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Pharmacokinetics of Gabapentin during Delivery, in the Neonatal Period, and Lactation: Does a Fetal Accumulation Occur during Pregnancy?

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Summary: *Purpose*: To study the pharmacokinetics of gabapentin (GBP) during delivery, lactation, and in the neonatal period.

Methods: GBP concentrations in plasma and breast milk were determined with high-performance liquid chromatography in samples from six women treated with GBP and in their offspring. Blood samples were obtained at delivery from mothers, from the umbilical cord, and from the newborns on three occasions during 2 days after delivery. GBP concentration also was determined in breast milk and in blood collected from five of the mothers and suckling infants 2 weeks to 3 months after birth.

Results: The umbilical cord/maternal plasma concentration ratios ranged from 1.3 to 2.1 (mean, 1.7). GBP plasma concentrations in the neonates declined with an estimated half-life of 14 h. Mean GBP plasma concentrations in the infants were 27% of the cord plasma levels (range, 12–36%) 24 h postpartum. The mean milk/maternal plasma concentration ratio was 1.0 (range, 0.7–1.3) from 2 weeks to 3 months. The infant dose of GBP was estimated to 0.2–1.3 mg/kg/day, equivalent to 1.3–3.8% of the weight-normalized dose received by the mother. The plasma concentrations in the breast-fed infants were ∼12% of the mother's plasma levels, but no adverse effects were observed.

Conclusions: Our limited observations suggest an active transplacental transport of GBP, with accumulation in the fetus as a consequence. We suggest that this could be by the specific L-type amino acid transporter 1 (LAT-1), which is expressed in the placenta. Newborns seem to have a slightly lower capacity to eliminate GBP than do adults. Transfer of GBP to breast milk is extensive, but plasma concentrations appear to be low in suckling infants. No adverse effects were observed in the newborn. Although more data are needed, our observations suggest that breastfeeding in conjunction with GBP treatment is safe.
Key Words: Epilepsy—Pregnancy—Gabapentin—Placenta—Pharmacokinetics—Breast milk.

Gabapentin (GBP) is widely used in the treatment of neuropathic pain syndromes and partial seizures. GBP is a γ-aminobutyric acid (GABA) analog that differs both structurally and pharmacologically from other classes of antiepileptic drugs (AEDs). The drug is rapidly absorbed from the gastrointestinal tract by amino acid–transport system L (System L) (1,2). Bioavailability is dose dependent, probably because of saturation of the transporter capacity (2). The plasma protein binding is <3%, and the volume of distribution, 0.9 L/kg. GBP is not metabolized and is excreted unchanged by the kidneys. The elimination half-life is ∼5 to 9 h after a single oral dose and is independent of the dose; the elimination rate is proportional to creatinine clearance (3). Despite the widespread use of GBP, information is scarce on its pharmacokinetics during pregnancy, the neonatal period, and breastfeeding. We are aware of only one relevant unpublished study on healthy subjects conducted by the manufacturer, quoted in a review article (4). After single oral doses of 400 mg of GBP to five healthy women, the mean (±SD) milk/maternal plasma GBP concentrations ratio was estimated to 0.7 (±0.1).

Clearly, more pharmacokinetic data from delivery and lactation are needed to permit a rational use of GBP during this very vulnerable period of life of the offspring. We therefore report data on transplacental transfer, serum concentrations in the newborn, distribution in breast milk, and drug concentrations in the nursed infant from six mother–child pairs in which the mother was prescribed GBP for the treatment of epilepsy or pain disorders.

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TABLE 1. *Characteristics of women treated with gabapentin during pregnancy and of their newborns*

Patient number	Age (yr) at delivery	Indication for treatment	Concomitant antiepileptic drugs (mg/day)	Other medications	Gestational age at birth (wk)	Birth weight (g)	Apgar scores (at 1 and 5 min)	Day after birth when nursing was commenced
1	22	Epilepsy	Carbamazepine (1,200) Lamotrigine (625)	Folic acid Vitamin B_{12}	40 + 0	3,665	9–10	[a]
2	29	Pain syndrome	None	Ketobemidone Enoxaparin sodium Propoxyphene	33	2,030	8–10	7
3	25	Epilepsy	None	Prednisolone Phenylpropanolamine Calcium Ferrous sulfate	39 + 4	4,060	9–10	1
4	26	Pain syndrome	None	Folic acid Acetaminophen Ferrous sulfate Nitrofurantoin	41 + 3	2,930	9–10	1
5	42	Epilepsy	Topiramate (125) Lorazepam (2)	None	39 + 5	3,735	9–10	1
6	29	Epilepsy	Clonazepam (2)	None	42 + 0	3,740	9–10	1

[a] Breastfeeding from 11 h to day 7.

SUBJECTS AND METHODS

This study comprised six women receiving GBP treatment during pregnancy and lactation (their characteristics are summarized in Table 1). Although one had a premature delivery at gestational week 33, all women had uneventful deliveries and gave birth to healthy children. In one infant (of patient 3), mild hypotonia and cyanosis developed 8 hours after birth, but the infant was discharged from hospital after 4 days in a completely normal state. Five of the mother–infant pairs were studied both at delivery and during lactation; one contributed data from delivery only.

