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Bidirectional interaction between oral contraception and lamotrigine in women with epilepsy – Role of progestins

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ABSTRACT

Purpose: To investigate the effects of various progestins in combined oral contraceptives (COCs) on lamotrigine (LTG) serum concentrations and, *vice versa,* the potential impact of LTG on progestin serum levels during the menstrual cycle.

Methods: Twenty women with epilepsy (WWE) undergoing LTG monotherapy and COC (LTG group; mean ± SD [median; range] age 24.2 ± 4.6 [23.0; 18–37] years) as well as fourteen controls on COC (24.9 ± 5.6 [22.5; 20–39] years) were assessed for eligibility and all agreed to participate in the study and remained for data analyses.

Results: LTG levels differed significantly between phases of inactive pill and active pill use ($p = 0.004$), particularly with drospirenon ($p = 0.018$) and levonorgestrel ($p = 0.068$) as progestogen component but not with gestoden ($p = 0.593$). Furthermore, the LTG group showed significantly lower progestin levels during inactive pill when compared to active pill use with respect to levonorgestrel ($p = 0.042$) and drospirenon ($p = 0.018$) but not to gestoden ($p = 0.109$). Progestin concentrations did not differ between patients and controls ($p > 0.05$).

Conclusions: The findings suggest that drospirenon and levonorgestrel but not gestoden seem to reduce LTG serum concentrations when being co-administered in WWE which might be of importance concerning seizure risk. Vice versa, no effect of LTG on several progestins could be demonstrated, arguing against a potential loss of contraception safety with LTG.

1. Introduction

In women with epilepsy (WWE), the use of oral contraceptives (OCs) in parallel with antiepileptic drugs (AEDs) might influence efficacy of both possibly leading to increased seizure frequency and/or unwanted pregnancies [1]. On the one hand, there is a mounting wall of literature that links the so-called enzyme-inducing AEDs (e.g. carbamazepine (CBZ), oxcarbazepine, phenytoin) to possibly enhanced risk of contraceptive failure [1]. On the other hand, potential teratogenic effects of AEDs have to be considered in WWE when therapy is chosen since the use of particular anticonvulsants might lead to an increased frequency of major or minor malformations during early pregnancy [2–4]. As a consequence, recent studies from the UK show an increasing prevalence of lamotrigine (LTG) prescribing (from 0.08 to 0.8 per 1000 females) whereas the prevalence of valproic acid and CBZ prescribing decreased from 0.94 to 0.63 and from 1.00 to 0.54, respectively, due to potential adverse effects concerning child development [5–7]. LTG, a non-enzyme-inducing AED metabolized primarily via hepatic glucuronidation by UGT 1A4 [8], is generally agreed to be reduced by combined oral contraceptives (COCs) in plasma hypothetically via the estrogen component [9–12]. As a matter of fact, however, COCs have an estrogen *and* a progestogen component with progestogen compounds classified as first-, second-, third- and fourth-generation. Norethisterone, norethindrone, ethynodiol diacetate, and lynestrenol are categorized as first-generation, levonorgestrel and norgestrel are the second-generation and desogestrel, gestodene as well as norgestimate

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are third-generation progestogens whereas drospirenon is a fourth-generation progestogen.

To date, data concerning effects of various gestagens/progestins on LTG serum concentrations are sparse and far from conclusive whereas data concerning potential effects of LTG on different progestins, as part of COCs, are lacking.

The aim of the present study was to investigate possible effects of diverse progestins in COCs on LTG serum concentrations and, *vice versa,* the potential impact of LTG on progestin serum levels during the menstrual cycle.

2. Material and methods

2.1. Patients

This prospective cross-sectional cohort study was conducted at the Department of Neurology, Medical University Innsbruck, Austria. Non-institutionalized WWE on chronic AED monotherapy (treated for > 3 months) with LTG were recruited for the study during outpatient visits. Epilepsy was defined according to the last Classification of the International League Against Epilepsy 2017 [13]. Patients were seizure free, baseline clinical characteristics are presented in Table 1. Additionally, healthy females seen as outpatients for routine or pre-operative investigations were recruited as controls. All patients and controls are non-smokers, do not suffer from alcohol abuse or concomitant diseases, and do not take any additional medication. The main exclusion criteria were as follows: pregnancy, breast feeding, hormonal therapy other than COC, implanon or vaginal ring and other medication or concurrent disorders that might affect LTG or COC pharmacokinetics. Furthermore, subjects known to suffer from any diseases likely to affect sex-steroid hormone synthesis, including immobility, cerebral palsy, chronic or inflammatory disease, endocrine disease, genetic syndromes, major congenital malformations, cancer or any other neurological disorders except epilepsy were excluded from the study. The study protocol was approved by the local ethics committee and informed consent was obtained from all patients and controls.

