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Treatment of cyclical mastalgia with a medicinal product containing Agnus castus

Results of a randomized, placebo-controlled, double blind study
Geburtsh. u. Frauenheilk. 57 (1997) 569-574
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Treatment of cyclical mastalgia with a medicinal product containing Agnus castus.

Results of a randomized, placebo-controlled, double-blind study

Original title: Behandlung zyklusabhängiger Brustschmerzen mit einem Agnus castus haltigen Arzneimittel - Ergebnisse einer randomisierten, plazebo-kontrollierten Doppelblindstudie

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Summary: Objective: The efficacy of a preparation containing Agnus castus, formulated as a solution* (Mastodynon®) and as corresponding tablets (MA 1025 E1), was compared with placebo in mastalgia. Design: Multicenter, randomized, placebo-controlled, parallel groups, double-blind, double-dummy technique. Subjects: Patients had to have suffered mastalgia for at least three cycles and complain of breast pain on a least three days in the cycle before treatment was initiated. 104 patients were included in the “intention to treat” analysis (solution: n=34; tablets: n=32; placebo: n=38). Methods and main outcome measures: The duration of treatment was three cycles. To assess the efficacy, patients were required to indicate the intensity of breast pain on the visual, linear analog scale (VAS). As a confirmatory test, an analysis of covariance of the baseline-end-point difference with the factor “treatment group” and the covariate “VAS, cycle 0” was carried out. Estradiol-17β, progesterone, FSH, LH and basal prolactin were measured in the premenstrual weeks of cycles 0, 1, 2 and 3. Analysis of prolactin values after metoclopramide stimulation was carried out in cycles 0 and 3. Results: At the end of treatment, there was a significant difference between the VAS values for the solution and the tablets, respectively $p = 0.0067$; $p = 0.0076$ and those for the placebo group. The solution demonstrated onset of action after the first treatment cycle, which was faster than the tablet formulation. The treatment had no effect on progesterone, FSH and LH. Under both active formulations, the estradiol-17β values decreased somewhat more strongly than under placebo. The basal prolactin levels fell significantly in comparison with placebo, by 4.35 ng/ml ($p = 0.039$) under the active solution and by 3.7 ng/ml ($p = 0.015$) under the active tablets. In comparison with placebo, the stimulated prolactin

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levels at the end of treatment tended to be lower under both active formulations. **Conclusion:** The solution and the tablets of the preparation containing *Agnus castus* are effective in mastalgia. Basal prolactin levels dropped significantly with both forms of the preparation. The subjective tolerance was good.

**Introduction**

By the time menopause occurs about half of all women in a gynecological practice complain of premenstrual, mostly painful tension of the breast. The peak age for this is around 34 years [14]. Mastodynia as a very frequently occurring single symptom is the essential cardinal symptom of the premenstrual syndrome. A causal relationship with a latent hyperprolactinemia is assumed for mastodynia in particular [3, 5, 6, 13, 15, 16, 18, 19]. Raised serum levels of the prolactin hormone stimulate the growth of lobuloalveolar breast tissue and lactation. In the case of latent hyperprolactinemia the breast tissue is stimulated subchronically in an unphysiological manner and therefore feels so swollen that movement or touching of the breast is perceived as painful. Frequently, the latent form of hyperprolactinemia is manifest in the menstrual phase with decreasing progesterone and estradiol levels, i.e. in the week before menstruation [5, 16].

According to *in vitro* and *in vivo* studies, *Agnus castus* extract (e.g. contained in Mastodynon®*) has an inhibitory effect on prolactin release [7, 8, 20, 21]. This is a dopaminergic effect owing to stimulation of the pituitary dopamine receptors [7, 8, 21]. In the case of remedies containing *Agnus castus*, a reduction of slightly pathological or latently raised prolactin levels has already been observed [12, 17].

