■ Clinical commentary

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Pharmacokinetic data on brivaracetam, lacosamide and perampanel during pregnancy and lactation

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ABSTRACT – We present pharmacokinetic data during pregnancy and lactation for brivaracetam, lacosamide and perampanel based on two case studies. Patient 1 used brivaracetam as monotherapy and gave birth to twins. Patient 2 used a combination of brivaracetam, lacosamide and perampanel. In both patients, serum drug concentrations were monitored throughout the pregnancies. Drug concentrations were also analysed in umbilical cord blood at birth, in serum from the offspring and in breastmilk after five days and 3-11 weeks. There were minor changes in concentration/dose-ratios for brivaracetam and lacosamide. The mean milk/serum ratios for brivaracetam and lacosamide were 0.71 and 0.83, respectively, five days and 3-5 weeks after delivery. The perampanel serum concentration increased by up to 80% in Patient 2 during the last part of gestation. The mean milk/serum-ratio for perampanel was 0.13, unchanged from five days to five weeks after delivery. Whereas serum concentrations of brivaracetam and lacosamide remained fairly stable throughout pregnancy, perampanel concentrations seemed to steadily increase towards the end. The distribution to milk was considerable for brivaracetam and lacosamide and low for perampanel. More studies on mother-infant pairs are warranted to confirm these results in larger groups.

Key words: epilepsy, pharmacokinetics, therapeutic drug monitoring, antiseizure medications (ASMs)

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Therapeutic drug monitoring (TDM) data on the most recently approved antiseizure medications (ASMs), brivaracetam, lacosamide and perampanel, during pregnancy is scarce. According to their product characteristics, these drugs are not recommended for use during pregnancy, and distribution to breastmilk is unknown [1-3]. The indications of these drugs include add-on treatment for focal epilepsy, and for perampanel also add-on for generalized epilepsy. Up to 50% of pregnancies are unplanned, and thus we need to be aware of gestation-induced pharmacokinetic changes, and breastmilk and infant concentrations for all ASMs [4]. Real-life experience with careful monitoring is consequently a useful source of data when pregnancy occurs. TDM facilitates safe and optimized drug treatment in epilepsy and should be implemented to adjust for pharmacokinetic variability that may be pronounced and unpredictable in relation to pregnancy [5-7]. We present pharmacokinetic data on brivaracetam, lacosamide and perampanel during gestation, in breastmilk and in the nursing infant.

Methods

Patient 1 was a 25-year-old, who had juvenile myoclonic epilepsy with generalized tonic-clonic seizures and myoclonic jerks. She had previously used valproate, levetiracetam and zonisamide. Due to psychiatric adverse effects from levetiracetam, she had changed to brivaracetam monotherapy, 75 mg BID, which she tolerated well.

Patient 2 was a 32-year-old, who had focal epilepsy with sporadic focal to bilateral tonic-clonic seizures and frequent focal-onset seizures with impaired awareness. She had been rejected for epilepsy surgery and had tried a large number of ASMs. She experienced improvement on triple ASM therapy: brivaracetam at 100 mg BID, lacosamide at 200 mg BID, and perampanel at 8 mg OD.

Written consent to present anonymized data on the use of ASMs during pregnancy along with clinical data was obtained from both patients.

ASM concentration measurements were collected from the TDM database at The National Center for Epilepsy. Samples were collected at St. Olav University Hospital, and data retrieved from medical records. The serum concentrations were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS), Thermo Scientific, Prelude Endura-MD, RECIPE's ClinMass®TDM-Platform (MS9200) (https://recipe.de/products/antiepileptic-drugs-serum/). The precision of the method was a coefficient of variation of 10-15%, and reproducibility generally below 10% but up to 20% at the limit of lowest quantification (LLOQ), which was 0.47, 1.23 and 0.089 mmol/L for brivaracetam, lacosamide and perampanel, respectively. Blood samples were routinely drawn at steady-state, drug-fasting in the morning, with time of previous drug intake reported. Total drug concentrations in serum were routinely measured. Breastmilk was handled as serum samples, although without a validated analysis, to give a quantifiable level of serum-milk distribution. Foremilk and hindmilk were collected in Patient 1 and 2.

