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Valproic acid concentrations in nursing mothers, mature milk, and breastfed infants in monotherapy and combination therapy

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ABSTRACT

Valproic acid (VPA) is currently one of the four most often prescribed antiepileptic drugs (AEDs) in pregnancy. However, only a small number of studies have measured suckling infant serum levels of the drug. We studied the transport of VPA from breastfeeding mothers to the mature milk and breastfed infants and the influence of comedication with enzyme-inducing AEDs. The data of 30 nursing women treated by VPA were analyzed retrospectively. Mature milk, maternal, and infant serum levels were collected between the 6th and 32nd postnatal day and measured by gas chromatography during the years 1996–2017.

Valproic acid levels varied from 5.4 to 69.0 mg/L (mean: 39.0 ± 16.1 mg/L) in the maternal serum, from <1.0 to 16.7 mg/L (mean: 1.6 ± 3.9 mg/L) in the milk, and from <1.0 to 17.5 mg/L (mean: 4.2 ± 4.3 mg/L) in the infant serum. The milk/maternal serum level ratio ranged from <0.03 to 0.25 (mean: 0.03 ± 0.06) and the infant/maternal serum level ratio from <0.03 to 0.61 (mean: 0.11 ± 0.13). Sixty-seven percent of milk and 33% of infant VPA concentrations were below the limit of quantification. No correlations were observed between maternal serum and milk levels or between maternal and infant serum levels. In conclusion, none of the milk or infant serum VPA levels reached the lower limit of the reference range used for the general population with epilepsy, so the degree of VPA exposure in breastfed infants is less than during gestation. Nevertheless, if signs of potential adverse reactions manifest, infant serum concentrations should be measured.

1. Introduction

Valproic acid (VPA) is very effective in the treatment of all types of seizures, particularly idiopathic generalized epilepsy, and in the treatment of the manic phase of bipolar disorders. It is currently one of the four most-often prescribed antiepileptic drugs (AEDs) in pregnancy, together with lamotrigine (LTG), carbamazepine (CBZ), and levetiracetam [1,2]. Valproic acid concentrations in cord blood have been reported to be either lower (or the same as) or much higher than maternal concentrations. In an earlier study, we found a wide range of the umbilical cord/maternal serum concentration ratio (mean: 1.46, range: 0.64–2.49) [3]. Valproic acid excretion into breast milk has been described in some studies, and the milk/maternal serum concentration ratio was found to be between 0.007 and 0.10 [4–18]. Nevertheless, only a small number of studies with a small number of probands have measured the infant serum levels, and the data about the risk of VPA exposure to the breastfed infants are limited (Table 1). Wide infant/maternal serum concentration ratios have been reported with the range of 0.01–1.05 [4,6,9,10,13]. However, methodological issues, including different infant ages at the time of sampling and a small number of patients, make these studies incomparable. Breastfeeding during VPA monotherapy does not appear to adversely affect infant growth or development, and breastfed infants were found to have slightly higher intelligence quotients (IQs) and enhanced verbal ability than nonbreastfed infants at 6 years of age in a study by Meador et al. [19]. Breastfed infants are at risk for VPA-induced hepatotoxicity, so they should be monitored for jaundice and other signs of liver damage during maternal VPA therapy [20]. A case of thrombocytopenia has been reported by Stahl et al. [18], so monitoring breastfed infants for unusual bruising or bleeding is also useful. Valproic acid is extensively metabolized in the liver mainly by glucuronidation (UGT1A3 and UGT2B7 isoenzymes), β-oxidation, and hydroxylation (CYP2C9, CYP2C19, CYP2A6, and CYP2B6 isoenzymes). Phenytoin (PHT), primidone (PRM), CBZ, and LTG enhance the metabolism of VPA whereas

Abbreviations: AEDs, antiepileptic drugs; CBZ, carbamazepine; Cl, apparent oral clearance; LTG, lamotrigine; PHT, phenytoin; PRM, primidone; VPA, valproic acid; IQs, intelligence quotients.

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Table 1
Review of literature (N_1 = number of mothers, N_2 = number of breastfed infants, M = maternal, Mi = milk, I = infant) [4–18].

