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Prevalence of valproate syndrome in Europe from 2005 to 2014: A registry based multi-centre study

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ABSTRACT

Women with epilepsy need to continue to take anticonvulsants during their pregnancies to prevent seizures from occurring. Since the 1980's, it has been known that the use of valproate (an anticonvulsant) in the first trimester of pregnancy is associated with an increased risk of spina bifida. Recent studies have also demonstrated increased risks of other congenital anomalies as well as a risk of cognitive impairment. Doctors in the EU are now advised not to prescribe valproate in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. This study aimed to determine if there has been a reduction in the numbers of babies born with valproate syndrome in Europe from 2005 to 2014. Data from 15 European congenital anomaly registries, who are members of EUROCAT (A European network of population-based registries for the epidemiologic surveillance of congenital anomalies), identified 28 cases of valproate syndrome in 2.74 million births from 2005 to 2014. The prevalence of valproate syndrome in Europe significantly decreased from 0.22 per 10,000 births in 2005/6 to 0.03 per 10,000 births in 2013/14. One registry, Ile de la Reunion, had the majority of cases (17). After excluding these cases there still remained a decreasing trend even though it no longer reached statistical significance due to the small number of cases. This study emphasises the continued need for European collaboration in analysing rare exposures and rare anomalies.

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1. Introduction

Epilepsy effects about 0.5% of women of childbearing age (Wallace et al., 1998). It is necessary for these women to take anticonvulsants in order to prevent seizures from occurring, particularly during pregnancy when the seizures can be harmful to the women and also the fetus (Charlton et al., 2015; Tomson et al., 2016). However, first trimester exposure to anticonvulsants has been shown to increase the risk of congenital anomalies, particularly neural tube defects, occurring in the fetus (Dravet et al., 1992; Kaneko et al., 1999; Samren et al., 1997). Valproate has been identified as being more teratogenic than many other antiepileptic medications, increasing the risk of spina bifida and other congenital anomalies including atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis (Jackson et al., 2016; Jentink et al., 2010b; Tomson et al., 2015). The term fetal valproate syndrome was first described in 1984 (DiLiberti et al., 1984) and includes facial dysmorphism, congenital anomalies and neurodevelopmental problems. Prospective studies have also identified an increased risk of cognitive function and neuro-developmental problems in children with in-utero exposure to valproate (Bromley et al., 2014; Cummings et al., 2011; Wood et al., 2015). Advice to pregnant women to avoid taking valproate was first considered in 1984 (DiLiberti et al., 1984) and the warnings have been consistently strengthened with the National Institute for Clinical Excellence (NICE) Clinical Guidelines in 2012 recommending that women and girls of childbearing potential should be informed of the risks of malformation in an unborn child (2012). The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency in 2018 recommended new measures to avoid valproate exposure in pregnancy. However, if treatment with valproate has been providing good seizure control, women may be reluctant to change to another less efficient medication before or during pregnancy (Tomson et al., 2016). In addition other antiepileptics, such as Carbamazapine, are also teratogenic (Jentink et al., 2010a) and although the newer generation of antiepileptics (such as lamotrigine and levetiracetam) appear safer there is limited information on their effect on the developing fetus. As many pregnancies are also unplanned, it may be difficult to completely prevent fetal exposure to valproate, particularly in the first trimester.

European surveillance of congenital anomalies (EUROCAT) is a European network of population-based registries (http://www.eurocat-network.eu/). It surveys all pregnancy outcomes from high-quality multiple-source registries in Europe (Dolk, 2005). Annual statistical monitoring for five and 10 year trends in 94 non-independent congenital anomaly groups is performed to detect any changes in prevalence. The aim of this report is to determine if the prevalence of valproate syndrome has decreased in 15 EUROCAT registries from 2005 to 2014.

