Epilepsia, **43**(10):1157–1160, 2002
Blackwell Publishing, Inc.

Topiramate Kinetics during Delivery, Lactation, and in the Neonate: Preliminary Observations

*Inger Öhman, *Sigurd Vitols, †Gerhard Luef, ‡Birgitta Söderfeldt, and §Torbjörn Tomson

*Departments of *Internal Medicine, Division of Clinical Pharmacology and §Clinical Neuroscience, Karolinska Hospital, and ‡Department of Neuroscience and Locomotion, Linköping University, Stockholm and Linköping, Sweden; and †Department of Neurology, University of Innsbruck, Austria*

Summary: *Purpose:* To study the pharmacokinetics of topiramate (TPM) during delivery, lactation, and in the neonate.

Methods: TPM concentrations in plasma and breast milk were measured with fluorescence polarization immunoassay (FPIA) in five women with epilepsy treated with TPM during pregnancy and lactation. Blood samples were obtained at delivery from mothers, from the umbilical cord, and from the newborns on three occasions (24, 48, and 72 h) after delivery. Blood and breast milk also were collected from mothers 2 weeks, and 1 and 3 months postpartum. Blood samples also were drawn from the infants during breast-feeding. Three of the mother–infant pairs were studied both at delivery and during lactation; two contributed with data from delivery only.

Results: The umbilical cord plasma/maternal plasma ratios were close to unity, suggesting extensive transplacental transfer of TPM. The mean milk/maternal plasma concentration ratio was 0.86 (range, 0.67–1.1) at 2–3 weeks after delivery. The milk/maternal plasma concentration ratios at sampling 1 and 3 months after delivery were similar (0.86 and 0.69, respectively). Two to 3 weeks after delivery, two of the breast-fed infants had detectable (>0.9 μM) concentrations of TPM, although below the limit of quantification (2.8 μM), and one had an undetectable concentration.

Conclusions: Our limited data suggest free passage of TPM over the placenta and an extensive transfer into breast milk. Breast-fed infants had very low TPM concentrations, and no adverse effects were observed in the infants. **Key Words:** Epilepsy—Pregnancy—Topiramate—Pharmacokinetics—Breast milk.

An increasing number of women of childbearing age are treated with the new antiepileptic drug (AED) topiramate (TPM), resulting in more pregnant women being exposed to the drug. Information on the pharmacokinetics during pregnancy and breast-feeding is a prerequisite for the optimal use of a drug in such situations. For TPM, however, such data have been lacking.

TPM, which currently is approved as adjunctive therapy for the treatment of partial seizures, differs both structurally and pharmacologically from other classes of AEDs. TPM is a sulfamate-substituted monosaccharide D-fructose derivative. After oral administration, the absorption of TPM is rapid, and the bioavailability high (1,2). TPM has a low level of protein binding (9–17%), and its volume of distribution is 0.6 to 0.8 L/kg (1,3). The major route of elimination is renal. A small proportion is metabolized by hydrolysis, hydroxylation, and glucuronidation. The proportion metabolized increases markedly in patients concomitantly treated with enzyme-inducing AEDs (3).

Considering the growing number of women taking TPM while pregnant, this study set out to provide information on transplacental transfer of TPM, serum concentrations in the newborn, distribution in breast milk, and drug concentrations in the nursed infant. In view of the total lack of information at present, we considered it reasonable to publish preliminary observations based on our first five mother–child pairs.

SUBJECTS AND METHODS

Five women receiving TPM treatment during pregnancy and lactation were studied (their characteristics are given in Table 1). All women had uneventful deliveries and gave birth to healthy children (no malformations were observed), although one of the women had a premature delivery at gestational week 36. Three of the mother–infant pairs were studied both at delivery and during lactation; two contributed with data from delivery only.

Accepted May 8, 2002.
Address correspondence and reprint requests to Dr. I. Öhman at Department of Clinical Pharmacology, Karolinska Hospital, S-171 76 Stockholm, Sweden. E-mail: inger.ohman@ks.se

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

Patient number	Age (yr) at delivery	Type of epilepsy	Concomitant antiepileptic drugs (mg/day)	Other medications	Gestational age at birth (wk)	Birth weight (g)	Day after birth when nursing was commenced	Smoking status during pregnancy
1	22	Generalized	Carbamazepine (800)	Folic acid, flunitrazepam o.d.	41	3,520	First	No
2	23	Undetermined	Valproic acid (2,100)	—	39	3,855	First	No
3	25	Undetermined	Carbamazepine (800)	—	36	3,550	[a]	No
4	26	Partial	Carbamazepine (1,200)	Folic acid	41.5	3,160	Third	Yes, 6 cig/day
5	24	Partial	Carbamazepine (1,200)	Folic acid	39.5	2,720	[a]	Yes, 10 cig/day

[a] No breast-feeding.