Reference	N_1	Postpartum time	Maternal dose	M (mg/L)	Mi (mg/L)	Mi/M ratio	N_2	I (mg/L)	I/M ratio
[4]	16	4.3 ± 1.1 days (range: 3–6 days)	22.1 ± 7.0 mg/kg/day (range: 14.5–32.7)	36.4 ± 14.0 (range: 18.6–66.5)	1.8 ± 1.0 (range: 0.4–3.9)	0.05 ± 0.03 (range: 0.01–0.10)	5	<1.0–13.4	<0.04–0.40
[5]	13	Up to 12th week	18.4 ± 7.2 mg/kg/day			0.025 ± 0.01			
[6]	6	4–19 weeks	750–1000 mg/day	39.4–79.0			6	0.7–1.5	0.01–0.02
[7]	6	3–82 days	9.5–31.0 mg/kg/day	4.7–102.2	0.034–5.4	0.027 ± 0.015 (range: 0.0071–0.052)	2	0.50–0.55	
[8]	5			30.5–55.3	0.4–3.9	Median 0.03 (range: 0.01–0.07)	1	4.4	
							1	Undetectable	
[9]	4	1st–3rd months	1200–1500 mg/day			0.05–0.10	1		0.08
[10]	4	1st week	1200–1800 mg/day	Average: 49.0 (range: 38.9–56.0)	Average: 1.8 (range: 1.0–3.8)	Average: 0.04 (range: 0.02–0.08)	3	Average: 28.3 (range: 13.0–41.0)	Average: 0.62 (range: 0.25–1.05)
[11][a]	1	1.9 weeks	500 mg/day				1	<0.0035	
	1	4.1 weeks	500 mg/day				1	<0.005	
[12][a]	1	6-17 days	1000 mg/day		1.4–3.0				
	1	1–43 days	1400 mg/day		1.4–3.5	0.02–0.03			
[13][a]	1	1 month	750 mg/day	65.0			1	4.0	0.06
	1	3 months	500 mg/day	67.0			1	1.0	0.015
[14][b]	1	62 h	500 mg/day	9.9	0.18	0.02			
		130 h		34.3	0.46	0.01			
[15][b]	1	5 days	1600 mg/day		7.2	0.05–0.10	1	7.5	
		29 days			3.0			Undetectable	
[16]	1	2 months	600 mg/day	14.9–34.3	<0.4–2.0	<0.02–0.06	1	<0.4–2.0	
[17]	1	2nd week	2400 mg/day	100.0	7.0	0.07			
[18]	1	3 months	1200 mg/day				1	6.6	

[a] Two different mothers.
[b] One mother in two different times.

clonazepam does not affect its pharmacokinetics [21]. The influence of a combination with enzyme-inducing AEDs to VPA pharmacokinetic during breastfeeding has not yet been studied. In our study, the transport of VPA from breastfeeding mothers to the mature milk and their breastfed infants was studied. Milk, maternal, and infant serum levels, its ratio, the maternal oral clearance of VPA, and the influence of comedication with enzyme-inducing AEDs (PHT, PRM, CBZ) were analyzed.

2. Material and methods

2.1. Study population

This study comprised the data of 30 nursing women (27 ± 5 years old) with epilepsy who were treated with VPA in monotherapy (or in combination with clonazepam) or comedicated with enzyme-inducing

Table 2
Dosage, maternal apparent oral clearance (Cl), valproic acid (VPA) milk (Mi), maternal (M) serum, and infant (I) serum levels in monotherapy and/or combination with neutral drugs versus combination with lamotrigine (LTG) or enzyme-inducing antiepileptic drugs in our cohort of patients (in three cases, only infant levels were asked).

