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Original article

Therapeutic monitoring of carbamazepine and its active metabolite during the 1st postnatal month: Influence of drug interactions

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ABSTRACT

Objective: To receive information about carbamazepine and its active metabolite 10,11-epoxide transport into mature milk and suckling infants.
Methods: In this cohort study, maternal serum, mature milk, and infant serum carbamazepine and epoxide levels were measured between the 6th and 29th postnatal day (carbamazepine in 1990–2017, epoxide in 1997–2017). Paired maternal serum, infant serum and milk levels were used for the assessment of ratios of this levels. The influence of combined treatment with enzyme-inducing antiepileptic drugs and valproic acid was assessed. Relationship between maternal serum, infant serum, and milk levels was also evaluated.
Results: Maternal carbamazepine levels were 1.4–10.4 mg/L, milk 0.5–6.7 mg/L and infant 0.5–2.6 mg/L. Maternal 10,11-epoxide levels were 0.3–5.4 mg/L, milk 0.3–3.7 mg/L and infant 0.3–0.6 mg/L. Highly significant correlations were observed exclusively between milk and maternal serum levels of both carbamazepine and 10,11-epoxide. Concomitant administration of enzyme-inducing antiepileptic drugs significantly increased the maternal apparent oral clearance of carbamazepine by approximately 130%. Carbamazepine combined with valproic acid significantly increased epoxide levels in milk and maternal serum but not in breastfed infants.
Conclusions: In breastfed infants, carbamazepine levels did not reach the lower limit of the therapeutic range used for the general epileptic population, and the majority of epoxide levels were less than the lower limit of quantification. Routine monitoring of carbamazepine in these infants is not compulsory. However, observation of breastfed infants is desirable. If signs of potential adverse reactions are evident, infant serum concentrations should be monitor.

1. Introduction

Carbamazepine (CBZ) is one of the most frequently prescribed antiepileptic drugs (AEDs) in pregnancy [1,2]. Breastfeeding during CBZ monotherapy does not appear to adversely affect infant growth or development, and most infants had no adverse reactions with the exception of drowsiness, poor sucking, recurrent regurgitations and vomiting. These conditions represent complications in some cases due to concurrent drug therapy. Infants, especially younger infants and exclusively breastfed infants, should be monitored for jaundice, drowsiness, and adequate weight gain when mothers use combinations of anticonvulsant or psychotropic drugs [3–8].

In humans, the most important route for CBZ metabolism is its epoxidation by cytochrome P450 (CYP) isoenzymes 3A4 and 3A5 to the active metabolite carbamazepine-10,11-epoxide. This metabolite has similar antiepileptic properties and is thought to be partially responsible for the toxicity of CBZ treatment [9] Phenobarbital (PB), phenytoin (PHT) and primidone (PRM) enhance the metabolism of CBZ through CYP3A4, and valproic acid (VPA) inhibits the metabolism of the epoxide by inhibition of epoxide hydrolase [10].

CBZ levels in umbilical cord blood at delivery were either not significantly different from maternal levels or lower, and wide interindividual variability of the umbilical cord/maternal serum level ratio was observed [11]. Data on its excretion into human breast milk and

Abbreviations: AEDs, Antiepileptic drugs; CBZ, Carbamazepine; Cl, Apparent oral clearance; CLZ, Clonazepam; CYP, Cytochrome P450; EPO, Carbamazepine-10,11-epoxide; I, Infant; LLoQ, Lower limit of quantification; LTG, Lamotrigine; LVT, Levetiracetam; M, Maternal; Mi, Milk; N, Number; PB, Phenobarbital; PHT, Phenytoin; PRM, Primidone; TPM, Topiramate; VPA, Valproic acid.

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breastfed infants remain sparse, especially data on CBZ-10,11-epoxide, which was only analysed in 14 breastfed infants in two study groups [6,12–26]. Maternal, milk and infant concentrations of both CBZ and CBZ-epoxide with their ratios are reported solely by Pynnönen et al. in three patients between 2 days - 5 weeks postpartum [18]. However, measurement of breast milk in the first 3–5 days postpartum can be misleading as it primarily contains colostrum. By the end of the first week, the milk is mature [27]. The influence of co-medication with enzyme-inducing antiepileptic drugs or enzyme-inhibiting valproic acid on CBZ pharmacokinetics during breastfeeding has not been studied to date.