Blood samples from the mothers and from the umbilical cords were collected at delivery. Capillary blood samples also were obtained by heel prick from the newborns on three occasions (24, 48, and 72 h) after delivery. Three mother–infant pairs were studied during lactation, 2–3 weeks after delivery. Two of those also contributed with data 1 month and 3 months after delivery, respectively.

After 2–3 weeks, when breast-feeding was established, a blood sample was drawn from the mothers and the infants before the morning dose, ~10–15 h after the last TPM dose to the mother. A sample of the milk also was taken at the same time. After completion of breast-feeding, the sampling procedure was repeated. The mothers were then allowed to take the morning dose of TPM.

TPM concentrations in plasma and breast milk were measured with fluorescence polarization immunoassay (FPIA) (4–7). With this method, the range of quantification is 2.8–94 μ*M,* and the limit of detection, 0.9 μ*M*. The between-day coefficient of variation (CV) is 10% at 2.8 μ*M* and 6.3% at 72.3 μ*M,* and the within-run CV, 0.5% at 2.8 μ*M* and 1.2% at 72.3 μ*M*. In the range 1.2–2.8 μ*M,* the CV is 20–25%.

Method validation also includes measurement of TPM in breast milk.

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

RESULTS

Maternal and umbilical cord TPM plasma concentrations at delivery and plasma levels in the infants up to 72 h after birth are given in Table 2. At delivery, the umbilical/maternal TPM plasma concentration ratios ranged from 0.85 to 1.06 (mean, 0.95). TPM plasma levels in the newborn declined rather rapidly. At 24 h, three of the infants with concentrations in the range of quantification had a mean of 40% (range, 33–45%) lower TPM levels than those in the umbilical cord. At 48 h postpartum, TPM plasma levels were undetectable in two of the infants, and three had detectable levels (mean, 2.1; range, 1.5–2.5 μ*M*). The half-life was estimated to ~24 h.

TPM concentrations in breast milk and simultaneous plasma concentrations in the mothers and nursed infants are shown in Table 3. Three weeks after delivery, the mean milk/maternal plasma TPM ratio was 0.86 (range, 0.67–1.1) before nursing, with minor changes after. The weight-adjusted relative dose, assuming a daily milk intake of 150 ml/day/kg, was ~3–23% of the maternal dose/day (absolute approximate dose to infant, 0.1–0.7 mg/kg/day). The plasma concentrations in two of the nursed infants 2–3 weeks postpartum were 1.4 and 1.6 μ*M,* respectively. One infant had a TPM concentration below the limit of detection. The concentrations in the breast-fed infants were ~10–20% of the mothers' plasma levels.

TABLE 2. *Maternal and infant topiramate concentrations at delivery and later*

Patient number	Topiramate dose (mg/day)	Maternal plasma at delivery (μ*M*)	Umbilical cord blood (μ*M*)	Infant plasma (μ*M*)		
				24 h after birth	48 h after birth	72 h after birth
1	150	7.6	—[a]	2.7	2.5	1.0
2	200	7.9	8.4	3.8	2.3	1.5
3	100	2.6	2.2	1.7	<0.9	<0.9
4	200	5.9	5.8	2.3[b]	<0.9	[c]
5	400	17	16	5.3	1.5[b]	<0.9

[a] Insufficient quantity for analysis.
[b] The levels are above the limit of detection, 0.9 μ*M*, but below the range of accurate quantification, 2.8 μ*M*. In the range 1.2–2.8 μ*M*, the coefficient of variation (CV) is 20–25%.
[c] Data missing.

TABLE 3. *Topiramate concentrations and milk/plasma concentration ratios at time of breast-feeding 2–3 weeks, 1 month, and 3 months after delivery*

Patient number	Topiramate dose (mg/day)	Time of sampling (days after delivery)	Mother's plasma (μ*M*)		Breast milk (μ*M*)		Nursed infant's plasma (μ*M*)		Milk/plasma topiramate conc ratio		Infant/plasma topiramate conc ratio	
			Before nursing	After completion of nursing	Before nursing	After completion of nursing	Before nursing	After completion of nursing	Before nursing	After nursing	Before nursing	After nursing
1	150	24	6.3	6.8	6.9	6.7	1.4[a]	1.3[a]	1.10	0.99	0.22	0.19
2	200	20	17	16	13.7	14.6	1.6[a]	1.9[a]	0.80	0.92	0.09	0.12
2	200	97	20	—	13.7	—	2.1[a]	—	0.69	—	—	—
4	200	14	2.4[a]	2.1[a]	1.6[a]	2.0[a]	<0.9	<0.9	0.67	1.0	—	—
4	200	27	4.2	—	3.6	—	—	<0.9	0.86	—	—	—

[a] The levels are above the limit of detection, 0.9 μ*M*, but below the range of quantification, 2.8 μ*M*. In the range 1.2–2.8 μ*M*, the coefficient of variation (CV) is 20–25%.

