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FILE: ■ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)

■ Menopause

■ Bone Turnover

■ Vaginal Mucosa

HC 060261-308

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RE: The Effects of a Proprietary Black Cohosh Extract on Bone Turnover, Vaginal Mucosa, and Blood Parameters in Postmenopausal Women

Wuttke W, Gorkow C, Seidlová-Wuttke D. Effects of black cohosh (*Cimicifuga racemosa*) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind placebo-controlled, and conjugated estrogens-controlled study. *Menopause*. 2006;13(2):185-196.

This randomized, double-blind, placebo-controlled (with both a positive [estrogen] and a negative [placebo]) clinical trial was conducted at 13 centers in the Czech Republic between 1998 and 2000 to further elucidate the potential benefits of a special black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) rhizome extract for postmenopausal women. A previously published article reported on this same trial's primary endpoints, i.e., menopausal symptoms (See HC 060436.243).²

This follow-up article reports on the secondary objectives: a comparison of "the effects of CR BNO 1055 extract (Klimadynon®/Menofem®; Bionorica AG, Neumarkt, Germany) on markers of bone turnover, hormones, sex hormone binding globulin (SHBG), lipids, parameters of vaginal cytology, and routine laboratory parameters with those of conjugated estrogen and placebo."

A total of 97 postmenopausal women aged 40-60 years old were randomized to 1 of 3 treatment groups. The study medication was a dried aqueous/ethanolic (58% vv) extract BNO 1055 of black cohosh rhizome. The hard gelatin capsules contained magnesium stearate and lactose as excipients. "Each capsule (batch no. 805005) declared 1.66 to 2.86 mg of native [black cohosh] extract, corresponding to 20 mg of herbal drug [i.e., dried rhizome]." The dose was 2 capsules per day. Note: This preparation is not the same as the Klimadynon product sold in United States. While both products have the same raw material and are manufactured with the same patented process, the declarations for the Drug-to-Extract-Ration (DER) are not identical (Klimadynon Germany 5-10:1, Klimadynon US 4.5-8.5:1)

due to regulatory and technical reasons. Also, in Germany for herbal medicinal products, the native extract has to be declared, not the extract preparation (containing excipients). Thus, for Klimadynon Germany the native part of the extract is per tablet 2.8 mg. The amount of extract preparation in this case is 20 mg per tablet (twice daily). For Klimadynon US (once daily), the declaration refers to the extract preparation. This means 32.5 mg extract (preparation) corresponding to 6.5 mg native extract per tablet.

The estrogen group received two 0.3 mg capsules daily of conjugated estrogen (CE) (Heinrich Mack Nachf., Illertissen, Germany). This preparation consisted of 75-85% estrone, 6-15% equilin, up to 4% equilenin, estradiol-17 α , 17 α -dihydro-equilin, 17 α -dihydro-equilenin 2-8%). The third group received 2 matching placebo capsules per day; placebo contents are not stated.

Study Background

Since the publication of research on the serious risks associated with conventional hormone replacement therapy (HRT), patients and doctors are seeking natural therapies to ameliorate menopausal symptoms and protect bone health. Extracts of the black cohosh rhizome are promising herbal alternatives. Numerous clinical trials have been conducted with black cohosh extracts to test their ability to reduce menopause symptoms. However, the authors state that many of these have had design flaws or have not been placebo controlled.

Preclinical research conducted during the past decade has increased the body of knowledge regarding black cohosh's effects and mechanisms of action. However, many concerns remain unsettled. For example, in in vitro binding studies with recombinant estrogen receptors, the black cohosh extract BNO 1055 did not bind to estrogen receptor alpha (ER α) or estrogen receptor beta (ER β). Nor did the extract have uterotrophic (stimulating the increase in uterus weight) effects in rodents. As a result, researchers concluded that black cohosh extracts did not contain estrogenic compounds. However, in subsequent research with cytosolic (the fluid portion of the cytoplasm exclusive of organelles and membranes) preparations of porcine uteri and human endometrium, the black cohosh extract displaced radiolabeled 17 β -estradiol (E₂). This data suggests "that yet-unknown substances of the [BNO 1055 black cohosh extract] are able to bind to a yet-unknown estrogen-binding protein," or possibly that there is non-specific binding.

