Treatment of climacteric symptoms with an ammonium succinate-based dietary supplement: a randomized, double-blind, placebo-controlled trial

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Abstract

Peri- and postmenopausal women commonly suffer from climacteric symptoms. We evaluated the effectiveness and safety of dietary supplement Amberen to relieve vasomotor and psychosomatic symptoms during the course of a 3-month, randomized, double-blind, placebo-controlled study. General clinical assessment, evaluation using the Greene climacteric test and Spielberger–Hanin test, determination of plasma levels of gonadotropins, estradiol, leptin and apolipoproteins were used to evaluate 42–60-year-old women with vasomotor and psychosomatic menopausal symptoms. One hundred and twenty-five women were enrolled in the study and randomized between two groups. Based on the Greene test results, there was a statistically significant improvement (p < 0.05) in 13 out of 21 menopausal symptoms in women who took Amberen. During the course and by the end of the study, patients showed statistically significant changes in the levels of estradiol, gonadotropins and leptin, and decreases in body weight and waist circumference. Spielberger–Hanin test showed that Amberen stabilizes patients’ psychological state with a statistically significant decrease in anxiety, increased stress resistance and improved adaptability. Comparative analysis of the vital signs measurements, blood tests and urinalysis did not show any negative effects of Amberen on the patients. Our findings indicate that Amberen can be considered a method of choice to relieve mild/moderate climacteric symptoms.

Keywords

Ammonium succinate, menopause, menopausal symptoms treatment, mitochondrial dysfunction, vasomotor and psychosomatic menopause symptoms

Introduction

Age-related dysfunction of neurohormonal regulation due to an increase in the hypothalamic threshold of sensitivity to input signals and a decline and eventual cessation of ovarian estrogen synthesis often lead to the development of so-called climacteric symptoms in peri- and postmenopausal women [1–3]. Some of these (vasomotor symptoms) can clearly be attributed to the reduced synthesis of sex steroids, while others (sleep disturbance, bodily symptoms, urinary tract symptoms, sexual problems and mood changes) may be of a multifactorial origin. Collectively, these symptoms describe the climacteric syndrome; however, this is not the only term for this set of symptoms. Moreover, the peri- and postmenopausal periods are marked by other age-related changes, including metabolic disturbance associated with obesity and the cardiometabolic risk [4,5].

Treatment of vasomotor and psychosomatic symptoms in peri- and postmenopause relies on replacement of the loss of estrogen secretion, neurotropic/vegetotropic and other effects, directed towards an improvement of psychological and physical health. A commonly used treatment is the peri- and postmenopausal hormone therapy (HT) with sex steroids, the most effective treatment available today [6–9]. However, because HT has some contraindications and certain risks, there has been a search for alternative treatments, particularly in recent years [6–8,10–12]. Preparations of botanical origin (phytoestrogens in the form of isoflavones from red clover or soya and Cimicifuga racemosa) are especially popular [12]. The selective serotonin reuptake inhibitors venlafaxine and fluoxetine have been found effective against vasomotor symptoms; also there is evidence for the effectiveness of an anticonvulsant gabapentin in this context [6,11].

Understanding the role of hypothalamic aging in the development of the climacteric symptoms lead some researchers to the idea of using methods that can restore the organ’s sensitivity to input signals. This “rejuvenating” restoration of hypothalamic sensitivity was demonstrated with small doses of amber acid [13].
As a result, dietary supplement Amberen was developed, the use of which showed high effectiveness in experiments with aged animals. Several clinical trials confirmed Amberen’s effectiveness in relieving menopausal symptoms in women [14].

The goal of this study was to evaluate the effectiveness and safety of Amberen in relieving vasomotor and psychosomatic symptoms in peri- and postmenopausal women.

Materials and methods
Randomized double-blind placebo-controlled study was conducted in accordance with the principles of the World Medical Association (Declaration of Helsinki): ‘‘Recommendations guiding physicians in biomedical research involving human subjects’’ and the National Standard of the Russian Federation ‘‘Proper clinical practice’’; the study was approved by the local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (Protocol No. 07–15, 2015).