	Weight (kg)	Dose (mg/day)	Dose (mg/kg)	Cl (L/kg)	M (mg/L)	Mi (mg/L)	I (mg/L)	Mi/M ratio	I/M ratio
VPA monotherapy									
Number	17	16	16	16	17	16	18	16	14
Median	68	900	11.6	0.29	38.2	<1.0	2.7	<0.03	0.09
Mean	71	797	11.3	0.39	37.4	1.6	3.7	0.03	0.10
SD	13	225	3.4	0.30	16.6	3.3	3.6	0.06	0.08
Min	53	300	3.6	0.18	5.4	<1.0	<1.0	<0.03	<0.03
Max	95	1050	16.1	1.40	65.3	13.3	11.6	0.25	0.22
VPA + LTG									
Number	3	3	3	3	3	2	4	2	3
Median	63	750	11.9	0.27	47.3		5.6		0.14
Mean	63	700	11.2	0.28	44.8		4.5		0.12
SD	5	87	2.1	0.12	13.6		3.1		0.11
Min	58	600	8.8	0.16	30.1	<1.0	<1.0		<0.14
Max	68	750	12.9	0.40	56.9	<1.0	6.6		0.21
VPA + inducers									
Number	9	10	9	9	10	10	11	10	9
Median	75	1000	16.1	0.35	43.9	<1.0	3.3	<0.04	0.08
Mean	78	1080	14.6	0.38	39.8	2.1	5.1	0.04	0.14
SD	15	520	5.3	0.19	17.1	5.2	5.9	0.08	0.20
Min	62	500	5.7	0.19	17.0	<1.0	<1.0	<0.04	<0.04
Max	109	2250	20.6	0.81	69.0	16.7	17.5	0.24	0.61
Total									
Number	29	29	28	28	30	28	33	28	26
Median	68	900	11.9	0.30	41.4	<1.0	3.1	<0.03	0.09
Mean	72	885	12.3	0.37	39.0	1.6	4.2	0.03	0.11
SD	14	369	4.2	0.25	16.1	3.9	4.3	0.06	0.13
Min	53	300	3.6	0.16	5.4	<1.0	<1.0	<0.03	<0.03
Max	109	2250	20.6	1.40	69.0	16.7	17.5	0.25	0.61

SD = standard deviation.

AEDs (PHT, PRM, and CBZ), and/or LTG, retrospectively. Mature milk, maternal, and infant serum levels were collected between the sixth and 32nd postnatal day (median: 7 days, most samples were taken in the morning before the first dose) and measured in our department between the years of 1996 and 2017. Measurement of breast milk in the first 3–5 days postpartum can be misleading, as its content is primarily colostrum. By the end of the first week, the milk is mature [22]. Request forms for routine therapeutic drug monitoring were used as the data source. The treatment details are summarized in Table 2.

2.2. Laboratory measurements

Total serum and milk levels of VPA were measured by gas chromatography using a gas chromatograph (Chrom 5, Czech Republic) with a glass-packed column 1200 × 3 mm filled with 10% SP-1000 on 80/100 Supelcoport (Supelco, USA). To caprylic acid (internal standard) in Eppendorf vials 50 μL of serum, 50 μL acetone and a small amount (approximately 30 mg) of solid ammonium sulfate were added and vortex-mixed. After centrifugation, 2 μL of the acetone layer was injected directly on column for analysis using flame ionisation detection. Performance characteristics of the method were as follows: linearity was found between 5 and 125 mg/L, both for blood and milk. The accuracy and precision were validated by U.S. Food and Drug Administration rules; the within-day and between-day precision and accuracy were studied at three concentration levels in both matrices. At tested concentrations, recovery in blood was between 97.2 and 103.5, the coefficient of variations were 3.5–5.5%, recovery in milk was 90.8–99.1%, and the coefficient of variations was 3.4–6.1%, respectively. The limit of quantification was estimated as 1.0 mg/L. The method was quality controlled in external quality control (EQC) RfB (Bonn, Germany) twice a year [3].

