

Teratogenicity of lamotrigine

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ABSTRACT

QUESTION One of my female patients has epilepsy and is currently receiving lamotrigine monotherapy. She has recently found that she is 6 weeks pregnant and is concerned about possible side effects of lamotrigine on her fetus. How should I advise her and should I switch to another antiepileptic drug?

ANSWER Lamotrigine (LTG) has not been associated with an increased risk for major malformations in monotherapy in most available studies. Risk of major malformations has been suggested when LTG was taken in doses higher than 200 mg/d and when clefts not caused by any known syndrome have been associated with LTG treatment. Therefore, safety for the fetus cannot yet be proven or rejected, although the drug does not appear to be a major human teratogen.

RÉSUMÉ

QUESTION Une de mes patientes souffre d'épilepsie et suit actuellement une monothérapie à la lamotrigine. Elle vient d'apprendre qu'elle est enceinte de 6 semaines et s'inquiète des effets secondaires possibles de la lamotrigine sur le fœtus. Quels conseils devrais-je lui donner et est-ce que je devrais lui prescrire un autre médicament contre l'épilepsie?

RÉPONSE Selon la plupart des études publiées, la lamotrigine (LTG) en monothérapie n'a pas été associée à un risque accru de malformations majeures. On a laissé entendre la possibilité de risque de malformations importantes lorsque la LTG était prise à des doses de plus de 200 mg/j et lorsque des fissures non causées par des syndromes connus ont été associées à un traitement à la LTG. Par conséquent, il n'est pas possible encore de dire si la sécurité du fœtus est menacée ou non, quoique le médicament ne semble pas être un tératogène humain important.

Epilepsy is the most common neurologic condition in the obstetric population, where women with epilepsy constitute 0.5% of all pregnancies.^{1,2} The goal of epilepsy treatment is seizure control using antiepileptic drugs (AEDs), despite the fact that the traditional AEDs are known teratogens. Lamotrigine (LTG) is a second-generation AED that is widely used for seizure control in epilepsy as well as in other neurologic and psychiatric disorders. It has been found to be similar in effectiveness to valproic acid.³

Between the years of 1999 and 2003, the use of LTG increased dramatically.⁴ However, because information on safety of LTG in human pregnancy is still limited, several pregnancy registries have been formed to monitor LTG safety in pregnancy.

Five registries and 1 large prospective study (Table 1³⁻⁸) recently summarized human studies of LTG. Overall, most of the reported data did not show evidence of increased teratogenic risk, as the rates of major malformations were well within the expected baseline rates. The exception is the North American Antiepileptic Drug Pregnancy Registry,⁷ which assessed first-trimester LTG monotherapy exposure (n=564). The prevalence of major malformations found among exposed infants in the first 5 days of life

was 2.7% (95% confidence interval [CI], 1.5%-4.3%). Three infants (0.53%) had isolated cleft palates and 2 infants (0.35%) had isolated cleft lips, resulting in a total of 5 infants (0.89%) with oral clefts. This is an apparent higher prevalence of oral clefts than that observed in the control group (0.037%, n=221 746). In this control group, the prevalence of isolated cleft palate was 0.016% with relative risk (RR) attributed to LTG of 32.8 (95% CI, 10.6-101.3), and the prevalence of isolated cleft lip was 0.021% with RR attributed to LTG of 17.1 (95% CI, 4.3-68.2).⁷ These results led to the issue of a report by GlaxoSmithKline Inc and Health Canada, warning of potential risks associated with LTG use.⁹ The good news is that the observed rates of cleft palate and cleft lip were still very low. Hence, while the relative risk might be high, the absolute risk is minimal. This single study will have to be confirmed by other studies, especially because no other existing registry has corroborated it.

Proper seizure control is the primary goal in treating women with epilepsy. Patients should understand the risks associated with uncontrolled seizures as well as the teratogenicity of the anticonvulsive medications in question. The benefits of treatment versus the risk of uncontrolled seizures should be discussed with each patient.