The study recruited women between 42 and 60 years of age, with vasomotor and psychosomatic complaints, in the late phase of the menopausal transition and postmenopause according to the STRAW + 10 classification [15]. Patients were not included in the study if any of the following was discovered during screening: cancers (including in the medical history); conditions requiring hospitalization in the next 6 months; endocrine diseases with abnormal hormonal secretion; any surgeries within 1 year of the screening; HT within 6 months of the screening; psychiatric diseases; diabetes mellitus and taking other supplements that may affect the climacteric syndrome.

Based on the above inclusion and exclusion criteria, 125 patients were enrolled in the study. The randomization was done using random number generation, evenly distributed in the 0–999 interval; the initial number for randomization was created by a computer’s pulse generator.

For all patients, the following data was collected: demographic and health, general and gynecological medical history. Anthropometric measurements (height, body weight, waist circumference, body mass index (BMI) calculated using the Kettle index) and vital signs were taken; patients underwent general and gynecological exams. Additional evaluations included blood panels (general and biochemical), urinalysis, electrocardiogram (ECG), mammogram and transvaginal sonography of pelvic organs.

In order to evaluate patients’ initial status and the effects of Amberen on the vasomotor and psychosomatic symptoms of the climacteric syndrome, the Greene Climacteric Scale and Spielberger–Hanin anxiety test were employed. The Spielberger–Hanin test evaluates situational anxiety (SA), personal anxiety (PA) and actual anxiety (AA)—an integral anxiety indicator. At the beginning and throughout the course of the study, blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (RIA Kits, Immunotech A.S., Prague, Czech Republic) and leptin (RIA-1624, DRG Instruments GmbH, Marburg, Germany) were measured.

After initial evaluation and randomization, the patients received the following treatment: two capsules (one white, 200 mg and one orange, 200 mg), once a day, in the morning with a meal, for 90 days. The placebo capsules contained high purity corn starch and looked identical to the Amberen capsules. The patients were given a 30-day Amberen/placebo supply at each visit. Evaluation of changes in the above-mentioned parameters from the initial values was done monthly.

The data obtained during the study was analyzed using MSOffice 2010 and Statistica 12. Comparison of the median/mean values for each parameter in the groups was done using Mann–Whitney U-test (nonparametric statistics) or Student’s t-test (for normal distribution). The Friedman test was used in dynamic analysis. For calculations of the Greene Climacteric Scale scores between groups, χ² test was used. Differences were considered statistically significant when p < 0.05 (95% confidence level).

Results
All of the 125 randomized patients completed the study: 62 in the Amberen group and 63 in the Placebo group. The mean age of the study population was 52.4 ± 5.02 years in the Amberen group and 51.97 ± 4.25 years in the Placebo group, and did not differ significantly. Seven (5.6%) of the patients were perimenopausal and 118 (94.4%) were postmenopausal.

Clinical evaluations and the analysis of medical documentation revealed gynecological or other pathologies in 61 (98.39%) patients in the Amberen group and in 60 (95.24%) patients in the Placebo group, with all illnesses in remission. Anthropometric parameters, initial results of the blood panels (general and biochemical), urinalysis, levels of apolipoproteins A1 and B, estradiol and gonadotropins did not differ significantly between the two groups. Results of the initial Greene test [16,17] (Table 1) and Spielberger–Hanin test (Table 2) evaluations were mostly comparable between the Amberen and placebo groups. The exceptions were the difficulty sleeping, difficulty concentrating, loss of interest in most things, irritability, headaches and loss of interest in sex symptoms, which occurred more frequently in the Amberen group.

