Topiramate in pregnancy

Preliminary experience from the UK Epilepsy and Pregnancy Register

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ABSTRACT

Objectives: Topiramate (Topamax®) is licensed to be used, either in monotherapy or as adjunctive treatment, for generalized tonic clonic seizures or partial seizures with or without secondary generalization and for prevention of migraine. The safety of topiramate in human pregnancy is largely unknown. Here we report on our experience of pregnancies exposed to topiramate.

Methods: This study is part of a prospective, observational, registration and follow-up study. Suitable cases are women with epilepsy who become pregnant while taking topiramate either singly or along with other antiepileptic drugs (AEDs), and who are referred before outcome of the pregnancy is known. The main outcome measure is the major congenital malformation (MCM) rate. Secondary outcomes include risk of specific MCM, minor malformation rate, birthweight, and gestational age at delivery.

Results: Full outcome data are available on 203 pregnancies. Of these, 178 resulted in live birth; 16 had an MCM (9.0%; 95% CI 5.6% to 14.1%). Three MCMs were observed in 70 monotherapy exposures (4.8%; 95% CI 1.7% to 13.3%) and 13 in cases exposed to topiramate as part of a polytherapy regimen (11.2%; 95% CI 6.7% to 18.2%). Four of the MCMs were oral clefts (2.2%; 95% CI 0.9% to 5.6%). Four cases of hypospadias were reported (5.1%; 95% CI 0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations.

Conclusions: The number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate. Although the present data provide new information, they should be interpreted with caution due to the sample size and wide confidence intervals. *Neurology*® 2008;71:272–276

GLOSSARY

AED = antiepileptic drug; **MCM** = major congenital malformation; **SGA** = small for gestational age.

It is widely accepted that prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCM) from the background risk of 1% to 2%[1-3] to between 4% and 9%.[3-5] However, except for lamotrigine,[5,6] levetiracetam,[7] and oxcarbazepine,[8] information is limited on the other newly available AEDs (vigabatrin, gabapentin, topiramate, tiagabine, pregabalin, and zonisamide).

Topiramate is licensed for use both in monotherapy and as adjunctive treatment for generalized tonic clonic seizures or partial seizures with or without secondary generalization. During 2004 it was also licensed by the Food and Drug Administration for prophylaxis of migraine.

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Table 1 Outcomes of pregnancies exposed to topiramate

	Topiramate monotherapy exposures	Topiramate as part of a polytherapy regimen
No. of exposures	70	133
Outcome		
Live births	62	116
Spontaneous abortions	6	12
Induced abortions	2	3
Stillbirths	0	2
Mean dose TPM (range), mg	245 (50–800)	299 (25-1,000)
Mean gestational age at enrollment (range), wk	14.5 (4–34)	14.9 (4–34)
Mean gestational age at delivery, wk	39.2	38.8
Mean birthweight, g	3,168	3,062
Sex		
Male	25	53
Female	35	61
Not recorded	10	19
Mode of delivery		
Spontaneous vaginal deliveries	35	59
Cesarean	17	34
Forceps	5	11
Ventouse	4	6
Abortions	7 (2 induced)	15 (3 induced)
Not recorded	2	8
Seizures in pregnancy		
Tonic-clonic ± other	15	45
Minor only	14	27
None	31	33
Not recorded	10	28
Major malformations [rate (95% CI)]	3 [4.8% (1.7–13.3%)]	13 [11.2% (6.7–18.2%)]
Any malformation [rate (95% CI)]	7 [12.9% (6.7–23.4%)]	23 [19.8% (13.6–28.0%)]

TPM = topiramate.

Topiramate has been shown to be teratogenic in mice, rats, and rabbits.[9] In mice doses as low as 0.2 times the maximum recommended human dose (400 mg/m^2) were associated with an increased frequency of (primarily) craniofacial defects.

