Effects of Flibanserin on the Pharmacokinetics of a Combined Ethinylestradiol/Levonorgestrel Oral Contraceptive in Healthy Premenopausal Women: A Randomized Crossover Study

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ABSTRACT

Purpose: This study aimed to investigate the effect of steady-state exposure to flibanserin, a 5-HT1A agonist/5-HT2A antagonist approved for the treatment of hypoactive sexual desire disorder in premenopausal women, on the single-dose pharmacokinetics of the contraceptive steroids ethinylestradiol and levonorgestrel in healthy premenopausal women.

Methods: Healthy female volunteers (N = 24) received 2 single doses of a combined oral contraceptive containing ethinylestradiol 30 μg and levonorgestrel 150 μg, either alone (reference) or preceded by treatment with flibanserin 100 mg once daily for 14 days (test). The 2 treatments were given in randomized order, with a 4-week washout period following the last administration of the first treatment. Plasma concentrations of ethinylestradiol and levonorgestrel were measured over 48 hours after dosing for the determination of pharmacokinetic parameters; the primary end points were Cmax and AUC0–∞ of ethinylestradiol and levonorgestrel.

Findings: Of the 24 women enrolled (mean age, 38.0 years), 23 completed the study. Mean (SD) Cmax and AUC0–∞ values of ethinylestradiol were 66.7 (16.3) pg/mL and 52.2 (18.7) ng · h/mL, respectively, with the oral contraceptive alone, and 50.1 (16.3) ng · h/mL and 53.3 (20.4) ng · h/mL, respectively, following flibanserin; again, in both cases, the 90% CIs of the reference/test ratios were within the range of 80% to 125%, indicating that flibanserin had no significant effect on the pharmacokinetic properties of levonorgestrel. All adverse events were mild to moderate in intensity (incidence: 12.5% and 70.8% with ethinylestradiol/levonorgestrel treatment alone and following administration of flibanserin, respectively).

Implications: Pretreatment with flibanserin 100 mg once daily for 2 weeks did not produce a clinically relevant change in oral contraceptive drug exposure following single-dose administration of ethinylestradiol/levonorgestrel. This finding is relevant to women with hypoactive sexual desire disorder who might prefer oral contraceptives to other forms of birth control. EudraCT No: 2006-006960-46. (Clin Ther. 2017;: ) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: ethinylestradiol, flibanserin, hypoactive sexual desire disorder, levonorgestrel, oral contraceptives, pharmacokinetics.
INTRODUCTION

Hypoactive sexual desire disorder (HSDD) is defined as chronic or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulties and cannot be accounted for by medications or concurrent medical conditions.1,2 Although the reported prevalence may vary according to the instrument used to assess sexual dysfunction,3 HSDD is acknowledged to be the most common condition affecting sexual desire in premenopausal1,2 and postmenopausal women.4,5 The pathophysiology of HSDD is not fully understood, but it is believed to involve an imbalance between excitatory dopaminergic and noradrenergic pathways and inhibitory serotonergic pathways in the hypothalamus and limbic system.1,4,5 These systems may therefore present therapeutic targets for the management of HSDD.1

Flibanserin is a serotonergic agent that acts as an agonist at 5-HT1A receptors and an antagonist at 5-HT2A receptors.1,2,6 It has been shown to have region-specific effects on monoamine levels in the human brain,7 and on the basis of such findings it has been proposed that flibanserin may enhance sexual desire by reducing serotonergic activity and enhancing dopaminergic and noradrenergic activity within the prefrontal cortex.2 In clinical trials, flibanserin has been shown to produce significant improvements, compared with placebo, in various measures of sexual desire and function in both premenopausal8–10 and postmenopausal11 women, and these improvements were sustained during long-term treatment.12,13 On the basis of these findings, flibanserin received US Food and Drug Administration approval in August 2015 for the treatment of HSDD in premenopausal women, making it the first product to be approved for this indication.14

Flibanserin is rapidly absorbed after oral administration and undergoes extensive first-pass metabolism by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2C19. Approximately 50% of its metabolites are excreted in the bile, and ~41% in the urine; excretion of the parent drug is negligible. In addition to being a substrate for CYP, flibanserin has been shown to be a weak phenobarbital-type inducer of CYP in rats, although there is currently no indication that it shows such activity in humans. Such findings suggest there may be a potential for drug–drug interactions between flibanserin and other drugs that are metabolized by CYPs. For example, contraceptive steroids such as ethinylestradiol and levonorgestrel are extensively metabolized by CYP enzymes, uridine diphosphate-glucuronosyl transferases (UGTs), or sulfotransferases.15–21 Ethinylestradiol is biotransformed by a combination of CYP and UGT enzymes.20–23 Among the involved CYPs, CYP3A and CYP2C9 appear to be the most important.20 However, coadministration of ethinylestradiol-containing contraceptives with ritonavir, the strongest of known CYP3A inhibitors,24 does not impair ethinylestradiol clearance in humans,25 indicating that CYP3A does not play a major role in ethinylestradiol metabolism in vivo. Rather, conjugation via UGT—mainly UGT1A1—and sulfotransferase enzymes accounts for most of the metabolic clearance in humans.21 In the case of levonorgestrel, there is essentially no published data on enzymes involved in metabolism. The product labels of oral contraceptives containing levonorgestrel suggest that sulfate conjugation, hydroxylation, and glucuronide conjugation play a role in clearance. In any case, concurrently administered medications with the potential to induce one or more of these enzyme systems may reduce circulating concentrations of these steroids, thereby potentially compromising contraceptive efficacy.15,17,26 This might be particularly relevant since some women using oral contraceptives may also be prescribed flibanserin, although it should be noted that the use of oral contraceptives may itself impair sexual desire in a significant proportion of women.27–32

The present study was undertaken to evaluate the effects of repeated dosing with flibanserin on the single-dose pharmacokinetics of ethinylestradiol and levonorgestrel. Although available clinical trial data does not provide an indication of a pharmacokinetic interaction, the probability of concurrent flibanserin and oral contraceptive use is sufficiently high to warrant a controlled pharmacokinetic study.

SUBJECTS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice, and the protocol was approved by the Ethikkommission der Landesarztekammer Baden-Württemberg (Stuttgart, Germany). Written informed consent was obtained from
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