In the Amberen group, analysis of the Greene Climacteric Scale results showed a decrease in the number of complains with reduction in their severity for the following symptoms (Table 1): feeling tense or nervous, difficulty sleeping, increased excitability, difficulty concentrating, feeling tired or lacking energy, loss of interest in most things, sadness or depression, crying spells, irritability, feeling of pressure or tightness in the head or other body parts, headaches, muscle and joint pain, hot flashes, night sweats and loss of interest in sex. Comparative analysis between the Amberen and placebo groups at the end of the study showed statistically significant differences in the following symptoms: increased heartrate or palpitations, difficulty sleeping, increased excitability, difficulty concentrating, feeling tired or lacking energy, loss of interest in most things, sadness or depression, irritability, headaches, muscle and joint pain, hot flashes, night sweats and loss of interest in sex. After 2 months of treatment, the symptoms that were initially more frequent in the Amberen group were observed with statistical significance more frequently in the placebo group.

Based on the results of the Spielberger–Hanin test (Table 2), the Amberen group had worse anxiety scores than the placebo group. After 1 month of treatment, all anxiety parameters had a statistically significant decrease in the Amberen group. Compared to the placebo group, Amberen patients showed a statistically significant decrease in PA and AA after 1 month of treatment and in SA, PA and AA after 2 months of treatment.

Analysis of the blood plasma hormones showed initial difference in the estradiol levels between the two groups with a statistically significantly higher concentration of the hormone in the placebo group. During the course of the study, patients in the Amberen group showed a significant increase in the estradiol concentrations, and after 2 months of treatment the levels of estradiol were statistically significantly higher than those in the Placebo group (Table 3). In the Amberen group, the levels of FSH and LH decreased with statistical significance after 2 months of treatment, but no significant difference in their values compared to the placebo group was observed. In the Amberen group, concentrations of leptin were characterized by a significant reduction that was approaching normal levels; in the placebo group, we observed an increase in the levels of
Table 1. The Greene Climacteric Scale results.

