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Serum concentration/dose ratio of levetiracetam before, during and after pregnancy

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Summary

Purpose: To investigate changes in levetiracetam (LEV) serum concentration/dose ratio (C/D-ratio) in relation to pregnancy.
Methods: Altogether 21 consecutive pregnancies in 20 women with epilepsy receiving LEV during gestation were studied retrospectively. The main target variable was the C/D-ratio before and during pregnancy, and in the post partum period. Secondary target variables were changes in LEV dose, concomitant use of other antiepileptic drugs and seizure frequency. Student's paired *t*-test and two-sample *t*-test for independent samples were used to test for statistically significant changes in C/D-ratio means.
Results: Mean C/D-ratio in the third trimester was 50% of the mean C/D-ratio at baseline ($p < 0.001$, $n = 11$). Baseline levels were reached within the first weeks after pregnancy. The interindividual variability was pronounced.
Conclusions: Serum concentrations of LEV declined significantly in the third trimester of pregnancy and increased rapidly after delivery.

Introduction

Levetiracetam (LEV) is a newer antiepileptic drug (AED) with efficacy in various seizure types.[1] Due to its rapidly increasing use, a growing number of women receive LEV during pregnancy. The volume of distribution of LEV is close to intra- and extracellular water and the protein binding is minimal. The major metabolic pathway (applying to 24% of an administered dose) is extrahepatic hydrolysis of the acetamide group. Most of the drug is excreted unchanged by the kidneys.[2]

A range of pharmacokinetic alterations may result from the pregnant state. Some important factors are changes in plasma volume and volume of distribution, altered drug protein binding, changes in metabolic

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capacity as well as increased renal blood flow with enhanced glomerular filtration rate.[3,4] While gestation-related factors are known to influence the pharmacokinetic properties of older generation AEDs,[4,5] relatively little is known about their impact on the newer AEDs, with the exception of lamotrigine, which has been extensively studied (for an overview, see Tomson and Battino[4]). A marked increase in apparent clearance has been demonstrated for lamotrigine. A similar finding has been made for the monohydroxy derivative of oxcarbazepine.[6,7]

Limited data on the pharmacokinetics of LEV during pregnancy has so far been reported. Two case series, of which one only has been presented as an abstract, suggest that the apparent clearance of LEV also increases.[8,9] This increase appears to be higher than can be accounted for by enhanced renal blood flow alone.[9]

The objective of the present study was to confirm the previously published results, and to provide further information on the course of the maternal LEV serum concentration/dose ratio (C/D-ratio) throughout pregnancy and the post partum period. Additionally, we aimed to gather information on the pattern of seizure control in pregnant women using LEV.

Material and methods

Women from two Norwegian epilepsy outpatient clinics, participating in the European antiepileptic drug and pregnancy registry (EURAP) were screened for the use of LEV. Altogether 21 consecutive pregnancies in 20 women were identified. Nineteen of the pregnancies were completed; spontaneous abortions occurred in two. Mean age at time of delivery was 29 years (range: 21–38 years). Data on drug use and dosage, seizure frequency, seizure type and the occurrence of status epilepticus were obtained prospectively at each trimester according to the EURAP protocol.[10] Seizures were recorded by patient diaries. Supplementary clinical and pharmacological data were retrospectively collected from the medical records of each subject. LEV was used in monotherapy in five pregnancies, and in combination with other AEDs in the remaining 16. Treatment characteristics (maximum doses in each trimester) are summarized in Table 1.

Blood samples were taken drug fasting (10–14 h after last dose) at different stages prior to, during and after gestation in 19 pregnancies. They were analyzed with a liquid chromatography–mass spectrometry (LC–MS) method. Levetiracetam was extracted from 100 μL serum with 500 μL dichlorometane:isopropanol (90:10) after addition of internal standard solution (d6-levetiracetam). After mixing and centrifugation the organic extract was evaporated to dryness with air, the residue was reconstituted in 100 μL acetonitrile, transferred to vials and injected on an Agilent MSD 1100 LC–MS system (Agilent, Palo Alto, CA). The LC–MS system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a G1316A column oven and a G1946A mass spectrometer. Separation was performed on a Zorbax XDB-C8 (150 mm × 4.6 mm) column with a mobile phase consisting of acetonitrile:formic acid 55:45. Levetiracetam was monitored after positive electrospray ionization at m/z 171.1, the internal standard d6-levetiracetam at m/z 132.1. The calibrated range of the method was from 5 to 500 μM. Six quality control samples covering the range from 25 to 250 μM were analyzed with every batch of unknown samples. Between-day relative standard deviation calculated from quality control samples was better than 16.9% at 25 μM and 7.7% at 250 μM. The limit of quantification of the method was 5 μM.