With regard to bone metabolism, the specific extract BNO 1055 has been shown to have effects similar to that of estradiol.¹ Ovariectomized rats were given either black cohosh extract or E₂ for a period of 12 weeks. In both groups "the ovariectomy-induced increased activity of osteoblasts [bone-forming cells] and osteoclasts [any of the large multinucleate cells closely associated with areas of bone resorption (as in a fracture that is healing)] was reduced to a normal equilibrium present in intact animals." (Bone tissue is constantly in a state of being torn down and built up. When one is young and growing, bone deposition dominates; during most of the adult life, the two forces are balanced and overall there is no net deposition or destruction of bone. In later midlife, as in menopause or in old age, one is generally losing bone tissue, i.e., breakdown dominates. Removing a woman's ovaries or having their function fail naturally, as in menopause, favors breakdown. Research suggests that the use of black cohosh returns these two opposing forces towards balance and a neutral

status – neither gaining nor losing bone.) In the same study, black cohosh was shown to be less effective at preventing bone loss than E₂, but its effect was significant in comparison with the untreated control group. Black cohosh extract also demonstrated a very mild vaginotropic effect on epithelial proliferation similar to that of E₂ in ovariectomized rats. Epithelial proliferation supports bacterial production of lactic acid, which protects the uterus and urinary tract from ascending vaginal infections. While E₂ is known to increase the possibility of thromboembolic events, there is no data available on the effects of black cohosh on blood-clotting parameters. Thus, BNO 1055 appears to have organ-specific beneficial activity, although the mechanisms of action remain unclear.

Trial Analysis

In the present clinical trial, fasting blood samples were collected in the morning before any food intake at baseline and after weeks 4, 8, and 12 for the measurement of E₂, FSH (follicle-stimulating hormone), SHBG, markers of bone turnover (CrossLaps [the C-terminal breakdown product of bone-specific collagen-1 α 1] and bone-specific alkaline phosphatase [bALP; a metabolic marker for bone formation]), serum cholesterol (total, HDL and LDL cholesterol), triglycerides, parameters of blood coagulation (activated thromboplastin time in seconds and thromboplastin time as INR — International Normalized Ratio), and hepatic enzymes (SGOT, SGPT, γ -GT). Samples of vaginal epithelial cells were taken with a brush at baseline and after 12 weeks as a measure of an estrogen effect using the "maturity index" (determined cytologically). The vaginal cells were smeared on a microscope slide, immediately fixed and stained. The maturity index was determined by calculating the percentage of parabasal, intermediary, and superficial cells per 500 cells.

Two of the 97 women dropped out prematurely and 33 women were excluded from the ITT (intent-to-treat) analyses due to their not meeting the inclusion criteria, e.g., being postmenopausal (had a menses or laboratory values did not confirm their postmenopausal status ($n=16$); 5 did not have enough hot flashes per day or had a body mass indices greater than 30. Thus, 62 women who met the inclusion criteria and successfully completed the trial were included in the per-protocol analysis (BNO 1055: $n=20$; conjugated estrogens: $n=22$; placebo: $n=20$).

Hormone Levels: Results showed that the conjugated estrogens significantly increased E₂ (estradiol) levels and suppressed FSH levels at weeks 4, 8, and 12. BNO 1055 had no significant effect on these hormones. No significant effect on LH (luteinizing hormone) levels was observed. Treatment with conjugated estrogens also resulted in a statistically significant increase in SHBG levels, while a slight decrease in SHBG levels was observed with both placebo and black cohosh extract.

Bone Turnover: Both black cohosh extract and conjugated estrogens had beneficial effects on serum markers of bone turnover. CrossLaps increased slightly, but not significantly with placebo, did not change with black cohosh extract, and decreased significantly at weeks 4 and 12 with CE treatment ($P<0.05$). CE treatment resulted in a significant increase in bALP after 4 weeks. However, this effect was not maintained at 8 and 12 weeks. Black cohosh extract treatment resulted in a significant increase in bALP after 12 weeks ($P<0.05$ versus placebo).