Serum concentrations, doses and concentration/dose (C/D) ratios were calculated for comparison between the two women, and mean values within one trimester were used to present changes in each trimester, in which two or three measurements had been performed. The mean values at Week 5 and four months postpartum were defined as baseline values due to lack of appropriate baseline values before conception for both patients. Only descriptive analyses were performed.

Results

Patient 1, using brivaracetam only, gave birth to healthy twins, a girl and a boy, by Caesarean section in Week 37. The twins were fed by combined breastfeeding and breastmilk substitute. Patient 2, who used brivaracetam, lacosamide and perampanel, delivered a healthy boy in Week 39. The baby was exclusively breastfed during the first six weeks postpartum. In both patients, doses were kept unchanged throughout the study (*table 1*).

For all three ASMs, there were minor to moderate changes in serum concentrations during pregnancy at constant doses (*figure 1A-C*). For brivaracetam and lacosamide, the concentration/dose ratio was mainly unchanged throughout pregnancy as compared to baseline values (*figure 1A, D*), but for lacosamide, a postpartal increase was observed (Patient 2). The serum concentrations of perampanel increased throughout the pregnancy by up to 80% in the last weeks before delivery. The three-fold increase in perampanel, five days after delivery (9.5 hours after drug intake), was an outlier possibly due to aberrant intake (*figure 1B, C*).

The serum concentration of brivaracetam in the twins at birth was similar to that of Patient 1 but decreased significantly by Day 5 postpartum (*table 1*). During partial breastfeeding, brivaracetam was below the limit of quantification in the serum of the twins both at Day 5 and Week 3 postpartum (<10% of the concentration in serum from the mother). In the offspring of Patient 2, however, the serum concentration of brivaracetam during exclusive breastfeeding was unchanged at 18-20% of the values in the mother at birth and at Day 5 and Week 5. Lacosamide and perampanel concentrations in the serum from this infant were 16-28% of the values in the mother, also at five days and five weeks. All three drugs were below the limits of quantification at the age of 11 weeks with partial nursing.