2. Material and methods

This cohort study used the data of 66 women (aged 26 ± 5 years) and their 63 breastfed infants (33 girls, 29 boys, 1 sex not stated) with a median weight of 3.3 kg (range 2.1–4.9 kg) and a median length of 50 cm (range 44–54 cm). Mothers received CBZ for the treatment of epilepsy either in monotherapy or in combination with "neutral" drugs (CLZ, LTG, LVT and TPM), in combination with enzyme-inducing AEDs (PHT, PRM and PB) or in comedication with enzyme-inhibiting valproic acid.

Mature milk, maternal serum and infant serum were collected between the 6th and 29th postnatal day (median 7 days), samples were generally obtained before the morning maternal dose and altogether analysed in our department. For statistical analysis, we received all three samples (maternal, milk and infant together) from 44 patients, maternal and milk samples from 16 patients, maternal and infant samples from 5 patients, milk and infant sample from 1 patient and 13 samples were taken from breastfed infants alone. Request forms for routine therapeutic drug monitoring were utilised as the data source. The study was appropriately reviewed and approved by the local ethics committee.

Total serum and milk concentrations of CBZ and CBZ-10,11-epoxide were measured by high-performance liquid chromatography with ultraviolet detection at 220 nm. CBZ concentrations were analysed in all samples between 1990 and 2017 and CBZ-10,11-epoxide only in a subgroup of 58 patients in 1997–2017, because analytical method for CBZ-10,11-epoxide was started since 1997. The separation was performed on a XBridge C18 RP column (3.0 × 150 mm, 5 μm, Waters) using an isocratically elution of mobile phase (water:acetonitrile: methanol:triethylamine, 74:21:5:0.1, v/v) with an analysis time of 15 min. The preparation of samples included liquid-liquid extraction using ether. The accuracy and precision were validated by the FDA rules, and the within-day and between-day precision and accuracy were studied at three concentrations. At tested concentrations, the within-day and between-day recovery was 95.7–109.7% for carbamazepine and 94.1–104.7% for epoxide, and the coefficients of variation were 2.2–8.2% for carbamazepin and 2.2–9.6% for epoxide in serum [28]. In milk, the recovery was 96.3–108.0% for carbamazepine and 97.6–115.0% for epoxide, and the coefficients of variation were 1.0–8.9% for carbamazepine and 1.3–14.8% for epoxide. The method was subject to quality control analyses using the external quality control (EQC) RfB (Bonn, Germany) twice a year. For statistical calculations, half of the concentration of the lower limit of quantification (LLoQ) was used for samples with concentrations less than the LLoQ [12,29]. The value for CBZ is 1.0 mg/L, and that for CBZ-10,11-epoxide is 0.5 mg/L.

Apparent oral clearance (Cl) was calculated for CBZ as follows: Cl (L/kg) = daily dose (mg/kg)/maternal serum CBZ levels (mg/L) [30]. Paired maternal serum, infant serum and milk levels were used for the assessment of the milk/maternal serum level ratio, the infant/maternal serum level ratio and the infant serum/milk level ratio. Paired CBZ and CBZ-10,11-epoxide levels were utilised for the estimation of CBZ-10,11-epoxide/CBZ ratios in milk, maternal serum and infant serum. The influence of combined treatment with enzyme-inducing AEDs and enzyme-inhibition valproic acid was assessed. We also evaluated the relationship among CBZ maternal serum, infant serum, and milk levels.