From older clinical studies with remedies containing *Agnus castus* we know that somatic symptoms, in particular mastodynia and emotional premenstrual symptoms, are significantly improved [4, 9]. Since these studies no longer fulfill the current standard in the clinical testing of medicinal products, the efficacy of the combination preparation containing *Agnus castus*, Mastodynon®, in liquid and solid form (MA 1025 E1) was to be confirmed in cyclic breast pain in a current double-blind trial.

**Patients and methods**

The multicenter, placebo-controlled double-blind study in 3 parallel groups was to include n = 120 women with mastodynia according to a randomization plan with ascending numerical order. The assignment to the treatment groups: active solution, active tablets and placebo was made on the basis of the admission examination. The frequency distribution of the three test sample forms was balanced out after every 12 cases. The planning of the number of

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cases was based on the assumption of a minimum difference at the end of treatment between the study medication and the placebo in the visual analog scale (VAS) of 15 mm with a standard deviation of 20 mm.

The patients were to have suffered from cyclical mastodynia for at least three cycles with breast pain on at least three days in the last cycle prior to the start of the study. Patients excluded from the trial were those with IIIrd degree galactorrhea, purulent/bloody mammary discharge, severe endocrinopathy, malignoma, necessary breast surgery, simultaneous treatment with analgesics or nonsteroidal antiphlogistics and having undergone alcohol withdrawal treatment. Pregnancy and lactation also signified exclusion from the study. During the course of the study the use of hormones - including oral contraceptives - or treatment with hormone-like medication was not permitted.

Treatment was preceded by what is known as an empty cycle (cycle 0) without treatment and during which the inclusion and exclusion criteria were determined. Following the admission examination with extensive anamnesis in cycle 0 the patients were given the active medication for the entire treatment duration of three cycles. The active solution was the drug Mastodynon®,. The type and concentration of the active substances of an active tablet (MA 1025 E1) corresponded to the individual dose of the Mastodynon® solution. The placebo solution was an ethanol-and-water mixture (55.4% v/v of ethanol) adjusted as closely as possible in taste and color to the active solution. The placebo tablets were visually identical to the active tablets and contained the following ingredients: potato starch, malt extract, lactose and magnesium stearate. In order to ensure a strictly double-blind procedure, the double-dummy technique was employed. This resulted in the following dosage instructions for the treatment groups:

**Active solution group:** twice daily 30 drops of active medication and 1 placebo tablet

**Active tablet group:** twice daily 30 drops of placebo and 1 active tablet

**Placebo group:** twice daily 30 drops of placebo and 1 placebo tablet

Checkups were carried out in the premenstrual week, i.e. 3 to 7 days before menstruation was expected, in cycles 0, 1, 2 and 3. During all these cycles the patients had to record in a daily pain journal whether they had none, mild or severe pain.

The target parameter for the efficacy of the treatment was a visual linear-analog scale on which on day 3 or 4 of menstruation the

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patients themselves marked the extent of the breast pain on the premenstrual days retrospectively. The scale ranged from 0 to 100 mm whereby the end points were identified as "no pain" (0) and "unbearable pain" (100). There were no graduations beside the end points. In order to avoid comparisons with previous evaluations, the VAS scales were to be sent to the attending physician by post immediately after completion. The levels of estradiol-17β, progesterone, FSH, LH and basal prolactin were determined by a central laboratory on the checkup dates of cycles 0, 1, 2 and 3. In cycles 0 and 3 the prolactin values were analyzed 30 min after metoclopramide stimulation in each case.

At every checkup additional premenstrual symptoms such as abdominal complaints, headache, edema and emotional disorders were inquired about according to the classification "yes" or "no".

In the intention-to-treat analysis of the target parameter for the testing of efficacy, missing values were extrapolated according to the "last value carry forward" principle (missing values replaced by the last previous value with dropouts being evaluated as treatment failures; cf. 1) since visual analog scales were not on hand for all patients for all cycles. According to this principle, patients were included who had been given the study medication and for whom a VAS was present in cycle 0 and in at least one subsequent cycle. The covariance analysis of the baseline-endpoint difference with the factor "treatment group" and the covariable "VAS in cycle 0" was carried out as a confirmatory test and the baseline-adjusted means of the treatment groups compared.