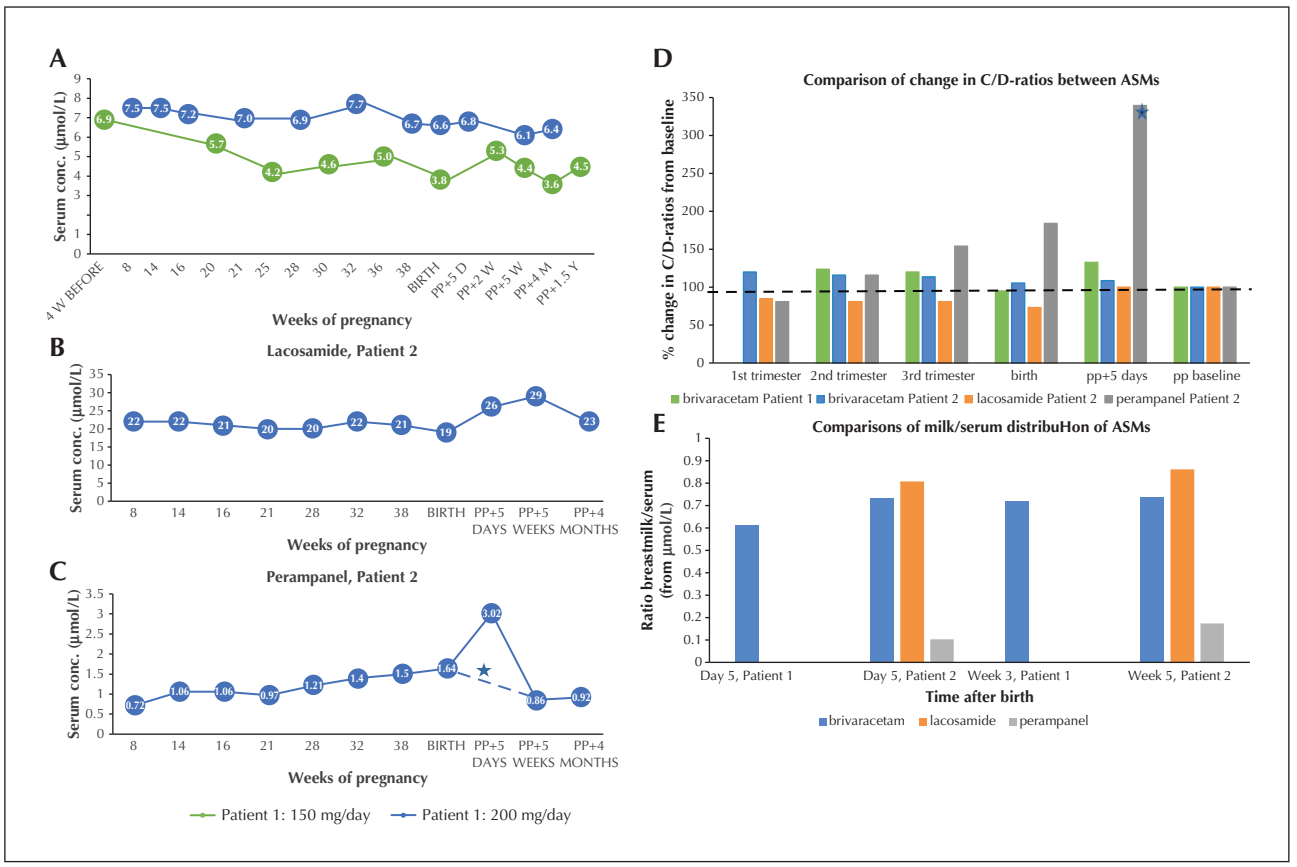
The distribution of ASMs to breastmilk was considerable for both brivaracetam and lacosamide. For brivaracetam, the milk/serum ratio was similar in both patients at five days and three to five weeks with a mean of 0.71. The foremilk concentration was somewhat higher than the hindmilk concentration of brivaracetam. The mean milk/serum ratio was 0.83 for lacosamide, whereas for perampanel this was only 0.13, both measured at five days and five weeks (*table 1, figure 1E*).

Clinical follow-up was as follows. Patient 1 had no seizures during the study. As the drug exposure of the infants was below quantifiable levels, she continued partial breastfeeding along with breastmilk substitute. Patient 2 continued to have mild focal seizures several times per week. Due to the moderate drug exposure

▼ **Table 1.** Measurements of antiseizure medications in mothers, breastmilk and offspring.

Patients, time points, antiseizure medications	Time since last dose (hours): mother	Serum concentration (µmol/L): mother	Breastmilk concentration (µmol/L)*	Mean ratio (Cmilk/ Cserum)	Serum concentration (µmol/L): offspring	Serum ratio (infant/ mother)
Patient 1						
Day of delivery						
Brivaracetam	3 h mother; 1 h umbilical cord	3.8	NA	NA	Twin 1: 4.1 Twin 2: 4.2, umbilical cord	1.08 1.11
Day 5 postpartum						
Brivaracetam	12 h morning and evening	5.3 and 4.4, morning and evening	3.6 and 3.2, foremilk and after 3 min, hindmilk	0.61	Twin 1: <0.5** Twin 2: <0.5**, partial breastfeeding	<0.11
Week 3 postpartum						
Brivaracetam	12 h	4.4	3.4 and 3.2, foremilk and after 3 min, hindmilk	0.75	Twin 1: <0.5** Twin 2: <0.5**, partial breastfeeding	<0.11
Patient 2						
Day of delivery						
Brivaracetam Lacosamide Perampanel	9.5 h 9.5 h 7.5 h	6.6 19 1.64	NA	NA	1.2 9.0 0.23 Serum conc.	0.18 0.47 0.14
Day 5 postpartum						
Brivaracetam Lacosamide Perampanel	12 h 12 h 9.5 h	6.8 26 3.02	5.0 21 0.31 foremilk	0.74 0.80 0.10	1.2 7.0 0.49, breastfeeding only	0.18 0.27 0.16
Week 5 postpartum						
Brivaracetam Lacosamide Perampanel	13 h 13 h 13 h	6.1 29 0.86	4.5 25 0.15 foremilk and after 10 min, hindmilk	0.74 0.86 0.17	1.2 8.0 0.23, breastfeeding only	0.20 0.28 0.27
Week 11 postpartum						
Brivaracetam Lacosamide Perampanel	NA	NA	NA	NA	<0,5** <3** <0.15**, partial breastfeeding	

