Association of lamotrigine with an increased risk of non-syndromic oral clefts.

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New data from the North American Antiepilectic Drug Pregnancy Registry (NAAED) suggest a possible association between exposure to lamotrigine monotherapy during the first trimester of pregnancy and cleft lip and/or cleft palate. In the NAAED registry, 2 cases of non-syndromic isolated cleft lip and 3 cases of isolated cleft palate occurred among 564 pregnant women treated with lamotrigine montherapy during the first trimester of pregnancy. The prevalence rate was 8.9 per 1000, which exceeded the 0.37 per 1000 rate observed in the control group (non epileptic) used in the study. Other pregnancy registries of similar size have not confirmed this observation.

Following these data, Swissmedic has decided to update the product information for all lamotrigine products:
« The post-marketing data from several prospective registries include more than 2000 women having received lamotrigine in monotherapy during the first trimester of their pregnancy. Although these data do not show an obvious increase in the overall risk of major congenital malformations associated with lamotrigine, a registry did however report an increase risk of non syndromic cleft palate and/or cleft lip. A complete analysis of 6 other pregnancy registries has not confirmed this observation. »

Subsequent to these statements, it appears important to address some facts in order to allow for an overall perception of the context in which lamotrigine is prescribed during pregnancy.

- Beyond 200 mg per day, an increase in the risk of malformation is suggested, dose-dependent, however, not exceeding the risk observed with other « older » antiepileptic [1]. Lamotrigine monotherapy at a dosage below 200 mg per day is considered, at present, as a reasonable choice to treat epileptic patients who wish to become pregnant or are already pregnant.
- The significant increase in the relative risk of malformation highlighted by these new data does not correlate with a very significant increase in the absolute risk inherent to all pregnancies: the absolute risk increase of orofacial clefts after exposure to lamotrigine estimated by these authors remains lower than 1% [2] and consequently will

not much affect the basal risk of birth defects (2 to 4%).

- An association between orofacial clefts and exposure to some "older" antiepileptic drugs (barbiturates, phenytoïne, valproate) has been known for a long time, and this recent publication does not suggest that the risk related to lamotrigine exposure exceeds that related to other antiepileptic drugs.
- The risk for the foetus related to seizures or their consequences for the mother (falls, etc…) is often considered as superior to the risk of malformation related to the antiepileptic drug exposure. Consequently, the choice of the an antiepileptic drug in pregnancy is above all conditioned by the type of epilepsy and the individual clinical response, and the teratogenic profile of the drug represents a secondary selection criterion.

References

1. Morrow J et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006;77:193-198.
2. Holmes LB et al. Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy (abstract). Birth Defects Research Part A: Clinical and Molecular Teratology. 2006; 76(5): 318.

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