2.2. Methods

The COCs were monophasic and the estrogenic content was solely ethinyl estradiol (EE). COC use comprised 3 weeks of active pills and 1 week of inactive pills. Blood samples were drawn at the end of the week of inactive pill use in WWE (S1) and during the third week of active pill use in WWE and controls on COCs (S2) as described recently [14]. Blood was drawn after a 10 -h overnight fast between 8 and 10 a.m. to avoid bias due to diurnal variation and post-dose variation from the medications. Each sample was centrifuged, aliquoted and immediately frozen at –80 C within one hour of sampling, and then stored until the assays were run. Serum levels of gestoden, drospirenon and levonorgestrel were measured by online solid-phase extraction-high performance liquid chromatography-tandem mass spectrometry (online SPE-LC–MS/MS) as described recently by our workgroup [15]. LTG serum concentrations were determined using HPLC-UV (Chromsystems, Gräfelfing, Germany).

Table 1
Baseline characteristics of the study populations.

	LTG group (n = 20)	Controls (n = 14)	*p*-Value
Age (years)	24.2 ± 4.6 (23.0;18–37)	24.9 ± 5.6 (22.5;20–39)	0.975
GE/FE	9/11		
Seizure frequency (per month)	0		
Epilepsy duration (years)	7.9 ± 5.0 (8.0;1–18)		
AED use (years)	4.1 ± 2.9 (3.0;1–12)		

Values are given as mean ± SD (median; range) or absolute numbers; GE, generalized epilepsy; FE, focal epilepsy according to 13^{-}; AED, antiepileptic drug.

2.3. Statistics

Data are presented as mean ± SD with medians in parenthesis or absolute numbers (percentage). Normal distribution of the data was tested using the Kolmogorow-Smirnov test. Since most variables were not normally distributed, nonparametric tests were used. The concentration-to-LTG dose ratio (CDR) was calculated by dividing serum concentration by total daily dose as previously described [16]. All statistical significance tests were performed two-tailed with an alpha level of < 0.05 indicating statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, IL, USA, Version 15.0).

3. Results

Twenty WWE undergoing LTG monotherapy and COC (LTG group; mean ± SD [median; range] age 24.2 ± 4.6 [23.0; 18–37] years) as well as fourteen controls on COC (24.9 ± 5.6 [22.5; 20–39] years) were assessed for eligibility and all agreed to participate in the study and remained for data analyses. Clinical characteristics are presented in Table 1.

Mean LTG dose per day was 244 ± 126 mg [200; 50 − 600 mg] and, overall, LTG levels differed significantly between S1 and S2 (mean ± SD [median; range] 6.7 ± 5.5 [4.8; 1.1–21.3] vs. 3.9 ± 6.0 [1.5; 0.0–22.9] µg/mL; $p = 0.004$). No significant difference in LTG dosages between drospirenon, levenorgestrel and gestoden group could be demonstrated ($p > 0.05$). Furthermore, detailed analyses showed greater LTG serum concentrations at S1 when compared to S2 reaching statistical significance with drospirenon (n = 7; 3.1 ± 1.2 [2.9; 1.6–4.8 vs. 1.6 ± 0.7 [1.4; 0.9–2.8] µg/mL; $p = 0.018$) and a tendency with levonorgestrel (n = 7; 8.1 ± 4.7 [7.1; 3.5–17.1] vs. 4.2 ± 4.6 [2.1; 0.0–10.6] µg/mL; $p = 0.068$) whereas there was no difference in LTG serum levels with gestoden (n = 6; 9.8 ± 7.9 [6.3; 1.1–21.3] vs. 8.6 ± 12.4 [1.9; 1.0–22.9] µg/mL; $p = 0.593$). Similar results were seen using the CDR to correct for varying daily doses (Table 2).