Blood samples from mothers and from the umbilical cords were collected at delivery. Blood samples also were obtained from the newborns on three occasions during the first 2 days after birth. Blood and breast milk were collected from mothers 2 to 3 weeks and, in one patient, 3 months postpartum. A sample was drawn from the mothers before the morning dose, ~10–15 h after the last GBP dose to the mother. A sample of the milk was taken at the same time. After completion of breastfeeding, a blood sample was drawn from the infant. The mothers were then allowed to take the morning dose of GBP.

GBP concentrations in plasma and breast milk were determined by isocratic reversed-phase high-performance liquid chromatography (RP-HPLC) with fluorometric detection (excitation, 350 nm; emission, 397 nm). This method is used in our therapeutic drug monitoring (TDM) laboratory and is a modified method after Löscher et al. and Forrest et al. (5,6). The method involves precipitation of plasma proteins with acetonitrile and the use of *o*-phthaldialdehyde (OPA) to convert the analytes to stable fluorescent complexes. With this method, the range of quantification is 4–150 μM, and the limit of detection 0.7 μM. The between-day CV is <8.

The Institutional Review Board approved the study, and the mothers gave their informed consent.

RESULTS

Maternal and umbilical cord GBP plasma concentrations at delivery and plasma levels in the infants ≤48 h

TABLE 2. *Maternal and infant gabapentin concentrations at delivery and postpartum*

		Gabapentin concentrations (μM)						
Patient number	Gabapentin dose (mg/day)	Maternal plasma at delivery	Umbilical cord blood	Infant plasma				
				6 h after birth	12 h after birth	24 h after birth	36 h after birth	48 h after birth
1	1,200	30	51[a]	39	27	17		
2	3,200	—[b]	61		42	22		5
3	900	30	53	40	26	13		
4	2,100	18	38		23	11		1.3[c]
5	1,800	40	52		19	6	2[c]	
6	1,800	42	77		36	20	9	

[a] Umbilical cord sample was missing but concentration is estimated by extrapolation based on postnatal infant plasma levels.
[b] Data missing.
[c] The levels are above the limit of detection, 0.7 μM, but below the range of quantification, 4 μM.

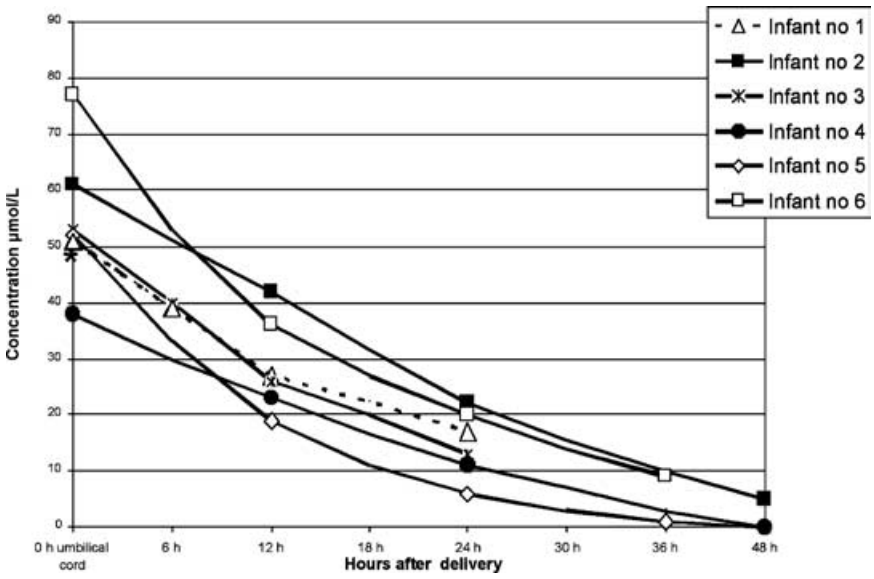

FIG 1. Gabapentin plasma concentrations in cord blood and in the neonates. The cord sample (∗) was missing in patient 1, and the plasma concentration is estimated by extrapolation based on postnatal infant plasma levels.

after birth are given in Table 2. At delivery, the umbilical-to-maternal GBP plasma concentration ratios ranged from 1.3 to 2.11 (mean, 1.74). GBP concentrations in the neonates thereafter declined rather rapidly to, on average, 27% of the cord plasma levels (range, 12–36%) at 24 h postpartum. The elimination half-life in the neonates was estimated to be ∼14 h. Data for calculation of cord/maternal plasma ratio was incomplete in two cases, in one due to missing maternal plasma concentration and in the second because of missing cord blood. In the latter case, the umbilical cord plasma concentration was estimated to be 51 μM by extrapolation from the infant's serum concentrations (shown in Fig. 1).