Statistical analysis was performed using GraphPad Prism version 5.00 for Windows, GraphPad Software (San Diego, CA, USA; www.graphpad.com). The D'Agostino and Pearson omnibus normality test was applied for test if the values come from a Gaussian distribution. Thereafter, we used the unpaired *t-test (when the values follow the Gaussian distribution) or the nonparametric Mann–Whitney test for the comparison of the distributions of two unmatched groups, and the Pearson correlation test (the Gaussian distribution) or the Spearman nonparametric correlation test were used for the correlation analysis. A value of $p < 0.05$ was considered statistically significant.*

3. Results

CBZ levels varied from 1.4 to 10.4 mg/L (median 4.5 mg/L) in maternal serum, from 0.5 to 6.7 mg/L (mean 2.1 mg/L) in breastmilk and from 0.5 to 2.6 mg/L (median 0.5 mg/L) in infant serum. The CBZ-10,11-epoxide levels ranged from 0.3 to 5.4 mg/L (median 0.9 mg/L) in maternal serum, from 0.3 to 3.7 mg/L (median 0.5 mg/L) in breastmilk and from 0.3 to 0.6 mg/L (median 0.3 mg/L) in infant serum. A highly significant correlation between milk and maternal serum levels of CBZ ($p < 0.0001$; Fig. 1a) was found, and boundary significance was observed between infant serum and milk levels of CBZ ($p = 0.0484$; Fig. 1b). No significant correlations were noted between infant serum and maternal serum CBZ levels ($p = 0.7824$; Fig. 1c), daily dose or dose related to maternal body weight. A significant correlation was exclusively found for CBZ-10,11-epoxide with milk and maternal serum levels ($p < 0.0001$; Fig. 2).

The milk/maternal serum level ratio varied from 0.13 to 1.50 (median 0.44) for CBZ and from 0.30 to 3.67 (median 0.63) for CBZ-10,11-epoxide. The infant/maternal serum level ratio was 0.05–0.70 (median 0.17) for CBZ and 0.11–1.00 (median 0.38) for CBZ-10,11-epoxide. The infant serum/milk level ratio was 0.07–1.13 (median 0.42) for CBZ and 0.16–1.00 (median 0.60) for CBZ-10,11-epoxide (Tables 1 and 2). Concomitant administration of enzyme-inducing AEDs significantly increased the maternal apparent oral clearance of CBZ by approximately 130% ($p < 0.0001$; Table 1). Combination treatment with enzyme-inhibiting VPA significantly increased the CBZ-10,11-epoxide/CBZ level ratio in maternal serum ($p = 0.0034$) and milk ($p = 0.002$), see Table 2. Statistical analysis of the influence of enzyme-inducing AEDs on CBZ-10,11-epoxide levels was not assessed because pregnant woman were not treated with this combination after 1997 (when CBZ-10,11-epoxide levels were first measured). In addition, the influence of valproic acid on the maternal apparent oral clearance of CBZ was not assessed given the small number of subjects receiving this combination. Differences in milk levels and the milk/maternal serum level ratio of CBZ compared to combination treatment with phenytoin versus phenobarbital (alone or as a primidone metabolite) are summarised in Table 3.

Greater than half (65%) of the maternal CBZ concentrations were in the therapeutic range of 4.0–12.0 mg/L [31], and 35% were lower. Only 7% of the milk CBZ levels were in the therapeutic range used for the general epileptic population, and 93% were lower. Infant serum level did not reach the lower limit of the therapeutic range used for the general epileptic population (4.0 mg/L), and 65% of infants exhibited values less than the lower limit of quantification (1.0 mg/L). Similarly, 91% of infant serum CBZ-10,11-epoxide levels were less than the lower limit of quantification (0.5 mg/L). Forty-six (58%) patients used CBZ as monotherapy, and 32 (41%) of women were treated in combination with other AED (including primidone metabolised to phenobarbital). In addition, one woman used CBZ in combination with phenytoin + clonazepam.

4. Discussion

This study assessed more than double the number of existing breastfed infants CBZ and its active metabolite CBZ-10,11-epoxide levels