| Group     | N  | Before treatment | After treatment | p² | p¹ |
|-----------|----|------------------|-----------------|----|----|
| 1. Heart palpitation |     |                  |                 |    |    |
| Amberen   | 62 | 38 (61.3%)       | 25 (40.3%)      | 0.0528 |    |
| Placebo   | 63 | 45 (71.4%)       | 43 (68.3%)      | 0.1193 | 0.0198 |
| 2. Feeling tense or nervous |     |                  |                 |    |    |
| Amberen   | 62 | 53 (85.5%)       | 47 (75.8%)      | 0.0070 |    |
| Placebo   | 63 | 49 (77.8%)       | 49 (77.8%)      | >0.05 |    |
| 3. Difficulty sleeping |     |                  |                 |    |    |
| Amberen   | 62 | 52 (83.9%)       | 26 (41.9%)      | 0.0000 |    |
| Placebo   | 63 | 44 (69.8%)       | 47 (74.6%)      | 0.0220 |    |
| 4. Increased excitability |     |                  |                 |    |    |
| Amberen   | 62 | 46 (74.2%)       | 24 (39.1%)      | 0.0013 | 0.0217 |
| Placebo   | 63 | 44 (69.8%)       | 46 (73.0%)      | 0.9068 | 0.0000 |
| 5. Panic attacks |     |                  |                 |    |    |
| Amberen   | 62 | 20 (32.3%)       | 11 (17.7%)      | 0.1489 |    |
| Placebo   | 63 | 14 (22.2%)       | 16 (25.4%)      | 0.8712 |    |
| 6. Difficulty concentrating |     |                  |                 |    |    |
| Amberen   | 62 | 50 (80.6%)       | 16 (25.8%)      | 0.0000 | 0.0478 |
| Placebo   | 63 | 37 (58.7%)       | 50 (79.4%)      | 0.0573 | 0.0000 |
| 7. Feeling tired or lacking energy |     |                  |                 |    |    |
| Amberen   | 62 | 60 (96.8%)       | 30 (48.4%)      | 0.0000 | 0.0000 |
| Placebo   | 63 | 59 (93.7%)       | 61 (96.8%)      | 0.0267 | 0.0000 |
| 8. Loss of interest in most things |     |                  |                 |    |    |
| Amberen   | 62 | 42 (67.7%)       | 16 (25.8%)      | 0.0000 | 0.0304 |
| Placebo   | 63 | 42 (64.3%)       | 42 (66.7%)      | 0.0295 | 0.0000 |
| 9. Sadness or depression |     |                  |                 |    |    |
| Amberen   | 62 | 51 (82.3%)       | 17 (27.4%)      | 0.0000 | 0.0000 |
| Placebo   | 63 | 42 (66.7%)       | 51 (81.0%)      | 0.0021 | 0.0000 |
| 10. Crying spells |     |                  |                 |    |    |
| Amberen   | 62 | 33 (53.2%)       | 24 (38.7%)      | 0.0343 | 0.0817 |
| Placebo   | 63 | 30 (47.6%)       | 32 (50.8%)      | 0.9335 | 0.0000 |
| 11. Irritability |     |                  |                 |    |    |
| Amberen   | 62 | 59 (95.2%)       | 25 (40.3%)      | 0.0000 | 0.0494 |
| Placebo   | 63 | 56 (88.9%)       | 56 (88.9%)      | >0.05 | 0.0000 |
| 12. Dizziness or fainting |     |                  |                 |    |    |
| Amberen   | 62 | 28 (45.2%)       | 21 (33.9%)      | 0.2613 |    |
| Placebo   | 63 | 20 (31.7%)       | 22 (34.9%)      | 0.8937 |    |
| 13. Feeling pressure or tightness in the head or other body parts |     |                  |                 |    |    |
| Amberen   | 62 | 38 (61.3%)       | 25 (40.3%)      | 0.0292 | 0.0496 |
| Placebo   | 63 | 31 (49.2%)       | 29 (46.0%)      | 0.8552 | 0.0000 |
| 14. Numbness or tingling in some body parts |     |                  |                 |    |    |
| Amberen   | 62 | 35 (56.5%)       | 28 (45.2%)      | 0.1855 | 0.0902 |
| Placebo   | 63 | 37 (58.7%)       | 37 (58.7%)      | >0.05 | 0.0000 |
| 15. Headaches |     |                  |                 |    |    |
| Amberen   | 62 | 52 (83.9%)       | 34 (54.8%)      | 0.0000 | 0.0000 |
| Placebo   | 63 | 51 (81.0%)       | 51 (81.0%)      | >0.05 | 0.0000 |
| 16. Muscle and joint pain |     |                  |                 |    |    |
| Amberen   | 62 | 53 (85.5%)       | 36 (58.1%)      | 0.0000 | 0.0000 |
| Placebo   | 63 | 59 (93.7%)       | 56 (88.9%)      | 0.7615 | 0.0000 |
| 17. Numbness of hands and feet |     |                  |                 |    |    |
| Amberen   | 62 | 30 (48.4%)       | 22 (35.5%)      | 0.3088 | 0.0965 |
| Placebo   | 63 | 27 (42.9%)       | 28 (44.4%)      | 0.4656 | 0.0000 |
| 18. Difficulty breathing |     |                  |                 |    |    |
| Amberen   | 62 | 26 (41.9%)       | 21 (33.9%)      | 0.4517 | 0.3106 |
| Placebo   | 63 | 20 (31.7%)       | 23 (36.5%)      | 0.9479 | 0.7469 |
| 19. Hot flashes |     |                  |                 |    |    |
| Amberen   | 62 | 53 (85.5%)       | 24 (38.7%)      | 0.0000 | 0.5025 |
| Placebo   | 63 | 48 (76.2%)       | 52 (82.5%)      | 0.0063 | 0.1514 |
| 20. Night sweats |     |                  |                 |    |    |
| Amberen   | 62 | 49 (79.0%)       | 22 (35.5%)      | 0.0000 | 0.3150 |
| Placebo   | 63 | 49 (77.8%)       | 50 (79.4%)      | 0.0573 | 0.0000 |
| 21. Loss of interest in sex |     |                  |                 |    |    |
| Amberen   | 62 | 51 (82.3%)       | 26 (41.9%)      | 0.0000 | 0.0000 |
| Placebo   | 63 | 40 (63.5%)       | 50 (79.4%)      | 0.0961 | 0.0000 |

Number of women with climacteric syndrome symptoms before and after treatment. p¹ represents p values, amberen and placebo groups before and after treatment comparison; p² represents p values, parameters before and after treatment within each group comparison (χ² test). Bold values indicates statistically significant p values.
Evaluation of the clinical and laboratory safety parameters did not reveal any differences between Amberen and placebo. No adverse reactions were observed.