Safety data for topiramate in human pregnancy are limited. A company sponsored abstract reported outcomes for 75 pregnancies exposed to topiramate.[10] Of 29 monotherapy exposures two malformations (micrognathia, phimosis) were noted. Of the remaining 46 pregnancies that had also been exposed to at least one other AED seven infants had a malformation (cleft palate, cleft lip, tetralogy of Fallot, hand malformation, ureteral stenosis, pyloric stenosis, and one infant with cleft lip and palate, fixed extension of upper limb, bilateral radial deviation of hands, brachydactyly, and hydrocephalus).

METHODS The UK Epilepsy and Pregnancy Register is a prospective pregnancy register set up to determine the relative safety of all AEDs taken in pregnancy. Here we report our results for first-trimester exposures to topiramate, through August 31, 2007.

Suitable cases are women with epilepsy who became pregnant while taking topiramate, either singly or along with other AEDs, and who were referred before the outcome of the pregnancy was known. The main outcome measure was the MCM rate. Cases where any prenatal test (fetal ultrasound, blood test) had shown an abnormality and cases resulting in a pregnancy loss (induced abortion, spontaneous abortion, stillbirth) in which an abnormality had been identified before referral to the register had been made were excluded.

A major seizure is defined as a tonic-clonic seizure. A minor or other seizure denotes seizures without convulsive activity.

Outcome data were collected at 3 months after the expected date of delivery by sending the patient's general practitioner a standardized questionnaire for completion.

An MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered during the first 6 weeks of life. Disorders not conforming to this definition were assigned as minor malformations based on the definitions and lists of disorders in the EUROCAT registry.[11]

The MCM rate was calculated as [total number of live births with an MCM] + [total number of pregnancy losses with an MCM] ÷ [total number of live births] + [total number of preg-

Table 2 Major congenital malformations with topiramate monotherapy

No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	200	29	G3P2	Partial	NR	41	3,850	F	Cleft lip and bilateral cleft palate
2	400	34	G3P2	NR	No	37	2,355	M	Hypospadias
3	600	27	G1P1	NR	Yes	39	3,289	NR	Cleft lip and palate

TPM = topiramate; GTC = generalized tonic–clonic seizure; NR = not recorded.

Table 3 Minor congenital malformations with topiramate monotherapy

No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Minor congenital malformation
1	50	26	G5P4	GTC	No	37	2,200	F	Sacral dimple
2	750	30	G1P0	Partial	No	41	2,810	F	Clicky hips
3	300	32	G3P2	GTC	No	40	2,860	F	Plagiocephaly
4	100	23	NR	Partial	Yes	38	2,860	M	Toe webbing
5	200	25	G1P1	Partial	No	41	3,660	M	Immature hip joints

TPM = topiramate; GTC = generalized tonic–clonic seizure; NR = not recorded.

nancy losses with an MCM]. Spontaneous pregnancy losses and induced abortions where no abnormalities were reported were not included for analysis as we do not know if they were examined in detail and therefore cannot know the outcome. The total numbers presented for each group are therefore either the total number of outcomes or the total number of informative outcomes—that is, excluding pregnancy losses with no abnormalities reported. Full details on study methodology have been previously reported.[5]

RESULTS Through August 31, 2007, complete outcome data were available on 203 prospectively reported pregnancies that had had first trimester exposure to topiramate, of which 70 had been exposed to topiramate in monotherapy.

Pregnancy outcome details for all exposures are shown in table 1. Of all pregnancies exposed to topiramate, 178 (87.7%) resulted in a live birth. Of these, 31 pregnancies had an abnormality of some kind (17.4%; 95% CI 12.5% to 23.7%) with 16 of these being an MCM (9.0%; 95% CI 5.6% to 14.1%). Four MCMs were oral clefts (2.2%; 95% CI 0.9% to 5.6%) with three infants having both cleft lip and cleft palate. Four cases of hypospadias were reported (5.1%; 95% CI 0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations. Full details on major and minor malformations are shown in tables 2 through 5.