2.3. Data analysis

Apparent oral clearance (Cl) was calculated for VPA: Cl (L/kg) = daily dose (mg/kg) / maternal serum VPA concentration (mg/L) [23]. Paired maternal serum, infant serum, and milk levels of VPA were used for the assessment of the ratio of milk/maternal serum and infant/maternal serum levels. Statistical analysis was carried out with GraphPad Prism version 5.00 for Windows, GraphPad Software (San Diego, CA, USA; www.graphpad.com). We used the D'Agostino and Pearson omnibus test for normality. The unpaired t-test or Mann–Whitney U test for comparison of distributions of two unmatched groups and the Pearson correlation test or the Spearman nonparametric correlation test were used for the correlation analysis. A p value of <0.05 was considered statistically significant. The study was appropriately reviewed and approved by the local Ethics Committee.

3. Results

Valproic acid levels varied from 5.4 to 69.0 mg/L (mean: 39.0 ± 16.1 mg/L) in the maternal serum, from <1.0 to 16.7 mg/L (mean: 1.6 ± 3.9 mg/L) in the milk, and from <1.0 to 17.5 mg/L (mean: 4.2 ± 4.3 mg/L) in the infant serum. The milk/maternal serum level ratio ranged between <0.03 and 0.25 (mean: 0.03 ± 0.06) and the infant/maternal serum level ratio from <0.03 to 0.61 (mean: 0.11 ± 0.13) — see Table 2. No correlations were observed between maternal serum and milk levels or between maternal and infant serum levels (Fig. 1). No significant differences were manifested for maternal daily dose, dose related to the maternal body weight, maternal Cl, milk, maternal, or infant serum VPA concentrations, milk/maternal serum level ratio, and infant/maternal serum level ratio between the two groups (VPA monotherapy versus VPA combination with CBZ, PHT, and/or PRM). Slightly less than a quarter (23%) of maternal VPA concentrations was analyzed in the reference range of 50–100 mg/L, and 77% were lower. Sixty-seven percent of milk and 33% of infant VPA concentrations were below the limit of quantification. None of the milk or infant serum VPA levels reached the lower limit of the reference range used for the population with epilepsy [24]. Valproic acid monotherapy was prescribed in 51% of women, and 46% of the patients used bicombinations with CBZ, PHT, PRM, LTG, or clonazepam; 3% (1 woman) had a triple combination with VPA, LTG, and topiramate.

4. Discussion

4.1. General discussion

The number of nursing mothers receiving VPA therapy was greater in our group (from one center using the same methodology) than in

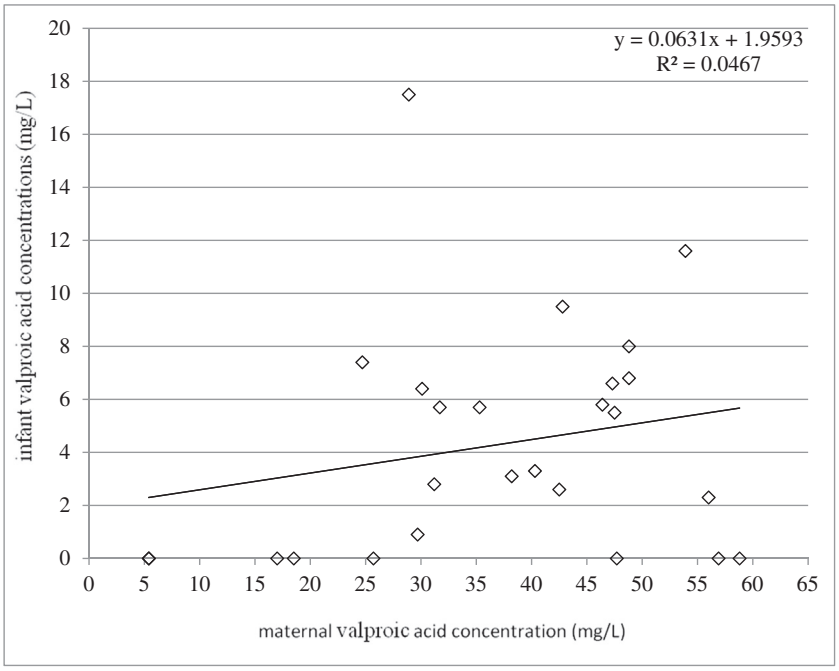

Fig. 1. Correlation between infant and maternal serum levels of valproic acid (number = 26; coefficient of correlation = 0.2176; p = 0.2856).