Informed consent was given by all patients.

The serum concentration/dose ratio (C/D-ratio) was used as the primary outcome measure, as doses were not kept constant during the study. The LEV C/D-ratio was calculated by dividing the serum concentration of LEV (expressed as μmol/L) by the total daily dose (in mg). Thus, the LEV C/D-ratio expresses the serum concentration per milligram LEV given. The last sample prior to pregnancy, or (if missing) a sample taken 2 or 4 weeks after pregnancy served as the baseline value for each subject. Thus, the term baseline refers to the non-pregnant state, which might be either before or after pregnancy.

Statistics

Results are presented as mean (±SD) or median, as appropriate, for each trimester and for the baseline. Student's paired t-test and independent samples t-test were used to compare mean LEV C/D-ratios in each trimester with the mean C/D-ratios before and after pregnancy.

A p-value ≤ 0.05 was considered statistically significant.

Results

C/D-ratio during pregnancy

The box plot in Fig. 1 shows the median C/D-ratio at each sampling time. It indicates a gradual decrease throughout pregnancy, with an almost immediate

Table 1 Treatment characteristics and clinical course during pregnancy

Patient number	Antiepileptic drug	Doses (mg/day)				Seizures (3 months prior to pregnancy and during pregnancy
		At conception	First trimester	Second trimester	Third trimester	
1	Levetiracetam	1500	1500	1500	1500	SPS: 8—10/month
	Carbamazepine	1200	1200	1200	1200	
2	Levetiracetam	2000	2500	2500	2500	CPS: 1/month prior to pregnancy, but none during
	Valproate	900	900	0	0	
	Lamotrigine	0	200	200	200	
3	Levetiracetam	3000	3000	3000	3500	CPS: 1/month prior to pregnancy and during the first trimester SPS: Sporadic in the third trimester
	Carbamazepine	1200	1200	1200	1200	
4	Levetiracetam	0	0	1500	2000	None prior to pregnancy CPS: 8—10/month in the first trimester GTC: 2 in the second trimester, 4 in the third trimester
	Valproate	1800	1800	1800	1800	
	Topiramate	300	300	300	300	
5	Levetiracetam	1500	1500	1500	2000	None prior to pregnancy Myoclonic: 1/month in the first trimester, 4/month in the second, but none in the third trimester
6	Levetiracetam	0	0	2000	2500	SPS: Daily prior to and during pregnancy
	Gabapentin	1200	1200	1200	1200	
	Lamotrigine	300	400	600	600	
7	Levetiracetam	2000	2000	2000	2000	None prior to pregnancy GTC: 1 in the first trimester, 2 in the second CPS: Sporadic
	Lamotrigine	550	600	700	800	
8	Levetiracetam	2000	2500	2500	2500	None
	Lamotrigine	150	300	300	400	
9	Levetiracetam	1500	1500	1500	1500	None
10	Levetiracetam	500	1000	500	0	GTC: 1/month prior to and during pregnancy CPS: Several prior to pregnancy and during the first and second trimester, less in third
	Oxcarbazepine	0	1200	2400	2400	
	Pregabaline	450	450	450	450	
11	Levetiracetam	1500	1500	1500	1500	None
12a[a]	Levetiracetam	1500	1500	n.a.	n.a.	GTC: One prior to pregnancy, but none during first trimester
	Lamotrigine	200	200			
12b	Levetiracetam	1500	1500	1500	2000	None prior to pregnancy CPS: 1/month during the third trimester
	Lamotrigine	200	200	300	300	
13	Levetiracetam	1750	1750	2500	2500	None prior to pregnancy GTC: 1 in the third trimester
14	Levetiracetam	1500	1500	1500	1500	None
	Valproate	900	1800	1800	1800	
15	Levetiracetam	2500	2500	2500	2500	CPS: 1/week prior to and during pregnancy
	Lamotrigine	150	150	150	150	

