but in an institution, which is independent from the first working group.

The study was conducted in compliance with the EC/GCP-Note for Guidance which were converted into standard operation procedures (SOPs), the recent version of the Declaration of Helsinki, and the Medical Preparations Act of the Czech Republic. Statistical analysis was performed in accordance with SOPs and on the basis of the CPMP Note for Guidance (Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorizations for Medical Products) and in accordance with the ICH guidelines E-3 (Structure and Content of Clinical Study Reports), E-6 (Good Clinical Practice: Consolidated Guideline), and E-9 (Statistical Principles for Clinical Trials). The quality of the data was extraordinarily high. No inconsistencies, contradictions, questionable information, or violations of the study protocol existed. Selection of patients with mastalgia for the current study could be considered as representative of all women with breast pain.

The current study demonstrated once again that VACS is effective and is a well tolerated treatment for breast pain. A comparison of this study with the recently published double-blind study demonstrated similar results with regard to the reduction in intensity of mastalgia (Fig. 6). The use

![Fig. 6](image_url)
of the visual analogue scale as a target variable to determine intensity of mastalgia intensity made it possible in these two independent studies to objectively determine subjective symptoms and their improvement during therapy. In addition to a validation of efficacy, the visual analogue scale has been confirmed as a suitable target criterion for demonstrating efficacy. The proof of the efficacy of VACS in the treatment of cyclically re-appearing mastalgia with this method, was demonstrated to be reproducible.

Tolerability was shown to be excellent. Adverse events were rare, and their severity was only slight. AE were not more frequent with VACS than in the placebo group. The favourable benefit–risk ratio justifies the use of Vitex agnus castus containing solution for at least 3 months in women with severe breast pain, before alternative drugs with a higher rate of side-effects are considered.

Acknowledgement

Bionorica Arzneimittel GmbH, Postfach 1851, 92308 Neumarkt/Opf., Germany.

References