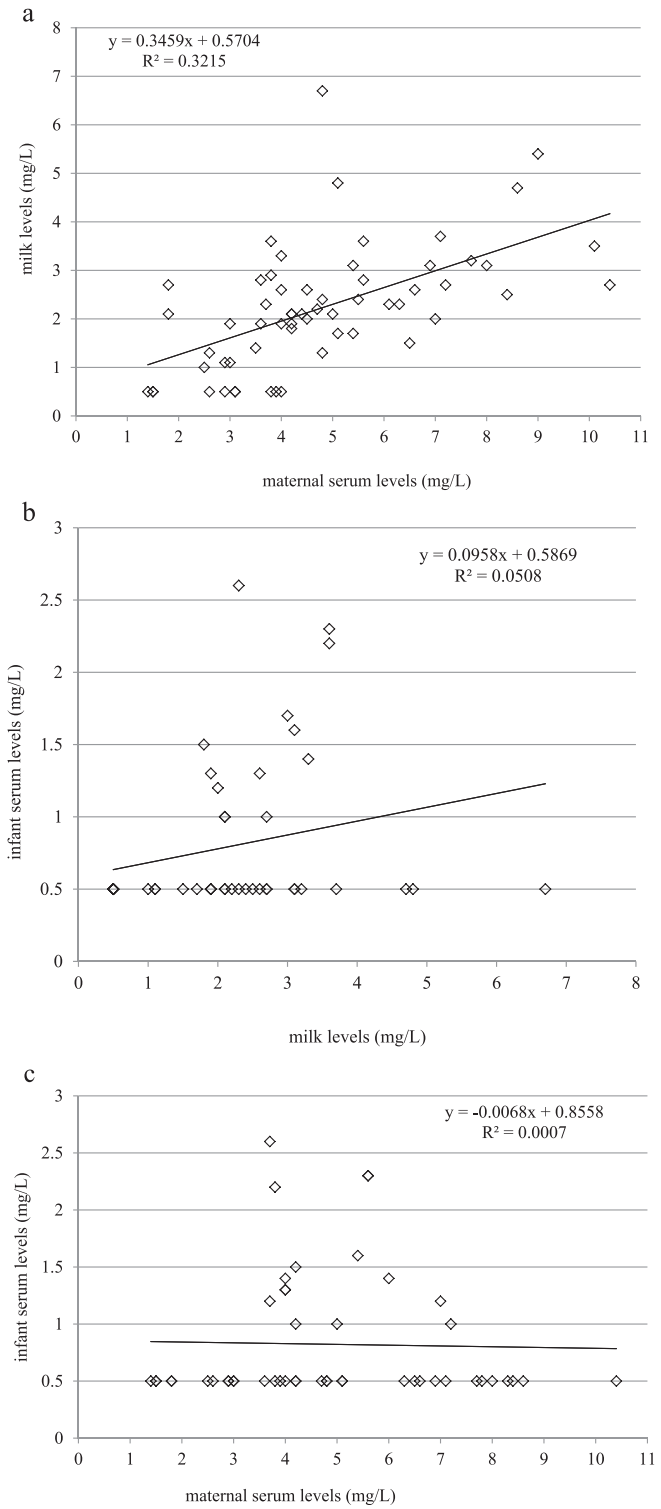

Fig. 1. a. Correlation between milk and maternal serum levels of carbamazepine.
number = 60; coefficient of correlation = 0.6363; $p < 0.0001$, b. Correlation between infant serum and milk levels of carbamazepine; number = 45; coefficient of correlation = 0.2960; $p = 0.0484$, c. Correlation between infant and maternal serum levels of carbamazepine;
number = 49; coefficient of correlation = 0.04049; $p = 0.7824$.

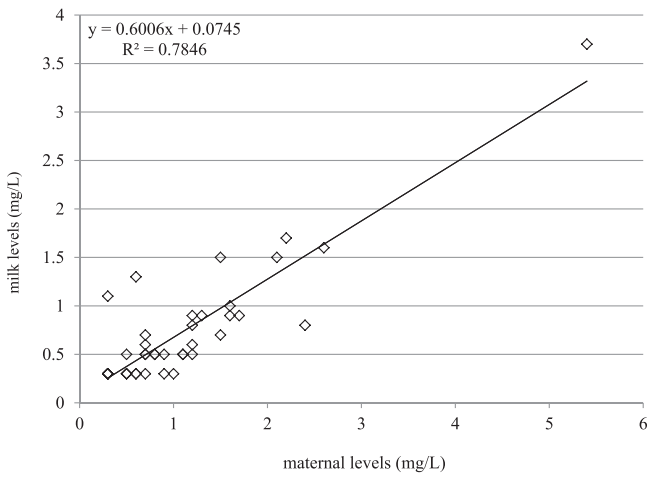

Fig. 2. Correlation between milk and maternal serum levels of carbamazepine-10,11-epoxide; number = 41; coefficient of correlation = 0.7405; $p < 0.0001$.