Table 1 (*Continued*)

Patient number	Antiepileptic drug	Doses (mg/day)				Seizures (3 months prior to pregnancy and during pregnancy
		At conception	First trimester	Second trimester	Third trimester	
16	Levetiracetam	1000	2000	2000	2000	None prior to pregnancy
	Carbamazepine	500	500	400	800	GTC: 1/month in the first trimester
						CPS: Increasing from weekly to daily throughout pregnancy
17	Levetiracetam	2000	2000	2000	2000	CPS: 4/month prior to pregnancy and during the first and second trimester, 2/month in the third trimester
	Oxcarbazepine	1200	1200	1200	1200	
18	Levetiracetam	1000	1000	1000	0	GTC: 1/month before and during the first two trimesters
	Topiramate	200	200	200	200	
	Valproate	1200	1200	1200	1200	Absences: Several prior to pregnancy and during the first two trimesters, rare in the third trimester
19[a]	Levetiracetam	1500	1500	n.a.	n.a.	None prior to or during first trimester
20	Levetiracetam	1500	1500	2000	2500	CPS: 1/week prior to and throughout pregnancy
	Topiramate	400	400	450	400	GTC: Several/month prior to pregnancy, less than 1/month in the first and second trimester, weekly in the third trimester
						Status epilepticus: Convulsive in the second and non-convuslive in the third trimester

[a] Spontaneous abortion in first trimester; n.a., not applicable; SPS, simple partial seizures; CPS, complex partial seizures; GTC, generalized tonic-clonic seizures.

increase after delivery. However, complete sets of C/D-ratios, i.e. pre-pregnancy, all three trimesters, and post-pregnancy values, were not available from all patients (Table 2). In seven patients we obtained sets from all trimesters and at baseline. The mean C/D-ratio (±SD) in these patients at baseline was 0.036 (±0.015). In all trimesters it was lower than at baseline, although not significantly lower in the first and second trimester. In the third trimester, the mean C/D-ratio was 0.022 (±0.010), which was significantly lower than at baseline ($p = 0.005$, $n = 7$). In addition to these seven patients, four patients provided blood samples from the third trimester and at baseline, but not from the first and second trimester. The C/D-ratio changes from baseline to the third trimester in these altogether 11 patients (seven with complete data from all trimesters plus four with third trimester data only) are shown in Fig. 2. Among these patients, the mean C/D-ratio (±SD) in the third trimester was 0.021 (±0.009), that is significantly lower than the baseline value of 0.042 (±0.018) ($p < 0.001$).

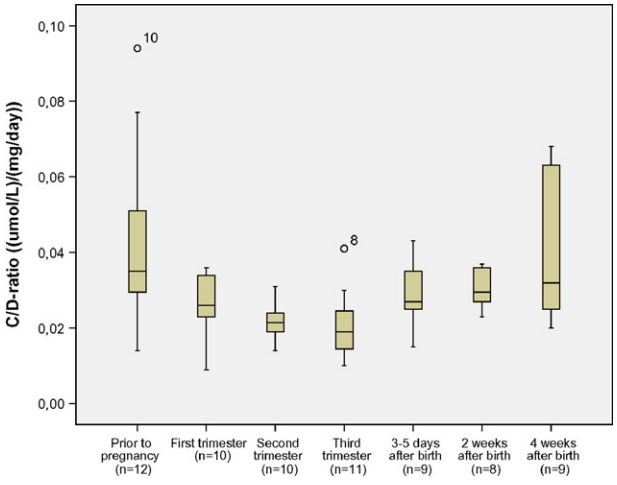

Figure 1 Boxplot showing the serum concentration/dose ratio [(μmol/L)/(mg/day)] of all samples prior to, during and post pregnancy. Numbers of samples available in each group are given at the bottom. Circles denominate outliers.