Discussion

The results of this study demonstrated that a course of dietary supplement Amberen has a positive effect on the menopausal symptoms. Based on the Greene test analysis, patients saw improvements in difficulty sleeping, increased excitability, difficulty concentrating, feeling tired or lacking energy, loss of interest in most things, sadness or depression, crying spells, irritability, headaches, muscle and joint pain, hot flashes, night sweats and loss of interest in sex.

The mechanism of Amberen’s action is not entirely clear. When speculating on the mechanism, one should recall that the main cause of the vasomotor complaints is the decrease in the levels of estrogens [18], likely leading to the dysfunctions of the brain’s neuronal systems, which experience a type of deprivation due to the changes in the usual hormonal homeostasis [19].

Amberen affects blood hormones and leads to a statistically significant increase in estradiol levels, which can in part explain the positive effect of the supplement on the menopausal symptoms. Estradiol’s effect on various tissues is directly related to its blood levels. Higher concentrations of estradiol are necessary to initiate endometrial growth, compared to those needed for the treatment of vasomotor symptoms [20,21]. Estradiol levels <80 pg/ml allow for therapeutic effects and remain safe in terms of excess proliferation. Thus, the average estradiol levels of 66 pg/ml achieved in our study can be considered physiologically comfortable and safe.

The aging of the central nervous system (CNS) and the decline in hypothalamic sensitivity to peripheral hormone signals play a significant role in the formation of the menopausal symptoms [22]. At the same time, steroid sex hormones affect the psychological functions of the nervous system: behavior, mood, learning, memory and verbal abilities [23].

Amberen treatment allowed for the stabilization of the patients’ psychological status, as evidenced by the results of the Greene Climacteric Scale and Spielberger–Hanin test. The frequency of depressive dysfunctions significantly decreased in women who took Amberen, compared to both the initial evaluation and the results in the Placebo group. A statistically significant decrease in anxiety (SA, PA, AA components) speaks to an increase in the women’s stress resistance, improvement in their adaptability, and general normalization of the psychological state.

These positive changes can be explained by other factors, beyond the “estrogen influence” hypothesis. A loss of adaptive abilities in any tissue is closely related to mitochondrial dysfunction, which lies in the base of both the CNS functional disruptions and formation of neurodegenerative diseases, including in postmenopausal women [24,25]. Moreover, cells with damaged mitochondria, react to estrogen signals in a different manner [26], producing negative clinical effects instead of the expected positive ones. Increased estradiol levels in combination with the improved mitochondrial function produced during Amberen supplementation allows for a high degree of safety and predictability in the treatment.

Stabilization of body weight and prophylactics against obesity take a special place in management of menopausal women. The problem of weight gain in women during peri- and postmenopausal periods is well known [27], but the cellular component of the cardiometabolic risk is often underestimated. Dyslipidemia, hyperglycemia and inflammation (all of which are tied to obesity) initiate secondary mitochondrial dysfunction [28,29], that has an

Table 2. Spielberger–Hanin test results.