2. Methods

2.1. Data sources

Data in this study were obtained from EUROCAT registries that use multiple sources of information to ascertain cases in live births, late fetal deaths (20 + weeks' gestation), and terminations of pregnancy for fetal anomaly at any gestation. Sources, depending on the registry, include maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; specialist services including paediatric cardiology; and hospital discharge and child health records. The majority of registries ascertain cases diagnosed up to at least one year of life, with some registries having no upper age limit for registration. All cases are coded to the International Classification of Diseases (ICD) version 10 with 1-digit British Paediatric Association (BPA) extension. Cases can have up to nine syndrome or malformation codes. All coding is completed using the EUROCAT guide 1.4.

Aggregate Data were extracted from the Joint Research Council (JRC)-EUROCAT Central database in October 2016. The Central Database is managed by the JRC-EUROCAT Central Registry which operates the European level-coordination activities of the EUROCAT Network as part of the European platform on Rare Diseases Registration. The JRC-EUROCAT Central Registry is located at the European Commission Joint Research Centre in Ispra, Italy.

Fifteen registries had submitted data to EUROCAT for at least nine of the ten years from 2005 to 2014 (the study period) were included in the analysis. Cases of valproate syndrome were those with an ICD/BPA 10 code Q8680 (congenital malformations due to valproate), with registries requiring a confirmation of diagnosis by a clinical geneticist or paediatrician, rather than just a record of the mother having taken valproate. The present analysis was performed in the framework of the routine calculation of the EUROCAT prevalence tables for surveillance, using aggregated data and therefore the written text descriptions of the anomalies were not available.

2.2. Statistical analysis

The ten-year trend in prevalence was examined by fitting a multilevel Poisson regression model on the number of cases of the anomaly in each two year period within each registry, with the total number of births occurring in the area covered by the registry as the exposure. Random-effects models were used in order to account for potential heterogeneity across registries. A second multilevel Poisson model was fitted combining each two years of data and entering them as a categorical variable to provide estimates (and 95% confidence intervals (CI)) of the prevalence for each two year period adjusted for the registries as some registries did not have data for the whole of the study time period. All analyses were performed using Stata version 12.

3. Results

Table 1 shows that 28 cases with valproate syndrome were reported in 2.74 million births from 2005 to 2014. One registry, Ile de la Reunion, had the majority of cases (17 out of 28). Fig. 1 shows that the prevalence of valproate syndrome in Europe has significantly decreased over the past ten years ($p < 0.001$) from 0.22 per 10,000 births in 2005/6 (95% CI: 0.11 to 0.39) to 0.04 per 10,000 births in 2013/14

Table 1
Number of cases of valproate syndrome and prevalence per 10,000 births in EUROCAT registries 2005–2014.

Registry	Number of Pregnancies	Number of cases of valproate syndrome	Prevalence per 10,000 births (95% CI)
Tuscany, Italy	299,869	0	0.00 (0.00–0.12)
North Netherlands	173,671	3	0.17 (0 .04–0 .50)
Emilia Romagna, Italy	400,208	1	0.03 (0.01–0.14)
Vaud, Switzerland	79,037	1	0.13 (0.00–0.70)
Zagreb, Croatia[a]	66,163	0	0.00 (0.00–0.56)
Malta[a]	36,820	0	0.00 (0.00–1.00)
South Portugal	181,903	0	0.00 (0.00–0.20)
Antwerp, Belgium	184,955	1	0.05 (0.00–0.30)
Basque Country, Spain[a]	185,352	1	0.05 (0.00–0.30)
Saxony Anhalt, Germany	171,877	2	0.12 (0.01–0.42)
Cork and Kerry, Ireland[a]	89,379	0	0.00 (0.00–0.41)
Wales, UK	347,032	1	0.03 (0.00–0.16)
Ukraine	303,935	0	0.00 (0.00–0.12)
Ile de la Reunion, France	145,764	17	1.17 (0.68–1.87)
South East Ireland	74,527	1	0.13 (0.00–0.75)
Total	2,740,492	28	0.10 (0.07–0.15)

[a] These registries only submitted data for nine years.