Impact Case Study

UoA 3A: Allied Health Professions, Dentistry, Nursing and Pharmacy (Nursing and Health Science)

Antiepileptic Drug (AED) Safety in Pregnancy - epidemiological surveillance of congenital anomalies (birth defects)

The EU-funded European Surveillance of Congenital Anomalies network (EUROCAT), is coordinated and led by *Professor Dolk* since 2000. Surveillance to ensure early detection of new teratogens (i.e. birth defect causing exposures) originated following the thalidomide tragedy when thousands of children were born with limb defects due to a medication used in early pregnancy. EUROCAT population-based registries (42 registries in 23 European countries covering 1.7M births annually) annually transmit a dataset to a central database (Centre for Maternal, Fetal and Infant Research, Institute of Nursing and Health Research, University of Ulster) where quality validation, and epidemiologic surveillance and research are conducted relating to causes and prevention. *Dr Maria Loane* leads EUROCAT Central Database Management and Surveillance since 2002.

This case study concentrates on antiepileptic drug (AED) safety in pregnancy. *Visiting Professor Lolkje de Jong van den Berg*, who led until recently the Medication Safety in Pregnancy Working Group, collaborates closely on this research. For newly licensed medications, safety information is limited to pre-marketing animal studies with limited ability to predict harm in human pregnancy, since pregnant women are excluded from clinical trials. Post-marketing surveillance (pharmacovigilance) is essential for early detection of safety concerns, particularly difficult for birth defects due to their rarity. Very large study populations are needed to provide sufficient statistical power. This research is relevant to regulatory decisions regarding medication safety and product safety information, and to clinical decision-making regarding risk and benefit of treatment options.

The AED research output relates to three epidemiological case-control studies performed 2007-2009 using EUROCAT data to address hypotheses (or evaluate signals) from the literature regarding teratogenicity of AEDs: new generation AEDs -lamotrigine and older AEDs- valproic acid/carbamazepine. An AED database was created for this referring to 3.9M births (19 registries, 1995-2005) including 98,075 livebirths, stillbirths or terminations with birth defects.

i) The lamotrigine study responded to a signal indicating an over 10-fold raised risk of orofacial clefts associated with lamotrigine, from the North American AED cohort. The study did not find evidence of an increased risk of orofacial clefts, nor have subsequent updates to the study. *Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and on behalf of the EUROCAT AED Working Group (2008), Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology,71, 714-722*

ii) Valproic acid was known to be teratogenic, but there was uncertainty about which specific birth defects were associated with valproic acid exposure. The valproic acid study confirmed that 7 of 14 birth defects suggested in the literature were significantly associated with valproic acid exposure, with up to 13-fold risk. This is the first study to specifically and systematically identify types of birth defect caused, with implications beyond clinical practice to elucidating teratogenic mechanisms of action. *Jentink J, Loane M, Dolk H, Barisic*

I, Garne E, Morris J, de Jong-van den Berg L for the EUROCAT Antepileptic Study Working Group (2010), Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations, The New England Journal of Medicine, 362, 2185-2193

iii) The carbamazepine study proceeded as for valproic acid, and in contrast confirmed that only one birth defect - spina bifida – is significantly associated with early pregnancy exposure, with a much less raised risk than for valproic acid. *Jentink J, Dolk H, Loane M, Morris JK, Wellesley D, Garne E, de Jong-van den Berg L for the EUROCAT Antiepileptic Study Working Group (2010), Intrauterine Exposure to Carbamazepine and Specific Congenital Malformations: Systematic Review and Case-Control Study, British Medical Journal, 341, c6581 URL: http://www.bmj.com/content/341/bmj.c6581.pdf%2Bhtml*

