Published in final edited form as:

Contraception. 2017 January ; 95(1): 5–9. doi:10.1016/j.contraception.2016.07.019.

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

[☆]Conflicts of interest: The author has recently served as a consultant or scientific expert for CSL Behring, Hoffman LaRoche, Asklepiion Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Cerebral Therapeutics, Retrophin Inc., and UCB Biopharma.

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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 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]). 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 ($CV\% = 100 \times SD / \text{Mean}$) 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 chromatography/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.

3. What is large variability?

The issue of variability requires both statistical and PK considerations. It is commonplace to see variability expressed as the SD or CV% along with an arithmetic or geometric mean as found in the citations listed in the tables. The means in the tables are typically geometric means as expected for making FDA bioequivalence comparisons [10]. Occasionally, the 95% confidence limits are provided; these closely reflect the $\text{mean} \pm 2$ SD. The advantage of the CV% over the SD is that it facilitates comparison of numerical values regardless of magnitude, for example, in comparing variability of $C_{\max}$ vs. AUC values. The range of values is often provided in PK, but this metric emphasizes the extreme values and possible outliers and neglects the central tendency that predominates for the observations. Provision of the CV% is the most common method of expressing variability in PK and was thus used in the tables.

There appears to be no consensus in PK as to what constitutes low, moderate or large intersubject variability. Owing to problems encountered in assessing bioequivalence, *intrasubject* variability is considered high when the CV% is greater than 30% for a reasonable number of study subjects [31]. Intersubject variability is expected to be greater (as has been shown for EE [3]), but qualitative and/or quantitative descriptions of such appear to be rather subjective.

Some examples of variability metrics can be found in the literature using search terms of “intersubject variability” and “pharmacokinetics.” Levy [32] described pharmacodynamic variability as “quite large” where parameters had CV% of 47 to 85. Beloeil et al. [33] listed norepinephrine clearances with a CV% of 83 as “major variability.” Rajeswara Rao and Someswara Rao [34] considered progesterone AUC values with 93 CV% as “highly variable.” Conway et al. [35] called 59 CV% for itraconazole AUC as “high variability.” Shah et al. [36] reported 92 CV% for tizanidine AUC as “large variability.” Sparreboom and Baker [37] reviewed the PK of 30 anticancer drugs. Clearances of most of the intravenous drugs exhibited a CV% of less than 40%, but the authors described several drugs with a CV % greater than 60% as showing “marked variation.” On the other hand, Gidal et al. [38] described gabapentin bioavailability values of 15% to 32 CV% as “relatively low.” These studies, except for Refs. [33,35], were typically carried out in homogenous groups of healthy volunteers. The author’s experience is that PK parameters will typically exhibit about 20% to 30 CV% in such subjects.

The consideration of low, moderate or high variability is both subjective and context-related. A diverse group of subjects or patients of both sexes, with a wide range of ages, co-administered drugs, varying smoking status, diverse body habitus and possibly underlying diseases will be expected to exhibit far greater variability in PK parameters than a homogenous group of young women. Thus, for typical PK studies in healthy subjects, less than 30% might be termed low; 30% to 60%, moderate; and greater than 60%, high variability. The presence of truly high variability is often a signal to seek possible genetic factors and use population PK methods to resolve covariates that might account for the PKs of such drugs. In the case of dosing EE and LNG, the determinants of time-dependent changes in metabolism and SHBG induction have become well appreciated and the execution of well-controlled clinical studies as described in the tables has clarified exactly how variable the PK of these drugs actually is.

4. Are OC PK highly variable?

Earlier assessments of EE and LNG PK, while perhaps correct at the time for the diverse array of studies of various products, doses, dosing times, sampling periods, types of subjects, and assays used up until then, may no longer be held as relevant for the products and conditions found today. Indeed, there is great consistency in the exposure metrics for both EE and LNG based on the products and studies listed in Tables 1 and 2. It is, in fact, reassuring that young healthy women will exhibit such similar plasma concentrations after multiple dosing of various products containing 30 mcg EE and 150 mcg LNG. Furthermore, the studies with single 750 mcg LNG tablets by Tremblay et al. [5] and Kook et al. [6] also showed moderate CV% values of 52% and 41% for AUC. For LNG in particular, complete

and consistent absorption from regular tablets is to be expected as this drug falls in the Biopharmaceutics Classification System Class I of drugs with high permeability and high solubility [39]. While the PK of EE is expected to have added variability owing to its first-pass metabolism [3,4,9], the metrics for its variability are similar to those for LNG. It is beyond the scope of this review to assess the variability for the wide array of other OC drugs and formulations. However, it can be noted that while norethindone PK was once described as highly variable [4], a multiple-dose study of an OC with 35 mcg EE and 1 mg norethindrone exhibited CV% values of only 34% for AUC, 26% for $C_{\max}$, and 51% for $C_{\min}$ along with similar metrics for EE [40]. Part of the reason that the studies listed in Tables 1 and 2 show much less variability compared to those described in earlier publications is that they are all multiple-dose assessments. The presence of some drug from previous doses creates an averaging effect for the steady-state dosing and the use of only a 0- to 24-h AUC obviates the need for extrapolation as needed for single-dose calculations of the total AUC. Lastly, for all of the studies described in this report, the expressed variability would likely be even less if the parameters were normalized for the dose per body weight basis.