C/D-ratio after delivery

Blood samples were collected 3–5 days after birth ($n = 9$), 2 weeks after birth ($n = 8$) and 4 weeks after birth ($n = 9$) (some data previously reported by Johannessen et al.[11]). The mean C/D-ratios at these

Table 2 Serum concentration/dose ratio [(μmol/L)/(mg/day)] of levetiracetam during and after pregnancy

Patient number	Prior to pregnancy	First trimester	Second trimester	Third trimester	3–5 days after birth	2 weeks after birth	4 weeks after birth
1	–	–	–	–	0.025	0.027	0.039
2	–	–	–	–	0.025	0.027	0.032
3	0.019	0.009	0.022	0.018	0.019	0.023	0.020
4	–	–	–	–	0.035	–	0.022
5	–	–	–	0.020	0.015	0.037	–
6	–	–	–	––	0.034	0.036	0.068
7	0.032	0.023	0.024	0.020	–	–	0.030
8	–	0.027	0.024	0.041	–	–	0.064
9	0.077	0.034	–	0.030	–	–	–
10	0.094	0.036	–	–	––	–	–
11	0.035	0.025	0.014	0.010	–	–	–
12a	0.048	0.028	n.a.	n.a.	n.a.	n.a.	n.a.
12b	0.048	0.027	0.021	0.029	–	0.032	–
13	0.054	–	0.016	0.015	–	–	0.063
14	0.041	–	–	0.013	–	–	–
15	–	–	–	–	–	–	–
16	0.029	0.023	0.021	0.014	0.027	0.036	–
17	0.030	–	0.019	–	0.038	–	–
18	0.014	0.015	0.030	–	–	–	–
19	–	–	n.a.	n.a.	n.a.	n.a.	n.a.
20	–	0.034	0.031	0.019	0.043	0.027	0.025
Mean	0.043	0.026	0.022	0.021	0.029	0.031	0.040
St. dev.	0.022	0.008	0.005	0.009	0.009	0.005	0.018

n.a., not applicable (spontaneous abortions).

sampling times were compared to the 11 samples from the third trimester using an independent samples *t*-test. The mean (±SD) C/D-ratio was 0.031 ± 0.005 ($n = 8$) 2 weeks after birth and 0.040 ± 0.019 ($n = 9$) 4 weeks after birth. These values were both significantly higher than the third trimester value of 0.021 ± 0.009 ($n = 11$; $p = 0.02$ and 0.01, respectively). There was a trend towards a statistically significant difference already 3–5 days after birth (mean (±SD) C/D-ratio was 0.29 ± 0.009 ($n = 9$); $p = 0.06$).

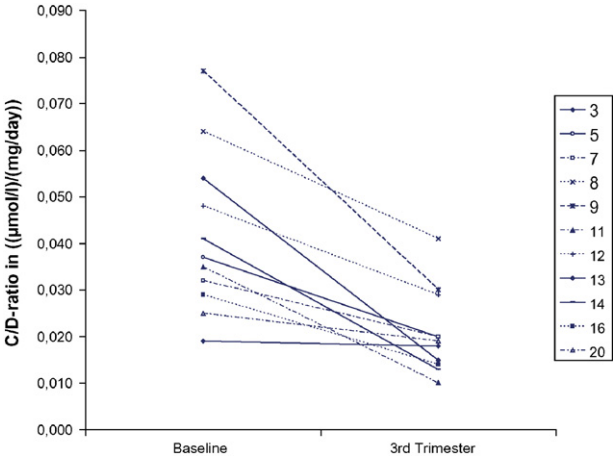

Figure 2 Individual serum concentration/dose ratios [(μmol/L)/(mg/day)] at baseline and during the third trimester, in 11 women on levetiracetam.

Dose adjustments

In 11 pregnancies, the LEV dose was increased (in two of them LEV therapy was started during pregnancy); four increments were performed in the first trimester, four in the second and six in the third trimester. In a total of 14 pregnancies, the dose of either LEV or concomitant AEDs was increased at least once (Table 1). AED dose increase was conducted during the first trimester in seven, during the second in six, and during the third trimester in 10 pregnancies. In two pregnancies, LEV was withdrawn.

Seizure frequency

Increased seizure frequency was observed in seven of the 19 completed pregnancies (Patients 4, 5, 7, 12, 13, 16, 20), in five of them during the third trimester. Reduced seizure frequency was observed in five (Patients 2, 3, 10, 17, 18); In the remaining pregnancies, the subjects were either seizure free prior to conception and throughout pregnancy, or their seizure frequency remained stable during the study period (Table 1). Among the seven patients

with increased seizure frequency, five had an increased number of generalized tonic-clonic seizures. One (Patient 20) experienced an incident of convulsive status epilepticus in the second trimester, and of non-convulsive status epilepticus in the third trimester, respectively. AED doses were increased in all seven patients with increased seizure frequency during pregnancy, and LEV was increased in six of them. However, the observed decline in LEV C/D-ratio was not more pronounced in the patients with increased seizure ratio than in the other subjects.