compared with all patients from previously reported studies altogether [6,12–26]. Highly significant correlations were exclusively found between milk and maternal serum levels of both CBZ and CBZ-10, 11-epoxide. On the other hand, no significant correlations were noted between CBZ infant serum levels and CBZ maternal serum levels, daily dose and dose related to maternal body weight. This result is in contrast to our previous report on lamotrigine treatment during breastfeeding [32]. Infant serum CBZ levels did not reach the lower limit of the therapeutic range used for the general epileptic population, and greater than half of the values were less than the lower limit of quantification. Moreover, most of the infant serum CBZ-10,11-epoxide levels were also lower than the lower limit of quantification. Compared with umbilical cord serum levels, infants experienced less exposure to CBZ during nursing [11].

Combination treatment with enzyme-inhibiting VPA significantly increased CBZ-10,11-epoxide levels in maternal serum and milk but not in infant serum likely due to the lower concentrations of both CBZ and VPA in breastfed infants [33]. Concomitant administration of enzyme-inducing AEDs significantly increased the maternal apparent oral clearance of CBZ by approximately 130%, which greater than that noted during delivery [11]. Furthermore, co-medication with phenytoin markedly decreased CBZ levels in milk. The milk/maternal serum level ratio was comparable to previous studies of CBZ [6,13–22] and CBZ-10, 11-epoxide [14–16,18] and was not affected by combination treatment with enzyme-inducing AEDs or enzyme-inhibiting valproic acid. The infant/maternal serum ratios of both CBZ and CBZ-10,11-epoxide were increased compared with that reported in a recently published study by Birnbaum et al. [12] with 11 women and their breastfed infants. Compared to this study, we collected venous blood samples (not dried blood spots) from breastfed infants who were younger with a median age of 7 days (range 6–29 days) versus a median age of 12 weeks (range 6–17 weeks). Moreover, compared with the study by Birnbaum et al. [12], we analysed CBZ and CBZ-10,11-epoxide milk levels simultaneously. CBZ and CBZ-10,11-epoxide levels were only measured in mothers, milk and breastfed infants in a study by Pynnönen et al. with three cases [18].

Routine therapeutic monitoring of carbamazepine and epoxide serum levels in breastfed infants is not necessary; however, if signs of potential adverse reactions are evident, infant serum concentrations should be measured.

5. Limitations of the study

There are several limitations in this study. We only analysed total CBZ and epoxide levels. However, in a study by Johnson et al. [30], the minimal changes of total and free CBZ and epoxide clearance during

Table 1
Maternal apparent oral clearance (Cl), maternal (M), milk (Mi) and infant (I) serum levels of carbamazepine (CBZ) and their ratios in monotherapy (and/or combination with "neutral" drugs) versus combination treatment with enzyme-inducers or valproic acid (VPA).

