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Commentary

Perspectives on variability in pharmacokinetics of an oral contraceptive product☆

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Abstract

The early literature and reviews have described the pharmacokinetics (PK) of oral contraceptive (OC) compounds such as ethinyl estradiol (EE) and levonorgestrel (LNG) in women as subject to large intersubject variability. This was partly due to the use of diverse radioimmunoassays, limited sampling periods and an incomplete understanding of single- vs. multiple-dose kinetics and the role of EE in causing both inhibition of hepatic metabolism along with induction of sex hormone binding globulin. Over the past two decades, LNG and EE have been used as target drugs for the assessment of possible drug interactions upon introduction of many new therapeutic agents. This has resulted in at least 17 publications that describe the PK of LNG and EE in women using various 150 mcg/30 mcg products under fairly standard multiple-dose conditions. A review of these studies indicates only moderate variability in the C_{max} and area under the curve both within and across these studies. There is impressive similarity in these drug exposure indices found in studies carried out with several products by investigators at numerous sites and countries.

Keywords: Pharmacokinetics; Oral contraceptives; Ethinyl estradiol; Levonorgestrel

1. Background

The following type of statement has appeared in various forms in describing studies of the pharmacokinetics (PK) of oral contraceptive (OC) drugs, "…what is readily apparent from the pharmacokinetic studies of EE and progestins is the large intersubject variability, with several-fold differences between subjects" [1–4]. While this type of description was based on early studies largely before 2000 and citing studies and reviews by Fotherby et al. as well as Goldzeiher and Stanczyk [4], it has been promulgated in at least two more recent publications describing the PK of 750 mcg levonorgestrel (LNG) tablets [5,6].

Fotherby and others have provided key insights into the PK of ethinyl estradiol (EE) and LNG utilizing the methods, studies and data available at the time. Changes in sex hormone binding globulin (SHBG) and enzyme inhibition caused by EE indeed produce differences in serum concentrations of total LNG between single- and multiple-dose studies [2,7–9]. Additional factors creating complexities may include the radioimmunoassay (RIA) being used, products, dosages, duration of blood sampling and types of subjects. Variability in exposures to OC components is of concern as higher concentrations may be associated with a greater incidence of side effects, while low concentrations may result in lack of efficacy [4].

Over the past two decades, EE and LNG have been used as target drugs for the assessment of possible drug interactions upon introduction of many new therapeutic

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agents. This has resulted in at least 17 publications that describe the PK of LNG and EE in women using various 150 mcg/30 mcg products under fairly standard multiple-dose conditions. The purpose of this communication is to assess this literature to reconsider whether there persists, "large variability among the different studies" for these OC products containing EE and LNG.

2. Literature assessment

Concerns for the possible interactions between OC and various therapeutic agents [9] have resulted in the publication of numerous study results reporting plasma or serum exposures of EE and LNG during multiple-dosing. These studies have usually followed a standard protocol where healthy women are recruited and a one-cycle regimen of OC tablets is first instituted. Subsequently, the women receive two additional cycles of the OC with the PK of the OC components assessed around day 21 in cross-over studies with and without co-administration of the potential interacting drugs. The steady-state metrics that are reported are the maximum observed plasma concentration (C_{max}), the area under the curve (AUC) during the 0 to 24-h dosing interval, the time of occurrence of C_{max} (t_{max}), either the 0- or 24-h plasma concentration (C_{min}), and sometimes the half-life ($t_{1/2}$). The publications utilize the Food and Drug Administration (FDA) bioequivalence criteria [10] to compare the C_{max} and AUC values of the OC drugs to determine if there is a statistically meaningful change in these parameters.

A search of the literature revealed 17 publications, all but 2 since 2001, where oral products containing 30 mcg of EE and 150 mcg of LNG were evaluated during the second or third cycle of OC dosing. Typical plasma concentration vs. time profiles for EE and LNG for the last (day 21) dosing interval are shown in Fig. 1 (digitized from Ref. [11]).