At 4 weeks, the milk/plasma ratio was 0.69 in one mother, and 3 months after delivery, the ratio was 0.86 6 h after dose intake in another mother. Plasma concentrations in the breast-fed infants were <0.9 μ*M* and 2.1 μ*M,* respectively.

CONCLUSION AND DISCUSSION

It should be acknowledged that our results are based on observations from only five patients at delivery and from five neonates. No more than three mother–child pairs were studied during nursing on five occasions. Furthermore, in many of the samples, TPM concentrations were below the range of quantification of the method we used for analysis, so these preliminary observations must be interpreted with caution. Nevertheless, some conclusions can be drawn. First, our observations suggest a considerable transfer over the placenta because the ratio between the drug concentration in umbilical cord plasma and maternal plasma was close to one. Second, the newborns seemed to have a reasonable capacity to eliminate TPM. Although our data do not permit a precise calculation of clearance and plasma half-life of TPM, the elimination half-life in the neonate could be estimated to ~24 h. This is close to the 20–30 h reported among adult healthy controls (8) and may seem surprising, considering the fact that TPM is eliminated mainly unchanged through the kidneys and that kidney function is not fully developed in neonates (9). However, four of five mothers also were taking carbamazepine (CBZ) during pregnancy. CBZ induces the metabolism of TPM (10), and it was previously shown that maternal intake of CBZ during pregnancy can induce fetal metabolism (11). Third, the passage of TPM into the breast milk was extensive, with similar TPM concentrations in milk and maternal plasma levels from 2 to 3 weeks up to 3 months after delivery. The intake of TPM of the infant was estimated to be ~0.1–0.7 mg/kg/day. However, this figure represents a minimal exposure, because the sampling was done before maternal intake of the morning TPM dose. Despite this, measured plasma concentrations of TPM in the suckling infants were low—in one case even below the limit of detection. Although a therapeutic interval has as yet not been defined for TPM, anticonvulsant effects have been reported at 15–50 μ*M* (12–14), levels that are much higher than those observed in the nursed infants. It is therefore not surprising that no adverse effects were observed.

In conclusion, our limited data suggest free passage of TPM over the placenta, and an extensive transfer into breast milk. The low plasma concentrations in the suckling infants (~10–20% of the mother's plasma levels) and the lack of adverse effects indicate minimal risk associated with nursing; however, it is advisable to monitor nursed infants of mothers treated with TPM until more experience has been gained. Additional studies are needed to confirm our observations, and more sensitive analytic methods should be applied for accurate estimation of TPM kinetics in the newborn.

Acknowledgment: Grants from the Swedish Medical Research Council (K97-17X-12225-01A) and Janssen-Cilag supported this study. We thank Dr. Anne-Marie Landtblom for contributing her patient to this study.

REFERENCES

1. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide and tiagabine. *Clin Pharmacokinet* 1996;31:29–46.
2. Langtry HD, Gillis JC, Davis R. Topiramate: a review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy. *Drugs* 1997;54:752–73.
3. Bialer M. Comparative pharmacokinetics of the newer antiepileptic drugs. *Clin Pharmacokinet* 1993;24:441–52.
4. Berry DJ, Patsalos PN. Comparison of topiramate concentrations in plasma and serum by fluorescence polarization immunoassay. *Ther Drug Monit* 2000;22:460–4.
5. Holland ML, Uetz JA, Ng KT. Automated capillary gas chromatographic assay using flame ionization detection for the determination of topiramate in plasma. *J Chromatogr* 1988;433:276–81.
6. DeGrella RF. Fluorescence polarization: a review of laboratory applications. *Am Biotech Lab* 1988;6:29–33.
7. Tang PH, Miles MV, Glauser TA, et al. An improved gas chromatography assay for topiramate monitoring in pediatric patients. *Ther Drug Monit* 2000;22:195–201.
8. Johannessen SI. Pharmacokinetics and interaction profile of topiramate: review and comparison with other newer antiepileptic drugs. *Epilepsia* 1997;38(suppl 1):S18–23.

9. Blackburn ST. Renal function in the neonate. *J Perinat Neonat Nurs* 1994;8:37–47.
10. Sachdeo RC, Sachdeo SK, Walker SA, et al. Steady-state pharmacokinetics of topiramate and carbamazepine in patients with epilepsy during monotherapy and concomitant therapy. *Epilepsia* 1996;37:774–80.
11. Bertilsson L. Clinical pharmacokinetics of carbamazepine. *Clin Pharmacokinet* 1978;3:128–43.
12. Patsalos PN. New antiepileptic drugs. *Ann Clin Biochem* 1999;36: 10–9.
13. Stephen LJ, Sills GJ, Brodie MJ. Topiramate in refractory epilepsy: a prospective observational study. *Epilepsia* 2000;41:977–80.
14. Reife R, Pledger G, Wu SC. Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults. *Epilepsia* 2000; 41(suppl 1):S66–71.