CBZ monotherapy + "neutral" drugs	Weight (kg)	Dose (mg/day)	Dose (mg/kg)	Maternal Cl (L/kg)	M (mg/L)	Mi (mg/L)	I (mg/L)	Mi/M ratio	I/M ratio	I/Mi ratio
N	43	37	35	35	44	41	42	40	31	28
median	67	600	8.1	1.52	4.5	2.3	0.5	0.44	0.17	0.38
mean	69	528	8.2	1.61	5.1	2.3	0.9	0.49	0.21	0.44
SD	13	200	3.5	0.66	1.9	1.0	0.6	0.26	0.16	0.29
min	45	200	3.0	0.59	1.8	0.5	0.5	0.13	0.05	0.10
max	100	1000	16.1	3.51	10.4	4.8	2.6	1.50	0.70	1.13
CBZ + inducers										
N	12	12	12	12	12	11	10	11	10	9
median	70	800	10.5	3.45*	3.6	1.0	0.5	0.40	0.15	0.50
mean	69	742	11.3	3.64	3.7	1.8	0.5	0.51	0.19	0.59
SD	14	198	4.2	1.96	2.0	1.9	0.0	0.41	0.10	0.41
min	45	400	6.3	1.38	1.4	0.5	0.5	0.13	0.06	0.07
max	96	1000	20.0	8.68	8.3	6.7	0.5	1.40	0.36	1.00
CBZ + VPA										
N	7	7	5	5	9	9	11	9	8	8
median	75	750	10.1	2.16	5.4	2.5	0.5	0.42	0.17	0.43
mean	80	750	9.8	1.87	5.6	2.5	0.7	0.42	0.18	0.50
SD	16	454	5.2	0.76	2.6	1.5	0.4	0.13	0.10	0.34
min	62	200	4.0	0.72	1.5	0.5	0.5	0.19	0.06	0.16
max	109	1200	17.6	2.67	9.0	5.4	1.6	0.60	0.33	1.00
Total										
N	62	56	52	52	65	61	63	60	49	45
median	69	600	8.6	1.83	4.5	2.1	0.5	0.44	0.17	0.42
mean	70	602	9.1	2.10	4.9	2.2	0.8	0.48	0.20	0.48
SD	14	259	4.0	1.37	2.1	1.3	0.5	0.27	0.14	0.32
min	45	200	3.0	0.59	1.4	0.5	0.5	0.13	0.05	0.07
max	109	1200	20.0	8.68	10.4	6.7	2.6	1.50	0.70	1.13

* $p < 0.0001$ - carbamazepine in monotherapy (and/or combination with "neutral" drugs) versus combination treatment with enzyme-inducers

Table 2
Maternal (M), milk (Mi) and infant (I) serum levels of carbamazepine-10,11- epoxide (EPO); ratio of EPO/carbamazepine (CBZ) levels in maternal serum, milk and infant serum; and ratio of milk/maternal serum level, infant/maternal serum level and infant serum/milk level of EPO in CBZ monotherapy (and/or combination with "neutral" drugs) versus combination with valproic acid (VPA).

CBZ monotherapy + "neutral" drugs:	M (mg/L)	Mi (mg/L)	I (mg/L)	EPO/CBZ ratio - M	EPO/CBZ ratio - Mi	EPO/CBZ ratio – I	Mi/M ratio	I/M ratio	I/Mi ratio
N	36	34	35	36	34	35	33	24	22
median	0.7	0.5	0.3	0.17	0.23	0.46	0.63	0.47	0.66
mean	0.8	0.5	0.3	0.17	0.24	0.42	0.80	0.56	0.73
SD	0.5	0.3	0.1	0.08	0.16	0.22	0.62	0.30	0.27
Min	0.3	0.3	0.3	0.05	0.08	0.12	0.30	0.19	0.27
Max	2.4	1.3	0.6	0.39	1.00	1.00	3.67	1.00	1.00
CBZ + VPA:									
N	8	8	10	8	8	10	8	7	7
median	1.9	1.5	0.3	0.26*	0.43**	0.60	0.70	0.19	0.31
mean	2.2	1.5	0.4	0.49	0.89	0.54	0.69	0.19	0.30
SD	1.4	1.0	0.1	0.43	0.99	0.23	0.17	0.05	0.15
Min	1.2	0.5	0.3	0.14	0.20	0.19	0.42	0.11	0.16
Max	5.4	3.7	0.6	1.29	3.00	1.00	1.00	0.25	0.60
Total:									
N	44	42	45	44	42	45	41	31	29
median	0.9	0.5	0.3	0.18	0.25	0.60	0.63	0.38	0.60
mean	1.1	0.7	0.3	0.23	0.37	0.45	0.78	0.47	0.63
SD	0.9	0.6	0.1	0.23	0.50	0.22	0.56	0.30	0.31
Min	0.3	0.3	0.3	0.05	0.08	0.12	0.30	0.11	0.16
				33					
Max	5.4	3.7	0.6	1.29	3.00	1.00	3.67	1.00	1.00

* $p = 0.0034$,
** $p = 0.002$ - carbamazepine in monotherapy (and/or combination with „neutral" drugs) versus combination with valproic acid

pregnancy do not necessitate measurement of the free fractions. The small numbers of patients on concomitant therapy with valproic acid does not allow assessment of its influence on the maternal apparent oral clearance of CBZ. In addition, statistical analysis of the effect of enzyme-inducing AEDs on CBZ-10,11-epoxide levels was not performed because pregnant women were not treated with this combination after 1997 (when CBZ-10,11-epoxide levels were initially analysed). CBZ levels in combination with enzyme-inducing AEDs were lower than the lower limit of quantification in all infants, and lower levels of CBZ-10, 11-epoxide are probable.