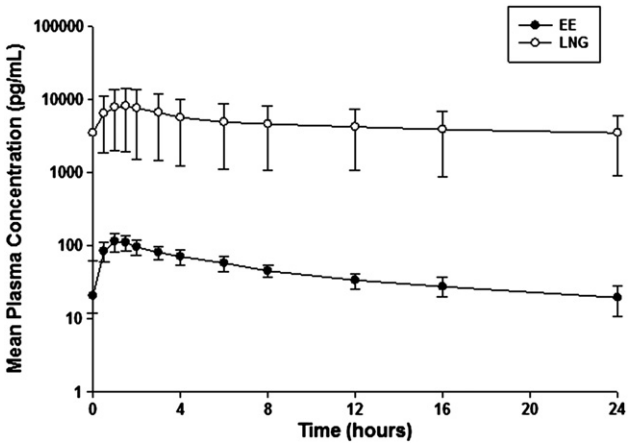

Fig. 1. Time course of mean (±SD) plasma concentrations of LNG and EE after multiple dosing of 30 mcg EE and 150 mcg LNG tablets in healthy women. The data were digitized from Ref. [11].

The 0- and 24-h C_{min} concentrations are very similar for each drug indicating steady-state conditions. The error bars at each time point depict moderate standard deviations (SDs) in these values for the group of women. The study metrics and references [7,11–26] are listed in Table 1 for LNG and Table 2 for EE. The mean values as originally reported and the calculated coefficients of variation (CV%=100×SD/Mean) are provided. Not all studies provided $t_{1/2}$ and C_{min} values, so the latter were often estimated (designated E) from the published graphs.

The studies listed in Tables 1 and 2 involved five or six different OC products, 16 different groups of investigators, several developed countries and three types of analytical methods. For LNG, the mean C_{max} across studies was 7276 pg/mL with a range of 5900 to 9900 pg/mL. The CV% for the various studies was low to moderate, 22% to 36%. The AUC for LNG averaged 85,559 pg·h/mL for 16 of the studies with a range of 59,900 to 112,900 pg·h/mL. The CV% for the AUC of the various studies was also low to moderate, 24% to 46%. The C_{min} values for all of the studies were similar with the CV% of 28 to 46% where reported.

For EE, the findings in regard to variability are similar with a mean C_{max} of 99.6 pg/mL, mean AUC of 917 pg·h/mL, mean C_{min} of 18.6 pg/mL and CV% values in the low to moderate range of 17% to 59%. The mean C_{max} and AUC for EE were fourfold to sixfold higher than the others for one study [26]; these anomalous study results were not used in the comparison for either EE or LNG, although the PK metrics for the latter are quite similar to others in the table. It can be noted that RIA methods were used in this study rather than the more reliable and less variable gas chromatography/mass spectrometry (GC/MS) or liquid chromatrography/MS (LC/MS) physicochemical methods [27]. However, two other studies using RIA methods yielded data similar to the MS methods.

The free or unbound concentrations of LNG and EE were provided for only one study [7]. All others reported measurements of total LNG and EE that, of course, include drug bound to albumin and SHBG. Statistical comparison of the $t_{1/2}$ is not required in assessing bioequivalence by the FDA [10], and thus, only a few of the published studies reported this parameter. As seen in Fig. 1, the 24-h steady-state time frame may not permit sufficient accuracy for assessing $t_{1/2}$ values that exceed 12 h. One study [28] extended blood sampling out to 48 h after one cycle of daily dosing of 20 mcg EE and 100 mcg LNG and found the $t_{1/2}$ of EE of about 16 h and that of LNG averaging 25.6±9.3 h, similar to the values in the tables. Our multiple-dose studies with 50 mcg EE and 250 mcg LNG tablets produced similar $t_{1/2}$ values as well [8]. However, the terminal half-life reflects only part of the time course of drug exposure or AUC. A better metric that accounts for the absorption process and poly-exponential kinetics of drugs with patterns such as observed in Fig. 1 for EE and LNG is the "Operational Multiple-Dose Half-Life." This parameter can be calculated from $t_{1/2op}=\ln 2\cdot\tau/\ln(C_{max}/C_{min})$, where τ is the 24-h dosing interval [29,30]. This value is about 10 h for EE and 16 h for LNG using the general mean values listed in the tables.