The evaluation of the pain journal was based on the relative number of pain-free days using a baseline-endpoint analysis.

The analysis of the hormone concentrations was carried out in those patients for whom values were present at least in cycles 0 and 3 (protocol correct collective). The stimulated prolactin values were compared exclusively in a subgroup of patients for whom a stimulated value of > 160 ng/ml was determined in cycle 0, since changes were to be expected mainly in stimulated prolactin values which were on the borderline of normal or raised. The explorative group comparisons were carried out with the Mann-Whitney U-test.

Adverse drug reactions were recorded as spontaneous reports on the checkup dates of cycles 1, 2 and 3 by type, severity, duration and frequency and descriptively by type, namely according to the WHO system organ classes and according to degree of severity.

The planning and implementation of the study took place between 1991 and 1995 in accordance with the "Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln" [principles for the proper implementation of clinical drug testing] (1987) and taking into account the GCP/EC Note for
Guidance (1990). An ethics commission voted its unreserved consent. After having had the purpose, procedure and risks of the study explained to them in detail the patients gave their oral consent to the study.

Results
The study included n=120 women whereby, despite the randomization and with nevertheless differing numbers of cases, i.e. numbers of cases larger or smaller than the block factor 12 in the four test centers, the following distribution resulted: active solution n=37, active tablets n=39, placebo n=44.

Eight patients dropped out of the study already in cycle 0 before they had been given the test medication. A further 8 patients (active solution: n=2; active tablets: n=3; placebo: n=3) dropped out after distribution of the test medication. For these patients VAS values were only available for the initial examination. Accordingly, the intention-to-treat analysis was able to include n=104 patients. About half of all the cases displayed a borderline normal or disturbed prolactin release before the start of treatment (n=18: basal prolactin > 16 ng/ml; n=38: stimulated prolactin in the upper reference range > 160 ng/ml up to above the reference range > 200 ng/ml after stimulation with metoclopramide). The tolerance was evaluated at n=122 women.

The three treatment groups were comparable. As regards the demographic data (cf. Tab. 1) as well as additional anamnestic parameters such as age at menarche, average cycle duration, pregnancies, severity of menstrual discomfort, fibrocystic characteristics in the breasts as well as other accompanying symptoms, only insignificant differences were present.

<table>
<thead>
<tr>
<th>Tab. 1</th>
<th>Demographic data of the patients (intention-to-treat collective)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mastodynon solution</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$\bar{x} \pm s$</td>
</tr>
<tr>
<td>median, n</td>
<td>32.2 ± 9.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$\bar{x} \pm s$</td>
</tr>
<tr>
<td>median, n</td>
<td>164.4 ± 6.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$\bar{x} \pm s$</td>
</tr>
<tr>
<td>median, n</td>
<td>59.6 ± 8.2</td>
</tr>
</tbody>
</table>

The VAS means for the target variables breast pain displayed differences (active solution: 60.3 ± 22.3 mm; active tablets: 54.6 ± 23.7 mm; placebo: 61.4 ± 20.2 mm) in cycle 0 for the individual treatment groups. In the confirmatory efficacy analysis these differences had to be taken into account since theoretically a greater treatment success was possible with higher initial values. The confirmatory evaluation of differences of the VAS values
between cycle 0 and the end of the treatment by means of covariance analysis yielded a significant influence of the factor “treatment group” (p = 0.0074). This was followed by comparisons of the treatment groups among themselves by means of baseline-adjusted VAS means. At the end of treatment the differences for the active solution (36.5 mm) and the active tablets (36.7 mm) differed significantly (p = 0.0067; p = 0.0076) from the placebo group (20.8 mm). The treatment effect occurred under the active solution more rapidly, however, i.e. already after one treatment cycle, than under the active tablets. After the first treatment cycle the adjusted reduction in the VAS under the active medication solution with 22.5 mm was significantly (p = 0.0472) larger than under the placebo (10.5 mm); the tablet group differed with a reduction of 11.5 mm only insignificantly from the placebo (p = 0.8497). In cycle 2 the reduction of the VAS values in both active medication groups (active solution: 31.7 mm, p=0.00992; active tablets: 27.4 mm, p=0.4006; placebo: 22.7 mm) was more distinct than under placebo.

