Lamotrigine in pregnancy

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This article is based on the presentation that won the Life Healthcare Best Poster Award at the SAAHIP Conference 2010.

Introduction

Lamotrigine, indicated for use in partial and primary generalised epilepsy, and registered for use in bipolar affective disorder, has recently been added to the essential medicines list in the public health system. This will result in increased consumption of lamotrigine in the future.

Being a relatively new drug in the public health arena, the effect of its usage in certain populations, such as pregnancy, is not well known.

What sources are available for evidence of safety of lamotrigine use in pregnancy?

As data on the effect of anticonvulsants on the human foetus are sparse, and randomised controlled trials done on human subjects would be unethical, pregnancy registers have been developed to assess the risk of major congenital malformations from in utero exposure to anti-epileptic drugs (AEDs).

In the case of lamotrigine, there are several registries around the world that monitor the effect of in utero exposure to this agent.

Is there a risk of major congenital malformations in women using lamotrigine?

Studies report a 2 to 3 fold increase in major malformations in children of women treated for epilepsy during pregnancy, and it has been suggested that this increase is due to the AEDs.

This begs the question – will a newer AED such as lamotrigine have a similar risk for major congenital malformations (MCMs) associated with in utero exposure? A look at pregnancy registers for lamotrigine shows a growing evidence base regarding the overall risk of MCMs in first trimester exposure to lamotrigine.

The UK Epilepsy and Pregnancy Register, with a total of 647 women on lamotrigine monotherapy, showed an MCM rate of 3.2% (95% confidence interval 2.1 to 4.9). Another study from Denmark with 51 women indicated a risk of 2.0% for MCMs. Initially, with 61 women, the Australian Pregnancy Register showed no incidence of MCMs with lamotrigine monotherapy, however a later report with 102 women showed a risk of 5.9%. The International Lamotrigine Pregnancy Registry (created and funded by GlaxoSmithKline, who manufacture lamotrigine) showed children with in utero monotherapy exposure to lamotrigine in the first trimester had an MCM rate of 2.9% (95% CI 1.6 to 5.1). No MCMs were reported for second or third trimester exposure, but this may be due to the fact that the majority of outcomes (94%) involved first-trimester exposure. This data was from 11 years of prospective monitoring of pregnancies, and was insufficient to evaluate uncommon or specific defects associated with lamotrigine exposure.

So, does lamotrigine exposure result in specific MCMs?

Data from the North American AED pregnancy registry showed an unexpectedly high prevalence of orofacial clefts in children exposed to lamotrigine monotherapy during the first trimester of pregnancy, with an increased risk of isolated cleft palate, or cleft lip deformity compared to unexposed controls (Risk Ratio 10.4; 95% CI 4.3 to 24.9).

There is a lack of consensus in the literature, as a case-control study published in 2008 showed no increased risk of isolated orofacial cleft relative to other malformations with lamotrigine monotherapy versus no AED exposure (odds ratio 0.80; 95% CI 0.11 to 2.85).

Is there a relationship between lamotrigine dose and the risk of MCMs in exposed infants?

Dose is a poor surrogate for AED exposure due to the pharmacokinetic changes of the drug during pregnancy; it is however the only available surrogate measure for exposure.

The literature does not show general consensus on dose-response for MCM risk with lamotrigine:

- the UK Epilepsy and Pregnancy Registry showed that there is greater risk for MCMs with higher doses, with an MCM rate of 5.4 (95% CI 3.3 to 8.7) for a daily dose greater than 200mg
- the International Lamotrigine Pregnancy Registry did not show a difference in frequency of MCMs with lamotrigine monotherapy up to doses of 1 200 mg/day in the first trimester, with an overall odds ratio for MCMs per 100 mg increase of 0.99 (95% CI 0.996 to 1.001)
- a report from the North American AED Pregnancy Registry also failed to observe a dose-response relationship between lamotrigine and MCMs

Box 1: Case presentation

A 27-year-old white female patient previously diagnosed with bipolar mood disorder presented five weeks pregnant on lamotrigine. The patient is concerned about the effect that the drug will have on her unborn baby.
Are there changes in lamotrigine pharmacokinetics in pregnant patients?