GBP concentrations in breast milk and simultaneous plasma concentrations in the mothers and nursed infants were available from five mother–infant pairs and are presented in Table 3. From 2 weeks to 3 months after delivery the mean milk/maternal plasma GBP ratio for sampling before nursing was 1.0 (range, 0.7–1.3). Assuming a daily milk intake of 150 ml/day/kg, the relative infant dose of GBP was estimated to be 0.2–1.3 mg/kg/day, which is equivalent to 1.3–3.8% of the weight-normalized dose received by the mother. At 2 to 3 weeks after delivery, two of the breast-fed infant had detectable concentrations of GBP, 1.3 and 1.5 μM, respectively (under the normal range of quantification of <4 μM), and one had an undetectable concentration. The levels of GBP in a plasma sample collected after 3 months of breastfeeding in another infant was 1.9 μM. The concentrations in the breast-fed infants were <12% of the mother's plasma levels and <5% of concentrations measured in the umbilical blood. No adverse effects were reported.

DISCUSSION

This study is based on data from our first six mother–child pairs. Although this small sample calls for caution

TABLE 3. *Gabapentin concentrations and milk/plasma concentration ratios at time of breastfeeding*

Patient number	Gabapentin dose (mg/day)	Time of sampling (days after delivery)	Gabapentin concentration (μM)			Ratios	
			Mother's plasma before nursing	Breast milk before nursing	Infant's plasma concentration after completion of nursing	Milk/maternal plasma gabapentin concentration	Infant/maternal plasma gabapentin concentration
1	1,200	12	10	7	[a]	0.7	
2	2,100	97	45	51	1.9[b]	0.8	0.04
4	600	21	11	11	1.3[b]	1.0	0.12
5	1,800	16	22	29	1.5[b]	1.3	0.07
6	1,800	14	27	34	[c]	1.3	

[a]No breastfeeding.
[b]The levels are above the limit of detection, 0.7 μM, but below the range of quantification, 4 μM.
[c]The level is below detection

in the interpretation, the consistency in the observations allow us to draw some interesting conclusions.

First, the observations of an umbilical cord/maternal plasma concentration ratio close to 2 indicate active transplacental transport of GBP. GBP crosses several membrane barriers in the body by System L. System L transports large neutral amino acids in a Na^+-independent manner. The L-type amino acid transporter 1 (LAT-1) is a transport protein belonging to this system, which in addition to GBP, transports amino acid–related compounds such as L-dopa, triiodothyronine, and thyroxine (7). LAT-1 is expressed the placenta, in the brain, small intestine, spleen, testis, and in fetal liver (1,8,9). As it is expressed in the placenta, we propose that LAT-1 is likely to be responsible for the facilitation of the transfer of GBP over the placenta. This would explain the apparent accumulation of GBP on the fetal side of the placenta. Our observations also suggest that the fetus is exposed to higher levels of GBP than the maternal plasma concentrations during pregnancy might indicate. The potential consequences of such exposure are unclear. Little is known about pregnancy outcome of women taking GBP during pregnancy. The only published study systematically addressing this issue reported 16 retrospectively or prospectively enrolled women taking GBP as monotherapy from the onset of pregnancy. One pregnancy resulted in an infant born with one kidney, whereas outcome was normal in the others (10).

It is tempting to speculate further on the possible implications of an active transport of GBP over the placenta, mediated by LAT-1. As this transporter protein appears to be saturable, GBP might theoretically compete with other substances, such as amino acids and thyroid hormones, transported to the fetus through the same mechanism. Whether such interactions can take place and what the consequences might be is unclear, and this was not investigated in our study.

Second, with an estimated plasma half-life of 14 h, the newborns seem to have a lower capacity to eliminate GBP than do adults. The elimination half-life among adults is normally 5–7 h. This discrepancy is expected, as GBP is eliminated mainly unchanged through the kidneys, and kidney function not fully developed in neonates (11).

Third, the passage of GBP into breast milk was extensive, with GBP concentrations in the milk about equal to those of the women's plasma GBP. The relative infant dose of GBP was estimated to be 0.2–1.3 mg/kg/day, which is equivalent to 1.3–3.8% of the weight-normalized dose received by the mother. These figures represent the minimum exposure, because the sampling was done before maternal intake of the morning dose of GBP. Nevertheless, the measured GBP plasma concentrations were low if at all detectable in all the suckling infants, and no adverse effects were reported. Plasma GBP plasma concentrations in the breast-fed infants were <5% of the plasma levels in cord blood. Exposure during fetal life is hence much higher than that during nursing.

In conclusion, our limited data demonstrate extensive passage of GBP into breast milk, but the low serum concentrations in the nursed infant and the lack of adverse effects indicate that breastfeeding in most cases is safe. It is, however, advisable to monitor nursed infants of mothers treated with GBP for potential adverse effects until more experience has been gained. Our observation of accumulation of GBP in the fetal compartment warrants further studies, which should include investigations of placental transfer of other drugs that are substrates for LAT-1.

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