Vaginal Cytology: Treatment with CE significantly increased the number of superficial cells compared with placebo ($P < 0.0001$), while BNO 1055 treatment resulted in a slight increase in the number of superficial cells. This increase approached statistical significance ($P = 0.0542$). However, the effect of estrogen on vaginal epithelial cell maturation was much stronger than the effect of black cohosh ($P = 0.0099$); thus, the estrogenic effects seen in this trial are tenuous at best.

Lipid Metabolism: Neither black cohosh extract nor CE had a significant effect on cholesterol metabolism, while serum triglyceride levels were significantly higher versus placebo in both the CE group and the black cohosh extract group ($P < 0.05$). However, the absolute amount of change recorded in these subjects was not likely to be clinically significant.

Hematologic and Clinical Chemistry Parameters: None of the 3 treatments had significant systemic effects on the investigated parameters of blood coagulation. There was no effect on hepatic enzymes, with the exception of a tendency toward decreased levels with BNO 1055.

Adverse Events: There were no significant changes in body weight after 12 weeks of treatment. Blood pressure and heart rate also remained unchanged. One woman in the placebo group reported vertigo as an adverse event, and one woman in the black cohosh extract group reported vertigo, headache, and hypertension. "In both cases changes in blood pressure and heart rate were not observed." [Writer's Note: It is not clear how someone reporting hypertension could have no change in blood pressure. Reply from Bionorica (6/26/06) via email to Lori Glenn: The blood pressure of this patient was normal in all except one visit, where an increase of about 20 mmHg of the value was measured. This singular slight blood pressure increase was interpreted by the investigator as "mild hypertension". The statement "[i]n both cases changes in blood pressure and heart rate were not observed" is based on the fact of blood pressure normalization at the next visit. Slight blood pressure fluctuations are normal.]

This study reaffirms "that CR BNO 1055 does not contain immunoreactive estrogen-like material." Nevertheless, the effects of this extract on markers of bone metabolism indicate bone anabolic effects, i.e., the bone sparing effects, have been demonstrated. The increase in bALP concentrations in the black cohosh extract group points toward an increase of osteoblast activity that began within the first 4 weeks of treatment. According to the authors, this is "the first demonstration of a plant-derived principle with primarily bone-forming properties." BNO 1055 treatment also resulted in slightly decreased osteoclastic activity, which could have a favorable impact on bone mineral density (BMD). Studies with larger numbers of subjects and longer treatment periods will be necessary to ascertain the effect of BNO 1055 extract on BMD.

BNO 1055 also stimulated the vaginal mucosa to produce more superficial cells to a degree that approached statistical significance. "This effect correlated with a significant decrease in the feeling of a dry vagina, which was published previously." It bears emphasis that there was a much weaker effect for the black cohosh extract than the result reported for estrogen, and vaginal dryness is generally a subjective measure in a cytological study of this type. This study examined several parameters that might indicate whether there is a possibility of hepatotoxicity due to a prior report of acute liver failure associated with a black cohosh preparation. None of the treatments in this trial increased liver enzymes. If anything, a slight

decrease in hepatic enzymes was noted with black cohosh extract treatment which argues against a toxic effect on the liver.

The only potential negative effect of black cohosh extract in this trial was the increase in serum triglycerides, which was analogous to that of CEs. The authors suggest that this increase may "most likely represent increased hepatic very-low-density lipoproteins, which may increase atherosclerotic risk."

The specific active compounds in black cohosh have not been identified, so it is not known whether the effects of BNO 1055 observed in this trial would be obtained from other black cohosh preparations. Thin layer chromatography analyses suggest that the chemical composition of aqueous/ethanolic extracts (like BNO 1055) differs from isopropanolic extracts of black cohosh rhizome (e.g. Remifemin®, Schaper & Brümmer, Salzgitter, Germany). The authors suggest practitioners must bear this in mind when choosing black cohosh preparations for clinical use.

— Cathleen Rapp, N.D.

Reference

¹Seidlova-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of *Cimicifuga racemosa* extract BNO 1055 in rats: bone, fat and uterus. *Maturitas*. 2003;44(1):S39-S50.

²Wuttke W, Seidlova-Wuttke D, Gorkow C. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas*. 2003;44(1): S67-S77.

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