Acknowledgments

This work was supported by National Institutes of Health Grant No. GM24211. The author appreciates the assistance of Mrs. Suzette Mis.

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Fig. 1.

Time course of mean ($\pm$ 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].

Table 1
Comparison of steady-state PK of LNG from various studies with 150 mcg LNG and 30 mcg EE given to healthy women

Product	No. of subjects	C _{max} (pg/mL)	C _{min} (pg/mL)	AUC (pg-h/mL)	t _{1/2} (h)	Assay method	Reference
Microgynon	9	6400 (22)	1600 (44)	59,900 (29)	26.0 (27)	RIA	[7]
Nordette	22	8300 (22)	3400 (28)	107,000 (24)	NA	NA	[11]
Microgynon 30	20	6599 (NA)	2137 (NA)	72,975 (NA)	33.6 (NA)	LC/MS	[12]
Portia	13	7000 (26)	2500 (40)	85,800 (24)	37.6 (50)	RIA	[13]
Microgynon 21	18	7960 (NA)	2130 (NA)	86,040 (NA)	24.9 (26)	GC/MS	[14]
Neovletta	22	6770 (31)	2020 (42)	79,400 (38)	NA	GC/MS	[15]
Microgynon 30	16	7858 (30)	3100 (E)	98,653 (34)	NA	LC/MS	[16]
Minidril	24	6500 (27)	1900 (E)	70,600 (35)	NA	GC/MS	[17]
Microgynon 30	14	7050 (22)	2000 (E)	72,000 (28)	NA	GC/MS	[18]
Microgynon	18	8200 (27)	3000 (E)	99,600 (39)	38.6 (34)	LC/MS	[19]
Microgynon 30	27	6652 (NA)	2300 (E)	75,970 (NA)	NA	LC/MS	[20]
Microgynon 30	25	6750 (32)	3200 (E)	98,000 (35)	NA	GC/MS	[21]
Microgynon or Ovranette	23	5900 (24)	1940 (46)	71,500 (35)	NA	GC/MS	[22]
Microgynon	23	6980 (25)	2400 (E)	85,400 (31)	NA	GC/MS	[23]
Microgynon 30	18	7600 (36)	3000 (E)	93,200 (41)	NA	LC/MS	[24]
Microgynon 21	23	9900 (34)	NA	112,900 (46)	NA	GC/MS	[25]
Microgynon ^a	16	10,400 (NA)	2660 (NA)	114,000 (NA)	NA	RIA	[26]
Mean		7276	2442	85,559	32.1		
SD		985	560	14,925	6.4		
CV, %		13.5	22.9	17.4	19.9		
N		16	15	16	5		

Values are mean (CV%).

NA, not available; E, estimated from graph;

^aNot included in mean calculations.

Table 2
Comparison of steady-state PK of EE from various studies with 150 mcg LNG and 30 mcg EE given to healthy women

Product	No. of subjects	C _{max} (pg/mL)	C _{min} (pg/mL)	AUC (pg-h/mL)	t _{1/2} (hr)	Assay method	Reference
Microgynon	9	114.0 (40)	11.0 (100)	778 (41)	NA	RIA	[7]
Nordette	22	112.0 (28)	18.0 (39)	1012 (24)	NA	NA	[11]
Microgynon 30	20	102.2 (NA)	14.6 (NA)	761 (NA)	19.5 (NA)	LC/MS	[12]
Portia	13	129.5 (27)	34.2 (31)	1414 (26)	28.0 (48)	RIA	[13]
Microgynon 21	18	116.8 (NA)	16.6 (NA)	985 (NA)	NA	GC/MS	[14]
Neovletta	22	99.7 (29)	14.0 (59)	864 (33)	NA	GC/MS	[15]
Microgynon 30	16	89.5 (39)	18.0 (E)	849 (31)	NA	LC/MS	[16]
Minidril	24	110.0 (28)	18.0 (E)	986 (27)	NA	GC/MS	[17]
Microgynon 30	14	84.8 (24)	12.0 (E)	746 (30)	NA	GC/MS	[18]
Microgynon	18	99.0 (17)	19.0 (E)	932 (24)	15.9 (32)	LC/MS	[19]
Microgynon 30	27	86.2 (NA)	16.0 (E)	828 (NA)	NA	LC/MS	[20]
Microgynon 30	25	69.9 (28)	22.0 (E)	844 (25)	NA	GC/MS	[21]
Microgynon or Ovranette	23	102.5 (29)	22.2 (47)	1077 (31)	NA	GC/MS	[22]
Microgynon	23	110.0 (27)	25.0 (E)	1111 (27)	NA	GC/MS	[23]
Microgynon 30	18	85.1 (33)	18.0 (E)	839 (30)	NA	LC/MS	[24]
Microgynon 21	23	82.2 (34)	NA	649 (46)	NA	GC/MS	[25]
Microgynon ^a	16	673.0 (NA)	76.7 (NA)	4310 (NA)	NA	RIA	[26]
Mean		99.6	18.6	917	21.1		
SD		15.7	5.7	183	6.2		
CV, %		15.7	30.9	19.9	29.4		
N		16	15	16	3		

Values are mean (CV%).

Definitions of abbreviations are the same as in Table 1.

^aNot included in mean calculations.