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Tibolone (Livial®) enhances warfarin-induced anticoagulation in postmenopausal women

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Abstract

Objective: To investigate the potential drug interaction between tibolone and warfarin in healthy postmenopausal women.
Methods and results: The study was designed as a double-blind, randomized, placebo-controlled, two-way crossover study in postmenopausal women. After stabilization of the International Normalized Ratio (INR; a standardized prothrombin time, PT) between 1.4 and 2.0 with warfarin, subjects were randomized to receive either tibolone (2.5 mg/day) or placebo for 21 days. After a 7-day wash-out period (during which warfarin treatment was continued) the treatments were crossed over. Primary efficacy parameters were INR and coagulation Factors II, VII, VIIa and X (means of measurements at Days 18 and 20 and Days 46 and 48). Treatment with tibolone induced a statistically significant increase in INR (estimate of mean difference = 0.40; $P = 0.002$), and a statistically significant decrease in coagulation factors. Treatments were generally well tolerated and no clinically significant adverse events were observed.
Conclusions: Tibolone enhances warfarin-induced anticoagulation in postmenopausal women, as reflected by increases in INR and decreases in coagulation Factors II, VII, VIIa and X, compared to placebo. It is advisable to monitor for changes in coagulation status during (and after discontinuation of) simultaneous use of tibolone and warfarin.

Keywords: Tibolone; Warfarin; Interaction; International Normalized Ratio (INR); Coagulation factors

The decrease in endogenous estrogen production occurring around the menopause is associated with climacteric symptoms, such as hot flushes and sweating episodes and a decrease in bone density. Estrogen-based hormone therapy is the most frequently used treatment for both climacteric symptoms and the prevention of postmenopausal bone loss. An alternative to this estrogen-based hormone therapy is tibolone (Livial®, N.V. Organon, Oss, The Netherlands). Tibolone belongs to the class of Selective Tissue Estrogenic Activity Regulators (STEAR) and, as such, has desired estrogenic effects on bone, vagina,

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climacteric symptoms, mood and well-being in postmenopausal women, while avoiding the undesired estrogenic effects on the endometrium and breast [1,2]. After oral administration, tibolone is rapidly converted by the intestine and the liver into two estrogenic metabolites (3α- and 3β-hydroxy-tibolone), which are responsible for its estrogenic effects on bone, vagina and climacteric complaints. A third metabolite, the Δ4-isomer, has progestagenic and androgenic activities and is formed in small amounts in the liver and intestine as well as locally in the endometrium, thereby preventing endometrial stimulation [3].

Since the introduction of Livial®, N.V. Organon has received a number of reports from a.o. the United Kingdom (through the Yellow Card Scheme) on a potential interaction between tibolone and warfarin, where an increased anticoagulation was observed shortly after Livial® was added to a pre-existing warfarin maintenance therapy. The onset of the potentiation of anticoagulation varied from 1 day up to approximately 2 months after co-administration. The details of some of these cases have been discussed in a manuscript by McLintock et al. [4].

From clinical studies it is known that the effects of tibolone on blood clotting differ from those of estrogen-based hormone therapy. Tibolone does not adversely affect blood clotting and has an activating effect on fibrinolysis [5–9].

To further investigate the possible interaction between warfarin and tibolone the formal interaction study presented here was performed, in which the effects of tibolone on blood coagulation (INR, Factors II, VII, VIIa and X) and safety in healthy postmenopausal women, stabilized on warfarin, were investigated. The indicated clotting parameters were chosen because warfarin inhibits the synthesis of coagulation Factors II, VII, and X by interfering with the Vitamin K cycle, leading to a prolongation of the prothrombin time (PT). For reasons of standardization, prothrombin time is currently expressed as the International Normalized Ratio (INR), which is calculated as the prothrombin time ratio (prothrombin time for the patient divided by the mean prothrombin time of normal subjects), corrected for the responsiveness of the thromboplastin reagent [10,11]. The design in healthy volunteers was chosen as controlled studies in patients on warfarin therapy are often difficult to perform.

1. Materials and methods

The study was designed as a double-blind, randomized, placebo-controlled, multiple dose, two-way crossover study to assess a potential interactive effect of tibolone on established warfarin-induced anticoagulation in healthy postmenopausal women.

Ethics approval of the study protocol was obtained from the Medical Ethics Committee of the 'Stichting Beoordeling Ethiek Bio-Medisch Onderzoek' in Assen, The Netherlands. The trial was conducted in compliance with the current revision of the Declaration of Helsinki and current ICH guidelines on Good Clinical Practice. The trial was conducted at a clinical research organization (Pharma Bio-Research in Zuidlaren, The Netherlands), and women were recruited from their pool of healthy volunteers for clinical trials. Women were eligible for inclusion if they were mentally and physically healthy, between 50 and 65 years of age, had a body mass index between 20 and 29 kg/m^2 and were at least 12 months after the last natural menstrual bleeding or hysterectomized with serum levels of FSH >40 IU/L and E_2 <20 pg/mL. Subjects were excluded if they had any contraindications to tibolone, warfarin or the combination of both compounds, or if they suffered from conditions that might affect the outcome of the study.

Concomitant administration of Vitamin K and/or Vitamin K supplements, or any medication known to interact pharmacokinetically with tibolone and/or warfarin and/or Vitamin K metabolism was prohibited. Oral (within the last 2 months) or transdermal hormone therapy (within the last month), hormone injections (within the last 6 months) or hormone implants at any time previously, as well as the use of investigational drugs within the last 90 days, were also not allowed. Use of other medications was to be avoided as much as possible. Consumption of alcohol was limited to 1 unit per day. Vitamin K rich foods (e.g. broccoli, cauliflower, liver) were to be avoided. Smoking was not allowed during the study period.

The study started with a 14-day run-in period, during which 20 subjects received individualized doses of warfarin (1 mg tablets, Marevan®, Goldsheat Healthcare, Surrey, United Kingdom) until their INR was stabilized between 1.4 and 2.0 (i.e. remained within this range for 3 consecutive days, with a variation in INR of less than 0.3). If necessary this run-in period was extended to 21