The volume of ingested breast milk, the timing of feedings and information on exclusively breastfeeding in the included infants are not known; however, this study presented a direct analysis of both CBZ and CBZ-10,11-epoxide concentrations in venous blood samples of breastfed infants along with measurements of drug concentrations in both mothers and mature milk. We were not able to demonstrate any relationship

Table 3
Differences in milk (Mi)/maternal (M) serum carbamazepine (CBZ) ratios in relation to combination treatment with phenytoin or primidone (PRM)/phenobarbital (PB); I = infant.

Patient	M (mg/L)	Mi (mg/L)	I (mg/L)	Mi/M ratio	Phenytoin: dose, level (mg/L)	Primidone/phenobarbital: dose, level (mg/L)
1	3.1	0.5	Not done	0.16	400 mg M = 9.1; Mi = 1.7	
2	1.5	0.5	0.5	0.33	400 mg M= 8.9; Mi = 2.6; I = 0.5	
3	4.0	0.5	0.5	0.13	475 mg M= 8.0; Mi = 0.5; I = 0.5	
4	1.4	0.5	0.5	0.36	400 mg M= 11.5; Mi = 5.8; I = 0.5	
5	2.9	0.5	0.5	0.17	400 mg M= 6.0; Mi = 1.8; I = 0.5	
6	1.8	2.1	0.5	1.17	400 mg M = 2.3; Mi = 0.5; I = 0.5	
Median (range)	**2.4 (1.4–4.0)**	**0.5 (0.5–2.1)**	**0.5 (0.5–0.5)**	**0.25 (0.13–1.17)**		
7	5.6	2.8	Not done	0.50		750 mg PRM: M = 5.8; Mi = 5.5 PB: M = 11.5; Mi= 7.4
8	4.8	2.4	0.5	0.50		750 mg PRM: M = 12.4; Mi = 4.7; I = 1.3 PB: M = 11.0; Mi = 3.7; I = 11.3
9	4.2	1.9	0.5	0.45		250 mg PRM: M = 2.0; Mi = 2.7; I = 0.5 PB: M = 3.1; Mi = 1.3; I= 0.8
10	2.5	1.0	0.5	0.40		250 mg PRM: M = 1.9; Mi = 2.0; I = 0.5 PB: M = 4.9; Mi = 1.7; I;= 2.8
11	4.8	6.7	0.5	1.40		50 mg (phenobarbital only) PB: M = 6.8; Mi = 6.9; I = 3.3
Median (range)	**4.8 (2.5–5.6)**	**2.4 (1.0–6.7)**	**0.5 (0.5–0.5)**	**0.50 (0.40–1.40)**		

between CBZ and epoxide levels and clinical effects in mothers or breastfed infants.

However, we hope that these new data from our study provide relevant information for the treatment of epilepsy during breastfeeding and breastfed infants' exposure to both carbamazepine and its active metabolite.

6. Conclusions

Reduced carbamazepine exposure was observed in breastfed infants compared with foetuses. Infant CBZ serum levels did not reach the lower limit of the therapeutic range used for the general epileptic population, and infant serum CBZ-10,11-epoxide levels were lower than the lower limit of quantification in most infants in this study. No correlations were found between infant serum levels of CBZ and maternal serum CBZ concentrations, daily dose or dose related to maternal body weight. A highly significant correlation was exclusively observed between milk and maternal serum levels of both CBZ and CBZ-10,11-epoxide. Combination treatment with enzyme-inhibiting VPA significantly increased CBZ-10,11-epoxide levels in milk and maternal serum but not in breastfed infants.

Routine analysis of CBZ and CBZ-10,11-epoxide serum concentrations in breastfed infants is not compulsory. However, observation of breastfed infants is desirable. If signs of potential adverse reactions are evident, infant serum concentrations should be monitor.

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