Title:

Pregnancy Registries: Larger Sample Sizes Essential. Holmes LB, Smith CR, Hernandez-Diaz S

Abstract:

Introduction: Most anticonvulsant drugs are teratogenic. The risks vary widely among drugs. Pregnancy registries were developed to improve data on fetal risks from "new" drugs.
Methods: Over 6,000 women from US and Canada have enrolled in the North American AED (antiepileptic drug) Pregnancy Registry since 1997. Of 24 mono-therapies evaluated, only two, phenobarbital (Holmes LB et al: Arch Neurol 2004; 61:673-8) and valproate (Wyszynski DF et al: Neurol 2005; 64:961-5), have shown a dramatic increase in the rate of all malformations (RR 3.4and 5.9) in small sample sizes (PB=77); VPA=149). 952 and 913 infants exposed to lamotrigine (LTG) and carbamazepine (CBZ) did not show significant increases in all malformations, but did have increases for oral clefts (RR 8.1 and 8.4), in comparison to the prevalence of isolated oral clefts (0.7/1,000) among 206,224 unexposed newborn infants at Brigham and Women's Hospital (BWH), Boston.
Results: In 2007, using less stringent release criteria, findings were released for six more drugs used as monotherapy: phenytoin (10/390=2.6%); clonazepam (2/50=4%); gabapentin (1/127-0.8%); topiramate (8/197=4.1%); oxcarbazepine (2/121=1.7%) and levetiracetam (4/197=2%). Only one drug showed a significant risk for all malformations: topiramate: 4.1% (RR 2.5; 95 CI 1.3-5.0 compared to BWH Surveillance [rate 1.62%] (Nelson K et al: N Engl J Med 1989; 320:19-23). There were 7 different malformations in the topiramate-exposed infants; two infants had a cleft lip deformity.
Discussion: These findings do not reach the release criteria for all malformations (lower 95 CI greater than 2.0) or the "Rule of Three" for specific malformations. These smaller sample sizes for these six drugs did not have statistical power to identify a 2X increase in all malformations in comparison to the external comparison group at BWH; more data is needed. A sample of 555 has 80% power to identify a two-fold increase in all malformations. Pregnancy registries should continue to enroll eligible women until they reach these larger sample sizes and can identify increased risks for specific malformations. We have documented an increased frequency of oral clefts after exposure to PB, VPA, CBZ, LTG and, now, possibly topiramate. The challenge is to understand why.

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