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Effect of eslicarbazepine acetate on the pharmacokinetics of a combined ethinylestradiol/levonorgestrel oral contraceptive in healthy women

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Summary
Objective: To investigate the effect of once-daily (QD) eslicarbazepine acetate (ESL) 800 mg and 1200 mg administration on pharmacokinetics of a combined ethinylestradiol/levonorgestrel oral contraceptive (OC) in women of childbearing potential.
Methods: Two two-way, crossover, two-period, randomized, open-label studies were performed in 20 healthy female subjects, each. In one period (ESL + OC period), subjects received ESL 800 mg QD in one study and ESL 1200 mg QD in the other study, for 15 days; concomitantly with the Day 14 ESL dose, an oral single dose of 30 μg ethinylestradiol and 150 μg levonorgestrel was administered. In the other period (OC alone), a single dose of 30 μg ethinylestradiol and 150 μg levonorgestrel was administered. Three weeks or more separated the periods. An analysis of variance (ANOVA) was used to test for differences between pharmacokinetic parameters of 30 μg ethinylestradiol and 150 μg levonorgestrel following ESL + OC and OC alone, and 90% confidence intervals (90%CI) for the ESL + OC/OC alone geometric mean ratio (GMR) were calculated.
Results: ESL significantly decreased the systemic exposure to both ethinylestradiol and levonorgestrel. GMR (90%CI) for AUC_{0-24} of ethinylestradiol were 68% (64%; 71%) following 1200 mg ESL and 75% (71%; 79%) following 800 mg ESL. GMR (90%CI) for AUC_{0-24} of levonorgestrel were 76% (68%; 86%) following 1200 mg ESL and 89% (82%; 97%) following 800 mg ESL.

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Conclusions: A clinically relevant dose-dependent effect of ESL administration on the pharmacokinetics of ethinylestradiol and levonorgestrel was observed. Therefore, to avoid inadvertent pregnancy, women of childbearing potential should use other adequate methods of contraception during treatment with ESL, and, in case ESL treatment is discontinued, until CYP3A4 activity returns to normal.

Introduction

Eslicarbazepine acetate (ESL) is a once-daily (QD) anticonvulsant approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalization. ESL is structurally distinct from carbamazepine (CBZ) and oxcarbazepine (OXC) although the three compounds are dibenz[b,f]azepine derivatives (Benes et al., 1999). This molecular distinction results in differences in metabolism (Hainzl et al., 2001). CBZ and ESL do not share any common metabolites and, in contrast to CBZ, ESL is not susceptible to metabolic auto-induction (Almeida et al., 2009; Bialer and Soares-da-Silva, 2012).

Following oral administration, ESL undergoes extensive first pass hydrolysis to its major active metabolite eslicarbazepine (also known as (S)-licarbazepine) (Falcao et al., 2007; Almeida et al., 2008a,b; Maia et al., 2008; Perucca et al., 2011), which represents approximately 95% of circulating active moieties and is believed to be responsible for its antiseizure effects (Pekcec et al., 2011; Pires et al., 2011; Sierra-Paredes et al., 2011; Soerensen et al., 2011; Torrao et al., 2011) most likely through blockade of voltage-gated sodium channels and type T calcium channels (Brady et al., 2011; Hebeisen et al., 2011). Plasma levels of ESL usually remain below the limit of quantification. Minor active metabolites are (R)-licarbazepine and oxcarbazepine. Steady-state eslicarbazepine plasma concentrations are reached within 4—5 days of once-daily dosing (Almeida and Soares-da-Silva, 2004; Almeida et al., 2005). Inactive metabolites in plasma are the glucuronic acid conjugates of ESL, eslicarbazepine, (R)-licarbazepine and oxcarbazepine, all found in minor amounts (Almeida et al., 2008b; Maia et al., 2008). More than 90% of an oral ESL dose is recovered in urine as ESL metabolites (Almeida et al., 2008b; Maia et al., 2008).

Antiepileptic drugs (AEDs) are widely used as long-term adjunctive therapy or as monotherapy in epilepsy or other indications and consist of a group of drugs that are highly susceptible to drug—drug interactions (Johannessen and Landmark, 2010). AEDs have been widely implicated as causing contraceptive failure in women taking oral contraceptives (OCs) (Luef, 2009). Some AEDs, such as CBZ, phenobarbital, phenytoin and others, induce the hepatic P450 enzyme system, thereby accelerating metabolism of steroids OCs and rendering these OCs less effective (Thorneycroft et al., 2006). In human liver microsomes, eslicarbazepine appeared to have minimal or no inhibitory effect on the activity of CYP isoforms — CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP2E1, CYP3A4, and CYP4A9/11 — as well as on the enzymes UGT1A1 and UGT1A6 and the epoxide hydrolase. A moderate inhibitory effect was found on the CYP2C9 and CYP2C19 activity. Studies with eslicarbazepine in fresh human hepatocytes showed no induction of CYP1A2, CYP3A4, and phase II hepatic enzymes involved in glucuronidation and sulphation (Bialer and Soares-da-Silva, 2012). The interaction between AEDs and hormonal contraception is particularly important for women with epilepsy; their pregnancies must be planned to optimize seizure control and minimize teratogenic risk (Davis et al., 2011). Drug interactions with steroid OCs became more important in recent years with the gradual reduction in the dose of ethinylestradiol (EE) from 80 to 100 μg/day to the present usual dose of 30—35 μg/day (Crawford et al., 1990).

The present two human pharmacology studies were performed to evaluate the effect of ESL administration on the kinetics of EE and levonorgestrel (LN), whose plasma levels considerably decrease by enzyme-inducing AEDs (Crawford et al., 1990).

Methods

Study design

Two two-way, crossover, two-period, randomized, open-label studies were performed by the BIAL's Human Pharmacology Unit (UFH, S. Mamede do Coronado, Portugal) to investigate the effect of ESL on the pharmacokinetics of a combined oral contraceptive containing 30 μg EE and 150 μg LN. Each study enrolled 20 healthy female subjects. Studies used a similar design (Fig. 1), only differing in the ESL dose: 800 mg (trial registration EudraCT No. 2007-006529-28) and 1200 mg (trial registration EudraCT No. 2004-004490-28).

Following informed consent and a screening period where the healthy condition was demonstrated and the eligibility criteria were confirmed, subjects were admitted at the UFH facilities for two periods. In one period (ESL + OC period), subjects received an oral QD dose of 800 mg ESL (one 800 mg tablet) in one study and 1200 mg ESL (two 600 mg tablets) in the other study, for 15 days (Day 1—Day 15). ESL tablets were manufactured by BIAL — Portela & Co. S.A. (S. Mamede do Coronado, Portugal). Concomitantly with the Day 14 ESL dose, an oral single dose of 30 μg EE and 150 μg LN was administered (one tablet of Microginon®, marketed by Bayer Portugal S.A., Carnaxide, Portugal in the first study and by Schering Lusitana, Lda, Portugal in the second study). In the other treatment period (OC alone period), an oral single dose of 30 μg EE and 150 μg LN was administered alone. The washout between the two treatment periods was 3 weeks or more. Administration of investigational products was only performed by authorized members of the UFH's clinical research staff. Investigational product administration was followed by hand and mouth checks.

On the evening of Day 13 of the ESL + OC period and on the evening of Day 0 of the OC period, subjects were admitted and stayed resident in the UFH until at least the 48 h post-OC