Fig. 1 shows the treatment-dependent course of breast pain intensity (box plot representation) on the basis of the visual analog scale for the individual treatment groups. The rapid reduction of the intensity of the breast pain under the active solution and the almost equally marked treatment effects of both active medication treatments at the end of treatment are clearly visible and they distinctly exceeded a placebo effect known from clinical studies in this indication.
In comparison with the placebo, premenstrual symptoms existing before the start of treatment such as abdominal complaints, tendency to edema, headache and emotional complaints were reported more rarely at the end of treatment under both active medication groups.

Owing to a cycle duration varying by ± 2 days, the number of days without pain was calculated as a proportion of the cycle duration in the evaluation of the pain journals. Here the number of pain-free days increased by 15% in the active medication groups and by 8% in the placebo groups.

The treatments had no significant influence on progesterone, FSH and LH. Owing to non-comparable estradiol-17β values at the admission examination, adjusted means were used for the evaluation. In comparison with placebo (10.8 pg/ml) the estradiol levels decreased somewhat more markedly under the active solution and the active tablets (28.5 pg/ml; 25.7 pg/ml). In comparison with placebo (n=38) there was on average a significant drop of the basal prolactin levels (Mann-Whitney U-test) between cycle 0 and 3 of 4.35 ng/ml (p=0.0039) under the active solution (n=31) and of 3.7 ng/ml (p=0.015) under the active tablets (n=32) see Fig. 2. For the prolactin release stimulated by metoclopramide a patient collective which displayed prolactin values > 160 ng/ml (upper third and above the reference range [10]) in the stimulation test at cycle 0 was analyzed as a sub-group (active solution: n=11; active tablets: n=12; placebo: n=13). In Fig. 3 each of these patients entered the difference of the stimulated prolactin values from cycle 3 - cycle 0 (vertical axis) as a function of the values in cycle 0 (horizontal axis). A regression line was calculated for each treatment group by means of conventional linear regression and entered in the graph [2]. The regression lines through the scattergrams of each treatment group describe the relationship between the initial value and the difference of the prolactin values. A horizontal line is an indication of the independence of both variables while a falling line signifies a reduction in the stimulated prolactin secretion.
Fig. 3  Reduction of the prolactin release stimulated with metoclopramide in cycle 3 as a function of the concentration of the prolactin levels in cycle 0: The horizontal axis shows the actual initial prolactin values for each patient with a stimulated prolactin value > 160 ng/ml in cycle 0 and the vertical axis the prolactin change (difference of the stimulated prolactin values from cycle 3 to cycle 0) for the same patient in the form of a symbol corresponding to the treatment group. With reference to the vertical axis a negative value represents a prolactin reduction. The regression lines are calculated so that they have a minimum distance to all symbols of each treatment group. The slope of the regression lines is a measure for the influence of the initial prolactin values on the reduction of the stimulated prolactin levels. While in the placebo group no dependence of the reduction of stimulated prolactin levels on the initial value can be detected (almost horizontal regression line), the regression lines of both active medication groups display a distinct downward slope. A reduction of the stimulated prolactin values is particularly distinct under the active medication treatments in patients whose initial values were > 200 ng/ml.

