

Changes in endogenous estradiol concentrations explain fluctuations in levonorgestrel (LNG) concentrations during continuous treatment with LNG releasing intravaginal rings



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INTRODUCTION

During treatment with low-dose levonorgestrel (LNG) for contraception in clinical phase I studies, **fluctuations over time were observed in LNG plasma concentrations** (see Figure 4) which cannot be described with help of the product's release profile and PK model. These fluctuations were even more distinct for the PD parameter serum **sex hormone binding globulin (SHBG)** which interacts with LNG.

Endogenous estradiol (E2) concentrations are known to be **positively correlated with SHBG concentrations** in premenopausal women [1]. However, **fluctuations in LNG concentrations during treatment with low-dose LNG containing contraceptives as a result of these interactions have not been well described.**

The goal of this analysis was to describe the PK of LNG in a phase I study investigating **LNG releasing intravaginal rings (IVRs)** and in particular to **explain the fluctuations in the LNG concentrations.**

METHODS

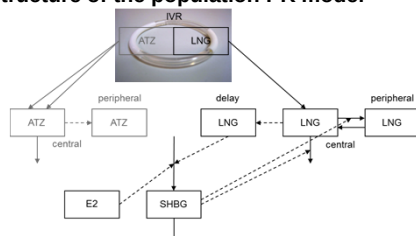
The pharmacokinetics (PK) of LNG was assessed in an **open-label phase I study** where the use of **LNG (and anastrozole (ATZ)) releasing IVRs** in the dose range of **20 to 40 µg/d** was investigated **over 56 days**, with a **ring change after 28 days**, in **66 healthy young women** by developing a population PK model using NONMEM (version 7.2.0). The median age was 29.5 years (range 22 to 36 years) and the median body weight was 63.3 kg (range 48.5 to 90.1 kg).

In order to describe the fluctuations, the assumption that **E2 has an effect on SHBG** was considered by including **E2 measurements as covariate in the NONMEM data file**. A "carry forward" rule was applied, i.e. if no E2 measurement was available on the date of the record, then the most recent E2 measurement was taken.

RESULTS

The **PK of LNG** was described by a **two-compartment model** including the **interaction of LNG and SHBG**, assuming binding of LNG to SHBG and delayed inhibition of SHBG synthesis by LNG, where a **turnover model for SHBG** was used (see Figure 1, black part).

Figure 1 Schematic representation of the structure of the population PK model



Data visualization showed that SHBG concentrations followed the observed increase and decrease in E2 concentrations shortly thereafter indicating that **E2 has a stimulating, delayed effect on SHBG concentrations, with higher E2 concentrations resulting in a stronger effect** (see Figure 2). This relationship was observed for most women in the study, although not equally apparent in each case. In case of no fluctuations in the E2 concentrations, also no fluctuations in the SHBG concentrations were observed (e.g. see Figure 2, top right).

Figure 2 Examples for E2 (dashed) and SHBG (solid) concentration-time plots (observed)

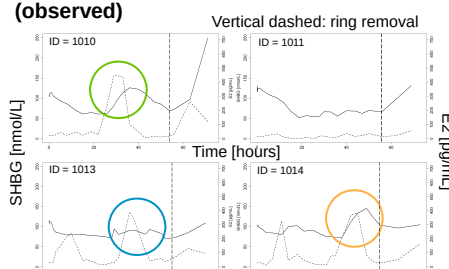
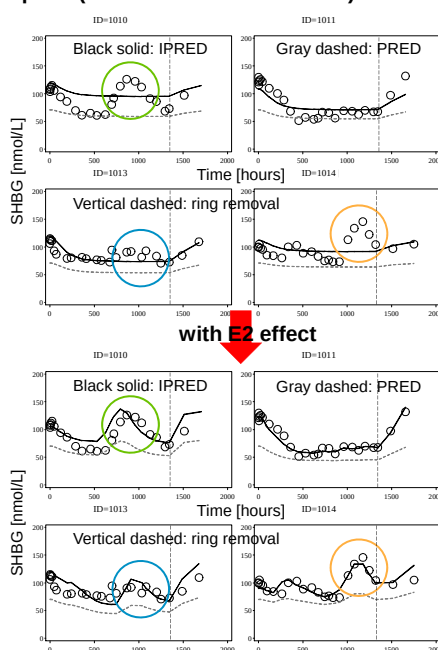


Figure 3 (top) shows SHBG concentrations where only the interaction with LNG, including the inhibitory effect of LNG on SHBG, was considered (simplified model). The average concentrations are well described, but due to the fluctuations the concentrations are partly under- or overestimated.

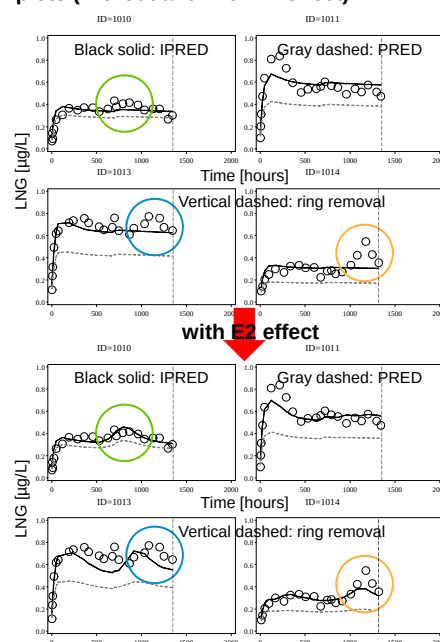
Including the E2 effect on the SHBG synthesis in the model led to a better description of SHBG concentrations (see Figure 3, bottom). The delay in the effect was considered minor and thus neglected.

Figure 3 Examples for observed and model-predicted SHBG concentration-time plots (without and with E2 effect)



Due to the interaction of LNG and SHBG, **also the PK of LNG was better described** (see Figure 4).

Figure 4 Examples for observed and model-predicted LNG concentration-time plots (without and with E2 effect)



CONCLUSION

The **PK of LNG** was well described by a population PK model where the interaction of LNG and SHBG was considered and **additionally a stimulating effect of E2 on the synthesis of SHBG** was assumed. Comparison of individual prediction and observations showed that **the effect of changes in endogenous E2 concentrations explains a considerable part of the fluctuations in the SHBG and, indirectly, LNG concentrations.**

Combined oral contraceptives such as Miranova® and Microgynon® which contain a higher dose of LNG (in addition to the estrogen ethinylestradiol), usually lead to suppression of follicular development, and thus estradiol production. This might be the reason why fluctuations as described here with lower LNG doses are not observed in those cases.

Including the E2 effect allows for the best possible description of the data. Depending on the available information (e.g. sparse sampling, no E2 data), a simplified model without E2 effect could be used e.g. for estimation of PK parameters where the influence of the LNG fluctuations is small.

REFERENCES

[1] Dowsett M, Attree S, Virdee S, Jeffcoate S. Oestrogen-related changes in sex hormone binding globulin levels during normal and gonadotrophin-stimulated menstrual cycles. Clinical Endocrinology (1985), 23, 303-312.