Discussion

Our data show a significant decline of the maternal LEV C/D-ratio in the third trimester, and a rapid increase within the first 2 weeks post partum (Table 2, Fig. 1). The drop of the C/D-ratio was pronounced, with the mean value being reduced to 50% compared to baseline ($n = 11$). In other words, on average a doubling of the LEV dose would be required to maintain baseline serum concentrations during the third trimester. However, as reflected by Fig. 2 and Table 2, the extent of these changes shows considerable intersubject variability. An accurate prediction of the course of the LEV serum concentrations in pregnancy in individual patients is therefore not possible. Our findings are in accordance with previous data on the impact of pregnancy on the apparent clearance of LEV. In a conference abstract, Pennell et al.[8] reported a prospective study of five pregnancies from the U.S., in which blood samples were obtained in each trimester and post partum. Serum concentrations were adjusted for different dosage and for weight changes, by calculating apparent LEV clearance [(dose/body weight)/serum concentration]. Mean LEV clearance in the third trimester was 154% of the baseline value, indicating that in the third trimester about 1.5 times the original LEV dose would be needed to keep serum concentrations at baseline levels. This finding is supported by a recently published case series from Sweden.[9] In 12 pregnancies, it was found that the apparent LEV clearance in the third trimester was 342% of the baseline value, indicating a need for an increase of the LEV dose of almost 3.5 times to keep serum concentrations unchanged. Pennell's, Tomson's and our study suggest that the dose-corrected serum levels of LEV during the third trimester are between 29% and 65% of baseline values, with the present findings close to the mean (50%). However, neither the present nor the Swedish study applies adjustments for body weight changes. As suggested by Tomson et al.,[9] this might partly explain the more prominent change in apparent LEV clearance compared to the U.S. study.

Increased renal blood flow may contribute to the observed decline in LEV serum concentrations during pregnancy. The kidneys are the primary organ responsible for the excretion of LEV, as 66% of an administered LEV dose is found unchanged in the urine.[12] Since glomerular filtration rate increases approximately 50% during pregnancy, renal LEV clearance is likely to increase, but the extent is unknown. Generally, the effect of pregnancy on renal drug clearance is highly variable, ranging from 20% to 65% for most drugs.[3] Another possible explanation for the decline in LEV serum concentration could be an increased metabolism during pregnancy. The primary site for the hydrolysis of LEV appears to be in the blood, and the metabolism does not involve the hepatic cytochrome P450 (CYP) system.[12] However, enzyme-inducing AEDs have been shown to decrease LEV serum concentrations by about 20–30%.[13,14] Thus, since LEV metabolism appears to be inducible, it cannot be ruled out that metabolic/endocrine changes during pregnancy may induce LEV metabolism.

Whatever the mechanism, a change in LEV serum concentrations of the found magnitude is likely to be of clinical significance. In our study, an increase in seizure frequency occurred in seven of 19 completed pregnancies; one patient had recurrent status epilepticus. However, a clear correlation between lowered LEV levels and seizure breakthrough could not be demonstrated, conceivably as LEV doses usually were increased as a response to seizures, and because only two patients used LEV as monotherapy. Nevertheless, similar observations from the EURAP registry concerning seizure control during pregnancy have recently been published.[10] Among the enrolled women, two thirds had a stable seizure frequency (the majority was seizure free), whereas one third experienced a change, half of them improved, the other half got worse. As expected, incomplete seizure control appeared to be associated with polytherapy and AED dose changes.

In conclusion, our results confirm the findings of earlier studies. We have shown that dose-corrected LEV serum concentrations drop to about 50% of baseline values in the third trimester of pregnancy, and rapidly increase within the first weeks post partum. Consequently, serial measurements of LEV serum concentrations throughout pregnancy and in the first weeks post partum are advisable, particularly in patients with brittle seizure control. A considerable number of women using LEV during pregnancy may experience worsening of their seizure frequency. The present findings are essential

for appropriate counselling and follow-up of women who need treatment with LEV during pregnancy.

Policy and ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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