Table 1. Summary of LTG registries findings

REGISTRY DETAILS	REGION	INCLUSION PERIOD	TOTAL NUMBER OF PREGNANCY OUTCOMES	MALFORMATION RATES OF LTG MONOTHERAPY	MALFORMATION RATES OF LTG + VPA POLYOTHERAPY	COMMENTS
GlaxoSmithKline International Lamotrigine Pregnancy Registry Interim Report ⁵	38 reporting countries	September 1992-March 2005	1246	2.8% (95% CI, 1.8%-4.4%) (n = 707)	11.8% (95% CI, 6.8%-19.3%) (n = 119)	87 retrospectively reported outcomes involving birth defects
UK Epilepsy and Pregnancy Register ³	United Kingdom	1996-2005	3607	3.2% (95% CI, 2.1%-4.9%) for all LTG monotherapies (n = 647); 3.2% (95% CI, 2.1%-4.9%) for LTG doses of 200 mg/d or lower; 5.4% (95% CI, 3.3%-8.7%) for LTG doses higher than 200 mg/d	9.6% (95% CI, 5.7%-15.7%)	Positive dose-response relationship for malformations in LTG monotherapy; malformation rates in LTG monotherapy at doses higher than 200 mg/d are not statistically different from expectant mothers taking VPA at 1000 mg/d or less Potential effect should be considered in future studies
Swedish Medical Birth Registry ^{5,6}	Sweden	1995-2004	>1300	4.8% (95% CI, 2.5%-8.3%) (n = 248)	27% (n = 30)	No consistent malformation pattern
Australian Pregnancy Registry ⁴	Australia	1999-December 2003	565	None reported (n = 61)		4 fetal malformations were observed in LTG polytherapy (n = 70), corresponding to 5.71% incidence rate; all 4 cases of LTG polytherapy with fetal malformations were using LTG with high doses of VPA (more than 1100 mg/d), while those treated with LTG combined with low VPA doses exhibited no fetal malformations
North American Antiepileptic Drug Pregnancy Registry ⁷	North America	1997-January 2006	564	2.7% (95% CI, 1.5%-4.3%) (n = 564)		5 infants (0.89%) had oral clefts; potential increased risk for non-syndromic cleft palate
Meador and colleagues ⁸	United States and United Kingdom	October 1999-February 2004	333	1.02% (95% CI, 0.03%-5.6%) (n = 98)		

CI—confidence interval, LTG—lamotrigine, VPA—valproic acid.

If anticonvulsants cannot be avoided, the most appropriate first-line drug for the seizure type should be used at the lowest effective dose, and monotherapy is preferable to polytherapy. In summary, the present reports do not suggest LTG to be a major human teratogen. Because only 1 study suggests increased risk of oral clefts, the finding must be corroborated before causation can be inferred. ❁

References

1. Yerby MS. Pregnancy and epilepsy. *Epilepsia* 1991;32(Suppl 6):S51-9.
2. Dansky LV, Andermann E, Andermann F. Marriage and fertility in epileptic patients. *Epilepsia* 1980;21(3):261-71.
3. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77(2):193-8.
4. Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J of Neurol* 2006;13(6):645-54.
5. GlaxoSmithKline. *The lamotrigine pregnancy registry* [Interim Report]. Wilmington, NC: Kende International Inc; 2007.
6. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs *in utero*, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. *Acta Paediatr* 2004;93(2):174-6.
7. Holmes LB, Wyszynski DF, Baldwin EJ, Habecker E, Glassman LH, Smith CR. Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy [Abstract]. *Birth Defects Res A Clin Mol Teratol* 2006;76(5):318.
8. Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, et al. In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 2006;67(3):407-12.
9. Dillon JA. *Health Canada endorsed important safety information on LAMICTAL® (lamotrigine) tablets* [Report]. Mississauga, Ont: GlaxoSmithKline; August 1, 2006. Available from: http://www.gsk.ca/en/health_info/LAMICTAL_DHCPL_ENG_FNL.pdf. Accessed 2007 Mar 7.

MOTHE RISK

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