For the three infants who had an MCM and who were exposed to topiramate in monotherapy the average total daily dose was 400 mg of topiramate compared to 238 mg in those without an MCM (p =

Table 4 Major congenital malformations with topiramate polytherapy

No.	Dose TPM during pregnancy/d, mg	Other AED doses during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	800	Clobazam 20; lamotrigine 550; vigabatrin 1,000	29	G2P1	Partial	No	40	2,381	M	Left hydronephrosis, dysmorphic
2	75	Ethosuximide 1,000; sodium valproate 1,000	39	G3P2	Partial	No	38	3,160	M	Pyloric stenosis
3	250	Lamotrigine 200	19	NR	NR	NR	NR	NR	F	Hernia and hydrocele
4	175	Lamotrigine 125	24	NR	Partial	No	38	2,530	F	Anal atresia
5	150	Sodium valproate 1,500	32	G2P1	GTC	Yes	42	3,660	M	Pyloric stenosis
6	150	Sodium valproate 200	24	G4P3	GTC	No	34	NR	F	Tracheoesophageal fistula
7	50	Sodium valproate 2,500	26	G3P2	GTC	Yes	41	3,400	M	Hypospadias
8	500	Sodium valproate 500	24	G1P0	NR	NR	40	2,455	F	Cleft palate, crossed toes
9	400	Lamotrigine 400	24	G1P0	GTC	NR	40	3,280	F	Bilateral dislocated hips
10	350	Lamotrigine 50	27	G2P1	JME	No	40	2,960	M	Harold type II Talipes, plagiocephaly
11	500	Carbamazepine 1,200; clobazam 10	28	G1P0	NR	Yes	38	NR	M	Congenital dislocated hip
12	800	Levetiracetam 500; lamotrigine 800	21	G1P0	Partial	Yes	33	2,460	M	Pyloric stenosis
13	250	Lamotrigine 300; phenobarbitone 60	37	G3P2	GTC	No	40	3,560	M	Left cleft lip and palate

TPM = topiramate; AED = antiepileptic drug; GTC = generalized tonic–clonic seizure; NR = not recorded; JME = juvenile myoclonic epilepsy.

Table 5 Minor congenital malformations with topiramate polytherapy

No.	Dose TPM during pregnancy/d, mg	Other AED doses during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Minor congenital malformation
1	100	Clobazam 20; lamotrigine 300; sodium valproate 1,000	30	G2P1	Partial	NR	37	2,920	M	Glandular hypospadias
2	800	Clobazam 10; lamotrigine 550; vigabatrin 1,000	27	G1P0	Partial	Yes	40	2,360	M	Abnormality of foreskin
3	400	Lamotrigine 600	21	G1P0	GTC	Yes	42	3.960	F	Dysmorphic features
4	100	Phenytoin 375; vigabatrin 2,000	25	NR	Partial	No	41	NR	F	Left ureteric reflux
5	300	Sodium valproate 1,500	21	G1P0	GTC	Yes	38	3,543	F	Patent ductus arteriosus
6	400	Carbamazepine 1,000; sodium valproate dose NR	18	G1P0	Partial	Yes	41	NR	M	Benign heart defect
7	50	Carbamazepine 800; sodium valproate 2,500	33	G1P0	GTC	Yes	39	3,230	F	Mild hypospadias
8	150	Carbamazepine 1,000	42	G1P0	Partial	No	38	3,535	F	Cavernous hemangioma
9	100	Carbamazepine retard 1,400; clobazam 10; levetiracetam 2,500	19	G1P0	Partial	Yes	40	3,210	F	Clicky right hip
10	150	Lamotrigine 200	36	NR	Primary generalized	No	41	3,850	F	Intra-abdominal cyst

TPM = topiramate; AED = antiepileptic drug; GTC = generalized tonic–clonic seizure; NR = not recorded.

0.123). Of the 61 cases exposed to topiramate in monotherapy for which there was information about gestational age, six infants (9.8%) were born at 37 weeks gestation or less. The average total daily dose for those born prematurely (250 mg) was not significantly different from those born after 37 weeks (246 mg ($p = 0.934$). Of the 56 monotherapy outcomes for which there were full data on gestational age and birthweight, 8 (14.3%) were small for gestational age (SGA). The mean total daily dose for those who were SGA (346 mg) was not significantly different from those who were not SGA (239 mg, $p = 0.084$).