Reports have shown marked decreases in serum concentration of lamotrigine during pregnancy. This may be attributed to:

- Reduced plasma protein binding (which would result in redistribution of the drug)
- Impaired absorption from the gastrointestinal tract, or
- Enhanced metabolic or renal elimination

It is unlikely to be due to decreased protein binding, as lamotrigine is approximately 55% protein bound, and this does not change during pregnancy.10,11

The metabolism of lamotrigine is primarily through glucuronidation, and studies have shown this 2-N-glucuronide pathway to be enzymatically induced during pregnancy.10

This has clinical significance as it requires dose adjustments throughout pregnancy to maintain therapeutic serum concentrations.

1. During pregnancy

Lamotrigine clearance rates have been shown to differ in each pregnancy trimester from baseline (i.e. non-pregnant) clearance rates. A high inter-individual variability in the degree of enhanced clearance has also been noted in the literature,12 thus making it important to individualise increases.

In the first trimester (weeks 0 to 12), lamotrigine clearance increases on average 197% above baseline, with further average increases of 236% in the second trimester (weeks 12 to 28) and 248% in the third trimester (weeks 28 to 40). The highest dosage adjustment was towards the end of the third trimester until birth. Changes in clearance are statistically significant between the last two trimesters and baseline rate, but not between the first trimester and baseline.11

2. Post partum

Women who do not have their lamotrigine dose tapered off are more likely to experience postpartum toxicity (such as dizziness, diplopia or ataxia), starting 8 to 10 days after delivery. This is due to rapid normalisation of lamotrigine clearance to the baseline rate, which takes about 2 to 3 weeks postpartum to achieve.13

These changes in lamotrigine clearance during pregnancy indicate the need for at least monthly therapeutic monitoring during the pregnancy, and weekly monitoring during the puerperium so as to adjust the dose to maintain therapeutic serum concentrations.

Discussion

There is currently no literature on the effect of lowered lamotrigine levels in the pregnant, bipolar patient, however it is assumed that with increased clearance, and thus lowered levels of lamotrigine, the patient may be at an increased risk for an acute affective episode.

Although there is a recognised risk for major congenital malformations in a child exposed in utero to lamotrigine, this is much less than that for the other generation AEDs.

During pregnancy there are metabolic changes that result in an increased metabolism rate of lamotrigine, decreasing lamotrigine levels to sub-therapeutic concentrations. A peak is reached towards the end of the third trimester until birth, which rapidly decreases to baseline levels after birth, necessitating decreases in dose to avoid toxicity. This effect has a high variability amongst women making guidelines for incremental increases during pregnancy difficult, requiring therapeutic drug monitoring. There does not seem to be consensus with regards to the effect of dose on the risk of MCMs, and it is currently advised that, if possible, the dose of lamotrigine during the first trimester should be limited to lessen the risk of MCMs.14

Box 2: Case conclusion

The patient, together with her doctor, decided to stop the lamotrigine at five weeks of pregnancy, and increase monitoring of the patient’s mental health. She was not put onto any other mood stabiliser, nor did she experience any affective episodes during her pregnancy, and gave birth to a healthy baby.

Conclusion

Pregnancy alters the metabolism of lamotrigine, and women who wish to remain on the drug throughout their pregnancy will require therapeutic drug monitoring so as to maintain therapeutic serum concentrations. First-trimester exposure to lamotrigine has a low risk of major congenital malformations relative to other AEDs, and this risk currently does not seem to be dose related.

Acknowledgement

I would like to thank Betty D Patterson for her assistance.

References

3. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Seizure 2006;17:166-171
9. Cunningham M, Ferber S, Quarte R, and the International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. Epilepsia 2007; **(4);1-4