EUROCAT Guide 1.3: Instructions for the Registration of congenital anomalies, a methodological guide developed by a process of consultation and consensus for EUROCAT research and surveillance, includes standardised congenital anomaly inclusion/exclusion criteria and classification and coding, used in the AED studies and all other EUROCAT studies, and available to other researchers in this field. This Guide also introduced the International Anatomic Therapeutic Classification coding of medication exposure for EUROCAT data, which, after a period of training and data source validation, has enabled the subsequent AED research. *EUROCAT (2005). EUROCAT Guide 1.3. Instructions for the registration and surveillance of congenital anomalies [Online], available at: http://www.eurocat-network.eu/ABOUTUS/DataCollection/GuidelinesforRegistration/Guide1_3InstructionManual*

Evidence of impact:

1. Enhancing awareness of women of childbearing age suffering from epilepsy and prescribed AEDs, and their Healthcare Professionals (HCPs), empowering both to make informed decisions through evidence-based practice that will reduce/prevent the risk of teratogenic harm to unborn children potentially exposed to AEDs.

The valproic acid study based on birth defect information of nearly 4M births had visibility in a high impact medical journal (NEJM) and in media. The reemphasis and further clarification and quantification of the known teratogenicity, was an important part of changing awareness and practice. The lamotrigine study which was largely negative was also important in helping women/HCPs make optimal medication choices based on updated patient information. Our research has been included in systematic reviews which inform evidence-based practice for women with epilepsy, but also with bipolar disorder, now a more common indication for use of some AEDs.

Contribution to Medscape, Motherisk and Patient.co.uk – authoritative, trusted, accessible online information for pregnant women/HCPs regarding the safety/risk to the developing foetus associated with maternal exposure to drugs. Rigorous literature reviewing allows rapid integration of new practice-changing evidence, such as our research on carbamazepine and lamotrigine.

2. A change in the process by which GSK practices post-marketing pharmacovigilance in relation to lamotrigine

In 2006, based on a signal from emerging data of the North American AED Pregnancy Registry, GSK alerted HCPs to a possible association of lamotrigine exposure with orofacial clefts. A US Federal Drugs Agency (FDA) warning followed (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/u cm126225.htm). GSK, FDA, UK Medicines and Health Regulatory Agency (MHRA) and European regulators (EMA) revised patient information, and agreed new research was needed to independently confirm this finding. GSK approached Prof. Dolk (2006) to establish the possibility of funding feasibility research by EUROCAT. EUROCAT offered more appropriate and powerful observational research methods, than heretofore possible using the GSK run International Lamotrigine Pregnancy Registry (1992-2010)**.** The results of the EUROCAT research that ensued were disseminated by confidential report to GSK and scientific paper. GSK shared the results with regulators who endorsed a revision to the core safety information provided in the Pregnancy and Lactation section of GSKs Global Data Sheet for lamotrigine, by insertion of - "*A case control study did not demonstrate an increased risk of oral clefts compared to other defects following exposure to lamotrigine*" . Based on our data, the regulators expressed an interest in monitoring a potential signal for club foot and lamotrigine, a study now underway within the GSK-funded research.

3. Benefit to the practice of other researchers in Europe

EUROCAT guidelines are utilised as the gold standard methodology by others when conducting research into birth defects and AEDs and are helping overcome non-comparability between studies. Another important impact is strengthening the system of signal generation and signal evaluation in AED pharmacovigilance among research groups worldwide, such that signals generated by one research study are evaluated by one or more others, as our methodology clearly adheres to and has promoted this approach. An indirect impact of this research is that, in order to ensure scientific independence and transparency in industry-sponsored research, Prof Dolk chaired the European Medicines Agency EncePP Working Group which developeda Code of Conduct for Scientific Independence and Transparency

4. Sustainable Impact

These studies were the first to use EUROCAT data for investigation of specific drugs. A PhD student at the University has since analysed the EUROCAT data in relation to antidepressant safety; The FP7 funded EUROmediCAT project co-ordinated by University of Ulster is looking further at newer generation AEDs, insulin analogs, antidepressants and antiasthmatic drugs, is testing new methodologies and has a wider aim of building a European system for reproductive safety evaluation.