NA: not applicable; *values for foremilk and hindmilk available for Patient 1 and 2, and foremilk available for Patient 2 at the first measurement and foremilk and hindmilk at Week 5 with exactly the same values (10 minutes between samples). **Values below the limit of quantification.



■ Figure 1. Pharmacokinetics throughout pregnancy of each antiseizure medication: (A) brivaracetam in Patients 1 and 2; (B) lacosamide in Patient 2; and (C) perampanel in Patient 2. The high serum concentration at Day 5 postpartum in Patient 2 was probably due to double dose intake. *illustrates the most probable course (C). All analyses were performed 10-13 hours after the last dose intake. Serum conc: serum concentration. The reference range for brivaracetam is 1-10 µmol/, lacosamide 10-40 µmol/ and perampanel 0.25-2.85 µmol/L [18]. (D) The percentage change in serum concentration/dose ratios (C/D-ratios) of the three drugs used in Patients 1 and 2, compared to baseline values (mean values from measurements at five weeks + four months postpartum); *perampanel at five days postpartum due to probable double dose intake. (E) Distribution of breastmilk/serum for Patients 1 and 2. gr1

of the infant during exclusive breastfeeding with brivaracetam concentrations within reference range and lacosamide and perampanel concentrations just below, half of the breastfeeding was substituted by infant formula from six weeks of age. At 11 weeks, infant drug exposure was negligible, and combined nutrition was continued.

None of the babies exhibited reduced wakefulness or feeding problems. At one year of age, the mothers reported unremarkable development.

Discussion

We present two patients with three recently approved ASMs during pregnancy, brivaracetam in both, and additionally lacosamide and perampanel in one, using multiple measurements in various matrixes. Routine use of TDM for these drugs demonstrates pronounced pharmacokinetic variability between patients [8-10].

Brivaracetam and lacosamide are partly metabolized through CYP2C19. Lacosamide is, however, partly excreted unchanged through the kidneys (40%). Therefore, a decrease in the clearance of lacosamide during pregnancy would be expected, consistent with the time course of the increased glomerular filtration rate, comparable to levetiracetam [11]. The unchanged course seen in this patient could not be explained. Perampanel is primarily metabolized through CYP3A4 and minor pathways (CYP1A2 and CYP2B6) (SPC-perampanel) [3]. During pregnancy, major changes in blood flow to eliminating organs and increased

hepatic activity occur. We therefore expected moderate changes and an increase in clearance, comparable to other ASMs, such as levetiracetam, topiramate and oxcarbazepine [5-7]. Reduced metabolism was not predicted for perampanel, as the CYP3A4 substrate, like carbamazepine, is considered to remain unchanged during pregnancy [6]. However, this has been seen for some antipsychotic drugs and caffeine due to decreased activity of CYP1A2 during pregnancy [12-14]. We cannot explain why the serum concentration of perampanel increased in Patient 2 other than due to possible reduced CYP1A2-dependent metabolism during pregnancy.

