Antiepileptic Drug (AED) Safety in Pregnancy – epidemiological surveillance of congenital anomalies

Summary

As pregnant women are excluded from clinical trials, safety information for newly licensed medications is largely limited to pre-marketing animal studies. Post-marketing surveillance (pharmacovigilance) is essential for early detection of safety concerns, which is particularly difficult for birth defects due to the rarity of cases. Very large study populations are therefore needed to provide sufficient statistical power.

This Ulster University research, the first to use EUROCAT data sets for pharmacovigilance, relates to case-control studies performed in 2007-2009 to address hypotheses from the literature regarding teratogenicity of both new and old antiepileptic drugs (AEDs). For this, an AED database was created referring to 3.9M births including 98,075 livebirths, stillbirths or terminations with birth defects.

Impact

The research outputs related to three key AEDs: lamotrigine, valproic acid and carbamazepine.

(i) The lamotrigine study responded to a signal indicating a greater than 10-fold raised risk of orofacial clefts associated with lamotrigine, from the North American AED cohort. The study did not support the original signal, nor have subsequent updates.

(ii) Valproic acid was known to be teratogenic, but specific birth defects associated were unknown. This is the first study to systematically identify types of defect caused, with implications beyond clinical practice to elucidating teratogenic mechanisms of action.

(iii) The carbamazepine study confirmed only one significantly associated birth defect – spina bifida, with a much less raised risk than for valproic acid.

This research conducted by the university delivered a range of impacts covering healthcare, commercial and research applications.

Enhancing awareness

The work of the study has enabled both epileptic women of childbearing age and their healthcare professionals to make informed decisions through evidence-based practice that will reduce/prevent the risk of harm to unborn children potentially exposed to AEDs in early pregnancy.

A change in commercial process

In the light of the university's findings, GlaxoSmithKline (GSK) has reviewed its post-marketing epidemiological surveillance of the new generation AED lamotrigine in pregnancy.

Methodological practice

Another important impact has been strengthening the system of signal generation and evaluation in AED pharmacovigilance worldwide, with signals generated by one research study evaluated by one or more others. Ulster University's methodology has promoted this approach.

Sustainable impact

These Ulster University studies were the first to use EUROCAT data sets for investigation of specific drugs. Since then we have had many approaches from pharmaceutical companies and researchers requesting information on other medications. A PhD student at the university has analysed the data in relation to antidepressant safety, and an ongoing GSK-funded study continues to study lamotrigine. A European Framework 7 funded study coordinated by the University is also looking at antiasthmatics and antidiabetics.

Ulster University's work has been included in systematic reviews, and has been contributed to authoritative information platforms for pregnant women – such as Medscape, Motherisk and Patient.co.uk – to address concerns regarding the safety/risk to the developing foetus associated with maternal exposure to drugs.