Significantly lower progestin levels during S1 when compared to S2 with respect to levonorgestrel (median [range] 0.0 [0.0-0.0] vs. 5.3 [3.1–10.2] ng/mL; $p = 0.042$) and drospirenon (2.9 [0.0–6.1] vs. 22.3 [11.8–27.4] ng/mL; $p = 0.018$) but not to gestoden (0.0 [0.0-.4.0] vs. 4.3 [3.9–7.9] ng/mL; $p = 0.109$) could be shown in the LTG group (Table 2). Progestin concentrations did not differ between patients and controls at S2 and no statistically significant association of any of the tested parameters with seizure frequency, duration of epilepsy, duration of therapy or type of epilepsy could be demonstrated. Mean dosage of EE was 26.3 ± 6.6 µg in the LTG group and 24.6 ± 5.8 µg in the control group ($p > 0.05$).

4. Discussion

This is the first pilot study suggesting a differential influence of various progestins on LTG serum levels in WWE. The most important finding is that particular drospirenon and probably levonorgestrel but not gestoden in COC seem to reduce LTG serum concentrations when being co-administered. Furthermore and *vice versa*, no effect of LTG on several progestins, as determined by online SPE-LC–MS/MS, could be demonstrated at all, which is of importance for WWE taking COC.

There are several aspects that deserve to be mentioned: first of all, there are little guidelines for the treatment and counseling of WWE on AEDs with COC [17,18]. The effects of progestins and EE on LTG levels are far from conclusive to date and various aspects of a potential bi-directional interaction have not been investigated yet. As seen in the

Table 2
Progestins and CDR in LTG treated patients.

	S1	S2	*p*-Value
Progestins (ng/mL)			
Drospirenon containing COC (ng/mL)	2.5 ± 2.5	21.4 ± 5.4	0.018
Levonorgestrel containing COC (ng/mL)	0.0 ± 0.0	5.9 ± 2.6	0.042
Gestoden containing COC (ng/mL)	0.6 ± 1.5	5.4 ± 2.2	0.109
CDR all patients ((mg/L)/(mg/d))	0.029 ± 0.022	0.016 ± 0.018	0.002
Drospirenon containing COC	0.014 ± 0.007	0.007 ± 0.004	0.018
Levonorgestrel containing COC	0.036 ± 0.026	0.022 ± 0.022	0.068
Gestoden containing COC	0.039 ± 0.023	0.027 ± 0.027	0.593

S1, blood samples at the end of the week of inactive pill use;
S2, blood samples during the third week of active pill use;
Values are given as mean ± SD; CDR, concentration-to-LTG dose ratio;
LTG, lamotrigine; COC, combined oral contraceptive.

present study and according to previous reports, LTG concentrations are considered to decrease during hormonal contraception [12,16], hypothetically caused by the N-2-glucuronide pathway [9,11]. *vice versa*, fluctuating endogenous progesterone and estrogen levels during the menstrual cycle do not seem to influence LTG clearance in vivo [19]. In conflict to our study, Reimers and coworkers reported solely EE, not progestogens, to reduce LTG serum concentrations in a small study in 2005 [16]. A few plausible explanations exist for these results: it has to be mentioned that, presumably due to the limited number of patients included, the progesterone-only group was compared as a whole group without subgroup analyses although the overwhelming majority used etonogestrel subdermal and only four out of 16 were taken orally. In addition, the progesterone-only compounds used were administered on a continuous long-term basis without regular drug-free intervals. Finally, no significant difference between the progesterone-only group and the EE group could be demonstrated and sampling was not standardized in relation to the menstrual cycle as suggested in previous studies [16]. Nevertheless, the reigning hypothesis has been that EE might affect LTG via induction of glucuronidation by UGT 1A4 [16,20].

In contrast, the present study shows a differential effect of various progestins in COC on AED serum levels. Drospirenon and levonorgestrel containing COCs led to a pronounced reduction of LTG serum concentrations during intake whereas gestoden does not seem to interfere which might be of importance with regard to seizure risk in WWE taking COCs.