prolactin release. In cycle 3 the stimulated prolactin values displayed a trend on average to be lower under the active solution by 48.02 ng/ml (p=0.543), under the active tablets by 47.0 ng/ml (p=0.479) than under placebo (22.7 ng/ml). Although the differences did not prove significant (Mann-Whitney U-test), owing to the limited number of cases and the marked scattering, the lower prolactin release after stimulation with metoclopramide under both active medication forms was clearly recognizable on the basis of the falling lines, in particular the higher the initial values had been at cycle 0.
The group with the active solution yielded 18 reports of adverse drug reactions by 13 patients (6 nausea, 3 stomach complaints such as heartburn and painful pressure in the stomach, 5 itching exanthema, 2 pretibial edema, 1 fatigue and 1 increased perspiration). Under the active tablets 20 adverse drug reactions were reported by 9 women (3 nausea, 5 stomach pain, 2 exanthema, 1 early menstruation, 1 increased menstruation, 2 hot flashes, 1 punctual, severe breast pain, 1 pressure in the ears, 1 peripheral circulatory disturbances, 2 dizzy feeling, 1 deteriorated general condition). In the placebo group 8 women (13 reports) complained of adverse drug reactions (3 stomach complaints, 2 edema, 2 dizzy feeling, 2 pain in varicose veins, 1 headache, 1 blood pressure drop, 1 insomnia and 1 irritability). The degree of severity was mainly classed as mild to moderate. Five of the adverse drug reactions (active solution: 3 nausea; active tablets: 1 nausea, 1 punctual, severe breast pain) were classed as severe, whereby in 3 cases (active solution: n=1; active tablets: n=2) the treatment was discontinued.

Discussion
About 50% of women of childbearing age complain of cyclic breast pain and it is often found very discomforting. The majority of the women therefore require treatment. To what extent a treatment measure is successful in a symptom can be best proven by means of a double-blind comparison with a placebo whereby the medication must be assigned according to a randomization plan. The subjectively perceived extent of the breast pain can be converted into “measurable” units by means of the visual analog scale. This makes checks during the course of treatment possible if it is avoided that the patients can make comparisons with previous evaluations.

The purpose of this study was to examine with scientific methods the efficacy of a medicinal product (Mastodynon®) which has been time-tested for decades as well as a comparable tablet form. In addition to intensive endocrinological analysis, attention was paid to the frequency and the degree of severity of adverse drug reactions.

The present study, carried out in a patient collective that was representative for the indication has shown that both tested drug forms were effective in breast pain in comparison with placebo whereby the medicinal product in the form of a solution displayed a more rapid onset of effect already after one treatment cycle. The prolactin-inhibiting principle of action already displayed in experimental and initial clinical trials of the drug Agnus castus [7, 8, 12, 17, 19, 21] was proven for the first time in this double-blind study. A significant difference of the basal prolactin levels between admission and final examination in comparison with placebo was demonstrated for both active medication forms. Here the mean prolactin reduction was at a comparable level to that already shown in patients with breast pain under treatment with bromocriptine [11]. As a function of the height of the stimulated
prolactin values after metoclopramide in cycle 0 a distinct reduction of the stimulated prolactin release towards the end of the treatment was remarkable for both active medication forms. These findings cause one to suppose both an inhibition of prolactin release and a reduced production of this hormone. To what extent the mild estradiol reduction observed under both active medication forms is repeatable and clinically relevant still needs to be examined.

Mainly non-specific side effects of mild severity were described under the two medicinal products. In the frequency with which these non-specific complaints were mentioned there is no difference to the placebo groups. The gastrointestinal symptoms occurring under the active medication forms such as nausea and stomach complaints are also not seldom observed with synthetic prolactin reducing agents.

In general, however, the subjective tolerance was good, and therefore the treatment possibility proven effective in this study should first be exhausted before using hormone replacement treatment or synthetic prolactin reducing agents in breast pain. Since the more rapid onset of effect observed in our study of the liquid dosage form is confirmed, in future a consecutive administration of both dosage forms might be considered since this would surely be conductive to compliance.

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Literature


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