|        | Anxiety | Time          | Amberen (n = 62) | Placebo (n = 63) | p* |
|--------|---------|---------------|------------------|------------------|----|
| SA     | Initial | 0.52 ± 9.72   | −4.16 ± 10.08    | 0.0094           |
|        | 30 days | −3.69 ± 10.51 | −2.52 ± 8.34     | 0.2850           |
|        | 60 days | −8.02 ± 7.82  | −0.86 ± 9.63     | 0.0000           |
|        | 90 days | −10.02 ± 7.78 | −0.14 ± 10.05    | 0.0000           |
| p²     | <0.05   | <0.05         |                  |                  |
| PA     | Initial | 15.94 ± 10.32 | 10.48 ± 8.86     | 0.0019           |
|        | 30 days | 9.92 ± 9.37   | 12.76 ± 9.05     | 0.0348           |
|        | 60 days | 6.13 ± 8.05   | 15.25 ± 8.76     | 0.0000           |
|        | 90 days | 3.40 ± 7.12   | 16.68 ± 8.92     | 0.0000           |
| p²     | <0.05   | <0.05         |                  |                  |
| AA     | Initial | 51.50 ± 18.86 | 41.30 ± 17.88    | 0.0023           |
|        | 30 days | 41.13 ± 18.42 | 45.32 ± 15.48    | 0.0479           |
|        | 60 days | 33.11 ± 14.72 | 49.44 ± 17.58    | 0.0000           |
|        | 90 days | 28.39 ± 13.99 | 51.81 ± 18.22    | 0.0000           |
| p²     | <0.05   | <0.05         |                  |                  |

Table 3. Blood plasma hormone levels.

| Hormones    | Time          | Amberen (n = 62) | Placebo (n = 63) | p* |
|-------------|---------------|------------------|------------------|----|
| Estradiol, pg/ml | Initial | 34.25 ± 13.65   | 43.27 ± 28.52    | 0.0009 |
|             | 30 days      | 49.32 ± 38.19   | 42.27 ± 27.77    | 0.0520 |
|             | 60 days      | 59.26 ± 38.19   | 41.33 ± 26.72    | 0.0000 |
|             | 90 days      | 66.12 ± 118.35  | 40.67 ± 25.10    | 0.0000 |
|             | p²           | <0.05           | <0.05            |      |
| FSH, mU/ml  | Initial      | 55.69 ± 29.38   | 49.36 ± 19.91    | 0.1222 |
|             | 30 days      | 53.28 ± 27.38   | 49.31 ± 18.85    | 0.2719 |
|             | 60 days      | 50.24 ± 25.07   | 48.37 ± 18.13    | 0.9018 |
|             | 90 days      | 46.88 ± 22.44   | 46.38 ± 18.82    | 0.9370 |
|             | p²           | <0.05           | >0.05            |      |
| LH, mU/ml   | Initial      | 33.40 ± 13.19   | 29.33 ± 11.97    | 0.1047 |
|             | 30 days      | 32.17 ± 14.48   | 30.11 ± 10.50    | 0.1706 |
|             | 60 days      | 31.32 ± 11.80   | 29.32 ± 10.21    | 0.5568 |
|             | 90 days      | 29.94 ± 10.52   | 29.83 ± 10.39    | 0.9449 |
|             | p²           | <0.05           | >0.05            |      |
| Leptin, ng/ml | Initial     | 29.82 ± 26.96   | 25.34 ± 25.27    | >0.1*  |
|             | 90 days      | 18.16 ± 16.63   | 26.45 ± 25.39    | <0.005*|
|             | p²           | 0.0000*         | 0.0025*          |      |

Indicated values are mean for normal and median for non-normal distribution, ±SD. p* represents p values, amberen and placebo groups before and after treatment comparison (Mann–Whitney test, *Kolmogorov–Smirnov test); p² represents p values, difference in parameters during the course of the study within each group (Friedman test). Bold values indicate statistically significant p values.
immediate effect on tissues’ functions. Amberen supplementation led to a statistically significant decrease in weight, BMI, and waist circumference. The reduction of fat tissue is indirectly shown by a statistically significant decrease in leptin levels [30,31]; this allows one to speculate about positive effects of the treatment in terms of the metabolic risk.

Therefore, dietary supplement Amberen has multiple positive effects and can be used to treat menopausal symptoms in women during menopausal transition and postmenopause.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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