Since gestoden, as the only third-generation progestin used in this study, showed relatively stable CDR during active and inactive pill use and bearing the above mentioned in mind (no influence on LTG serum concentrations in the gestoden/EE group), one could reasonably assume that different generations of progestins might also affect LTG kinetics in a different manner. Hypothetically, the lack of significant findings with gestoden might be due to direct effects, due to the stable serum levels as stated above or perhaps due to an interference with induction mechanisms of EE. Finally, although metabolisation of progestins is not fully understood yet and the evaluation of pharmacokinetic differences between the progestins used is beyond the scope of this study, an additive or potentiating effect of UGT induction through drospirenon and levonorgestrel seems to be conceivable.

The other flip of the coin is that potential effects of AEDs on COCs have to be considered to ensure complete birth control. As witnessed by a recent study, levonorgestrel concentrations decreased on LTG (COC containing 30 μg EE and 150 μg levonorgestrel) even without any corresponding evidence of ovulation and led to the assumption that contraception safety cannot be guaranteed [21]. To the best of our knowledge, this is the only study evaluating a possible influence of LTG on progestin concentrations as part of a COC to date. Pending this, the present study might add some important new data: as expected, levonorgestrel and drospirenon showed decreasing serum levels during the pill-free interval whereas gestoden did not show any variability (please see Table 1) and, of importance, progestin concentrations did not differ between patients and controls.

Therefore, this study uniquely adds to the evidence by filling a gap in the existing literature and will potentially change clinical practice. Due to the growing recognition that enzyme inducing AEDs (e.g. CBZ) possibly affect contraception safety through induction of the cytochrome P450 system [22], recommendations concerning COC usage in WWE comprise: a) EE dosage of COCs should be increased to 50 μg [23] though it is still far below ovulation inhibiting dosage (100 μg) and might increase the risk of side effects [22]; b) neurologists and gynaecologists should be aware concerning a potential bidirectional interaction between COC and lamotrigine including a differential role of progestins; c) During intake of high dosage progestins side effects should be monitored and AED serum concentrations measured regularly [22]; d) Continuous use of COCs without any pill free intervals might be plausible due to more consistent progestin and estrogen serum levels [22]; e) Alternatively, WWE could use non-hormonal contraception such as copper or silver intra-uterine devices (IUD).

Finally, some intrinsic limitations of the present study need to be outlined. In particular, the small sample size and the limited number of progestins (drospirenon, levonorgestrel and gestoden) do not allow us to make firm conclusions about possible interactions between other synthetic gestagens (including mini-pills and implants) and LTG beyond this group. In addition, these results suggest that albeit the progestin compound might have an impact on LTG serum concentrations, an additive or potentiating effect of EE cannot be ruled out.

5. Conclusion

In conclusion, this study suggests that particularly drospirenon and levonorgestrel but not gestoden in COC seem to reduce LTG serum concentrations when being co-administered in WWE which might be of importance concerning seizure risk. Vice versa, no effect of LTG on several progestins could be demonstrated at all, arguing against a potential loss of contraception safety with LTG. Of importance, neurologists and gynaecologists should be aware of the potential bidirectional interaction between COC and lamotrigine including the potential role of progestins. This should comprise discussing the characteristics of different COCs with the patients regularly. Much has to be done including *in-vitro* studies of the different progestational agents and LTG as well as prospective studies of larger sample sizes to corroborate our findings and to help practitioners know which agent would be recommended to use.

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Ethics

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author contributions to the manuscript

Dr. Rauchenzauner – analysis and interpretation
Dr. Deichmann - acquisition of data, analysis and interpretation,
Dr. Pittschieler - acquisition of data
Dr. Bergmann – acquisition of data
Dr. Prieschl – acquisition of data
Dr. Unterberger – acquisition of data
Dr. Rösing – study concept and design, critical revision of the manuscript for important intellectual content
Dr. Seger – analysis and interpretation, critical revision of the manuscript for important intellectual content
Dr. Moser – analysis and interpretation
Dr. Wildt – critical revision of the manuscript for important intellectual content
Dr. Luef - study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision

Declaration of Competing Interest

The study was funded by GSK. The authors have no conflicts of interest to declare in relation to this study.

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