all reported studies using varied and incomparable criteria. Moreover, we analyzed a larger number of infant serum concentrations than in all previous studies put together [4–18]. We observed no significant differences in maternal daily dose, dose related to maternal body weight, maternal Cl, milk, maternal, or infant serum VPA concentrations, milk/maternal serum level ratios, and infant/maternal serum level ratio between the two groups (VPA monotherapy versus combination with CBZ, PHT, or PRM). By contrast, concomitant medication with this enzyme inducer significantly increased the maternal Cl of VPA at delivery by about 30% [3]. No correlations were observed between maternal serum and milk levels or between maternal and infant serum levels. In previous studies, the milk/maternal serum concentration ratio was reported to be between 0.007 and 0.10 [4,5,7–10,12,14–17]. We observed a slightly wider range of this ratio (<0.03–0.25) and only 7% of the milk levels (13.3 mg/L and 16.7 mg/L, respectively) higher than the highest previously reported milk level (7.2 mg/L) [15]. The infant/maternal serum level ratio (range: <0.03–0.61) was similar to an earlier reported wide range of 0.01–1.05 [4,6,9,10,13]. None of the infant serum VPA levels were higher than the highest previously reported infant level of 41.0 mg/L [10]. Our results cannot be compared with published studies, owing to factors such as different infant ages at the time of sampling and a small patient sampling used in these studies. Given the retrospective nature of our study, we are unable to evaluate the milk time gradient over 24 h. However, the results of the LTG studies of Ohman et al. [25] and Newport et al. [26] showed that the time gradient is probably not a reason for the interindividual variability in the milk/maternal serum level ratio. Breastfed infant exposure to AEDs in milk varies, depending on multiple factors: maternal serum drug concentration, the milk/maternal serum level ratio, the milk volume ingested by the infant, and the absorption, metabolism, and excretion of the drug in the infant [27]. A higher infant/maternal serum level ratio can produce higher exposure of breastfed infants to VPA, indicating a possible higher risk of adverse effects. Nevertheless, the degree of VPA exposure in breastfed infants is still likely to be less than during gestation [27]. We found infant serum VPA concentrations of 4.2 ± 4.3 mg/L, which was about ten times lower than umbilical cord concentrations during delivery, as described in our previous paper [3]. None of the infant serum VPA levels in our group reached the lower limit of the reference range, contrary to our LTG study in which 16% of infant's serum levels were measured in the reference range used for the general population with epilepsy [28]. Therapeutic monitoring of breastfed infant serum VPA levels is not mandatory; however, if signs of potential adverse reactions are noted, infant serum concentrations should be monitored [27].

4.2. Limitations of the study

Lower VPA total daily dose in all three groups resulted in lower maternal VPA levels. In turn, this resulted in many instances of undetectable VPA levels in milk and infant serum. Perhaps the low VPA doses/low levels are due to the nature of the type of seizure being treated, where clinicians believe that patients with generalized epilepsy syndromes seem to respond to lower VPA level whereas medically refractory focal seizures require much higher VPA concentration to control both their focal and secondarily generalized seizures [29]. The variability (% coefficient of variation) in maternal serum, infant serum, and milk VPA levels is very high; more patients need to be studied in a much more frequent and structured fashion. We were not informed about any adverse effects in breastfed mothers in our cohort using the request forms for routine therapeutic drug monitoring as the data source. Unfortunately, we did not follow up adverse effects in infants.

5. Conclusions

This paper retrospectively determines VPA levels in mother's serum, human milk, and suckling infant serum over a 20-year period. No correlations were observed between maternal serum and milk levels or between maternal and infant serum levels. By contrast of delivery, a combination with enzyme-inducing AEDs did not increase the maternal Cl of VPA during the first postpartum month. Although a wide range of the infant/maternal serum level ratio was observed, the milk and infant serum concentrations of VPA were small, and none of the infant serum VPA levels reached the lower limit of the reference range used for the general population with epilepsy. However, if signs of potentially adverse reactions are noted, infant serum concentrations should be measured, but it is not necessary to do this routinely.

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Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

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