For polytherapy outcomes 32 combinations of at least one AED in addition to topiramate were recorded. Thirteen infants born with a major malformation were exposed on average to 342 mg per day of topiramate compared with 294 mg per day for live births without an MCM ($p = 0.539$). Of the 111 cases exposed to topiramate as part of a polytherapy regimen, for which there was information on gestational age, 17 infants (15.3%) were born at 37 weeks or less gestation. The mean total daily dose for those born prematurely (347 mg) was not significantly different from those born after 37 weeks (288 mg, $p = 0.891$). Of 103 live births exposed to topiramate as part of a polytherapy regimen and for which there were data regarding birthweight and gestational age, 20 infants (19.4%) were SGA. The mean total daily dose for those infants who were SGA (405 mg) was significantly different from those who were not SGA (260 mg, $p = 0.019$). We have no data on maternal weights in pregnancy.

Co-administration of valproate with topiramate either as part of a duotherapy regimen (n = 12, MCM rate 36.4%; 95% CI 15.2 to 64.6%) or as part of a regimen of three or more AEDs (n = 23, MCM rate 23.8%; 95% CI 10.6 to 45.1%) was associated with the highest rates of MCM. This compared with a lower rate of MCM for exposures not including valproate (n = 110, MCM rate 8.4%; 95% CI 4.3% to 15.8%).

DISCUSSION The MCM rate for monotherapy exposures to topiramate was well within the range quoted for other AEDs.[5] For polytherapy exposures the MCM rate was higher, consistent with previous reports comparing monotherapy and polytherapy exposures to all AEDs.[3-5] The MCM rates for combinations containing valproate in addition to topiramate were higher than for combinations not containing valproate. While it is not clear if this is a consequence of an interaction between these drugs, is a reflection of unidentified patient characteristics, or is due to valproate, which has increasingly been shown to be associated with a high risk of MCMs, either in monotherapy or as part of a polytherapy regimen,[5,12] is unclear. Clearly these results need to be replicated in larger numbers and from different registers before we might counsel women of child-bearing age

against using combinations including topiramate and valproate.

All of the MCMs observed have already been described in pregnancies exposed to AEDs other than topiramate and no apparent dose response was evident either for monotherapy or polytherapy exposures. We found the rates of oral clefts (2.2%) and hypospadias (5.1%) much higher than that reported in the United Kingdom. For oral clefts, which occur in 1 in 500 live births in the United Kingdom,[13] the observed rate was 11 times higher than the background rate. For hypospadias, which is estimated to occur in 1 in 300 live births,[14] the observed rate was approximately 14 times the background rate.

The mean birthweights for live infants exposed in utero to topiramate either as monotherapy or as part of combination therapy were within the normal range with a trend to lower birth weight in polytherapy exposures. Infants who were SGA were exposed to a significantly higher daily dose of topiramate but only when exposed to topiramate as part of combination therapy. In animal studies embryotoxicity (including reduced fetal weight gain) was observed at doses as low as 0.5 times the maximum recommended human dose.[9] Unfortunately we have no data on maternal weights, either before or during pregnancy, and therefore cannot comment on any potential interaction between maternal weights and the outcome of SGA.

While our results are preliminary, they are relevant not only in dealing with women with epilepsy of childbearing years. Topiramate is also licensed for use for migraine prophylaxis, an even more common condition which also occurs frequently in women of childbearing years. While the risks for adverse outcomes, including teratogenic endpoints, may differ between patient groups exposed to the same drug but used for different indications, the teratogenic potential of any agent is also likely determined by factors related to the structure and functional effects of the agent, the dose prescribed, and the timing of use. This is also likely to be the case for topiramate. Monitoring pregnancies in women with migraine exposed to topiramate should therefore be encouraged.

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