Effect of mavoglurant (AFQ056) on the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy women

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Introduction

Mavoglurant (AFQ056) is a structurally novel, selective metabotropic glutamate receptor 5 agonist under clinical development. It is expected to normalize excessive glutamatergic signaling that is believed to be associated with a variety of neurological and psychiatric diseases1.

Mavoglurant is metabolized by multiple cytochrome P450 (CYP) enzymes including CYP3A4, CYP2C9 and CYP2C19 and is not a strong inhibitor of inducer of drug metabolizing enzymes or transporters.

Given the early stage of clinical development, treatment with mavoglurant currently requires the use of contraception measures in women of childbearing potential.

Contraception may additionally be required as a consequence of other medicines used in the study, e.g. anti-depressants, neuroleptics and antiepileptics, some of which exhibit teratogenic potential2.

This study investigated the effect of concomitant administration of mavoglurant on the single-dose pharmacokinetics (PKs) of a commonly used low-dose combination oral contraceptive (OC) containing ethinyl estradiol (EE) and levonorgestrel (LNG).

Methods

Study design

This was a single-blind, open-label, two-period, fixed-sequence, drug–drug interaction study3.

Figure 1. Plasma concentration-time profile of levonorgestrel when oral contraceptive was administered alone or with mavoglurant

Study population

A total of 30 healthy, non-smoking women aged 18–40 years with body mass index (BMI) of 18.6–30 kg/m² and body weight of 50–80% were enrolled.

Participants were required to use double-barrier methods of contraception until study completion and not to use any OC for at least 28 days prior to first dosing.

Key exclusion criteria were the use of concomitant medications within 4 weeks before enrolment.

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Statistical analysis

Cmax and AUClast of EE and LNG were analysed separately on the logarithmic scale using a mixed effect model adjusted for treatment as fixed effect and for participants as a random effect. The probability of finding a PK interaction is provided if finding a PK interaction.

Safety and tolerability

There were no serious or severe AEs reported and there were no clinically significant abnormalities of haematological, clinical chemistry, urinalysis, ECG or vital sign data.

The most commonly reported AEs belonged to the system organ class of psychiatric and nervous system disorders. However, no association with adverse events and mavoglurant was observed.

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Conclusions

In summary, EE PK was unchanged, whereas Cmax and AUClast of LNG were 19% and 24%, respectively.

It has been hypothesized that the finding could be due to a modulation of protein binding given that LNG is known to exhibit stronger binding than EE to certain proteins such as sex-hormone binding globulin (SHBG)4. However, we could not identify any relevant impact of mavoglurant on the degree of LNG binding to SHBG (Novartis, data on file).

References


Disclosures

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