After ruling out analytical errors by tracking and re-evaluating the results, we believed that the outlier in perampanel serum concentration on Day 5, after delivery, was due to the drug being taken twice, as it was usually taken at bedside, a few hours after the two other ASMs. Although habitually strictly adherent, the patient could not rule out that this accidentally occurred, possibly associated with disrupted sleep rhythm in the postnatal period.

At birth, the serum concentrations of brivaracetam in the twins were comparable to that of the mother, as measured at assumed Cmax concentration one hour after dose intake in Patient 1. In Patient 2, however, the serum concentration of brivaracetam was low in the infant (18%), as measured 9.5 hours after the last dose intake. This could explain the discrepancy between the measured infant/mother ratios of 1.1 and 0.18. Following breastfeeding, limited to twice daily, the serum concentrations of brivaracetam in the twins were below the level of quantification. Moderate to high distribution to breastmilk was expected for brivaracetam and lacosamide due to their chemical properties and low/moderate protein binding; 36% and 14%, respectively [15]. The infant serum concentrations of brivaracetam and lacosamide were considerably lower than in breastmilk. As anticipated, there was a low degree of serum-milk distribution for perampanel due to a high degree of protein binding (95%) [15]. Unexpectedly, perampanel concentrations were higher in the serum of the infant than in breastmilk, which might be explained by accumulation due to the long half-life of perampanel, of about 100 hours in adults, and were maintained for longer due to immature CYP expression in the infant. CYP3A4 and CYP1A2 are drug-metabolizing enzymes with low activity in foetal life and increase after birth with considerable postnatal variability [13, 14, 16, 17]. Based on the current single patient findings, TDM of perampanel during pregnancy might actually support lowering the dose to avoid over-exposure of the foetus.

These results provide the first step towards gathering safety data on breastfeeding, which should include studies of more mother-infant pairs. Monitoring early effects on infants as well as long-term neurodevelopment, in addition to serum concentration measurements, can be useful.

Methodological considerations include the fact that there were only two patients and the results should be interpreted cautiously. Pharmacogenetic factors may also play a role and make the outcome unpredictable, regarding metabolic pathways through CYP2C19 and CYP3A4/5 [7]. Applicable serum concentration measurements before pregnancy are often absent, and therefore values at two time points after delivery at steady-state conditions were defined as baseline values. Partial non-adherence could not be ruled out, but this was discussed at each visit. Samples of breastmilk were analysed using a method designed and validated for analysing serum samples. Also, sampling at two time points during lactation, initially and after 10 minutes (foremilk and hindmilk), demonstrated similar values showing that a possible different composition of water/fat in the milk affecting the analysis or drug concentration was unlikely.

In conclusion, these patients demonstrated only minor to moderate changes in serum concentrations of brivaracetam and lacosamide during pregnancy, whereas perampanel levels seemed to increase prior to delivery. The distribution to milk was considerable for brivaracetam and lacosamide and low for perampanel. Unpredictable serum concentration levels in the nursing infant may be present, conceivably due to immature and variable expression of metabolizing enzymes in the postnatal period. Systematic TDM with sampling of serum from mother and child, as well as of breastmilk, provides important knowledge of pharmacokinetic parameters of drugs during pregnancy, after delivery and during lactation. ■

Supplementary data

Summary didactic slides available on the www.epilepticdisorders.com website.

Disclosures

EB has received speaker bursaries from Eisai and UCB. Others authors do not have any conflict of interest to declare.

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TEST YOURSELF

(1) During pregnancy, would you expect the serum concentrations of several newer antiseizure medications to:

A. increase due to increased clearance
B. increase due to decreased clearance
C. decrease due to increased clearance
D. decrease due to decreased clearance

(2) The distribution of drugs to breastmilk is dependent on:

A. the chemical properties of the drug
B. the half-life of the drug
C. the protein binding of the drug
D. the bioavailability of the drug

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section ``The EpiCentre''.