Original

Knowledge and understanding of the dangers of anti-epileptic drugs in pregnancy

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Background to IN-FACT

The Independent Fetal Anti-Convulsant Trust (IN-FACT) was launched in November 2012 to support and give relief and assistance to all affected persons whose disabilities were caused by their mothers taking a medication known as, or used as, an anti-convulsant medication to treat their condition during pregnancy. Not all children who are exposed to anti-convulsant drugs are affected and the level of risk is determined by known factors such as type of anti-convulsant, dose of anti-convulsant and unknown susceptibility factors. Children who are diagnosed with a fetal anti-convulsant syndrome (FACS) are diagnosed by a medical specialist due to a constellation of physical and neurodevelopmental deficits they may present with.

Prevalence of the problem

It is estimated that around 0.5–1% of newborns may be exposed prenatally to an anti-convulsant drug. Sodium valproate reportedly carries the largest risk to developing infants and continues to be prescribed widely across a range of neurological and psychiatric conditions (Bialer 2012). According to prescription records (DIN-LINK data) there were over 21,500 women taking sodium valproate in 2010 in England and Wales. Scientific data demonstrates that around 10% of children exposed to sodium valproate will be born with a major congenital malformation (Samrén *et al* 1997), their IQ is likely to be lower (Meador *et al* 2009), with 29% requiring additional educational support (Adab *et al* 2001) and 6% being diagnosed with significant social communication difficulties such as autism (Bromley *et al* 2008). The latest research published on 31st January 2013 (Bromley *et al* 2013) states:

'*A 6 or 10 times increased prevalence of neurodevelopmental disorders is reported here for children with a history of prenatal VPA* [valproate] *exposure respectively for monotherapy and polytherapy exposure…*

'*The increased prevalence of ASDs* [autism spectrum disorders] *within this group is consistent with previous retrospective clinical research and reports from animal studies*.'

So far in the UK, since valproate came onto the market in 1973, IN-FACT calculate that approximately 20,000 children may have been affected. Bearing in mind the birth figures given by the Office for National Statistics (ONS) and the percentage noted by Man *et al* (2012) this potentially affects a larger number of children than those affected by thalidomide.

Many children will not have received a diagnosis of FACS, particularly if they do not have a major congenital malformation such as a heart defect or spina bifida, as they are less likely to be referred to a clinical geneticist. It is therefore very difficult to ascertain a definite figure pertaining to the number of children affected in the UK.

History of the problem and the development of scientific knowledge over time

Throughout the 1960s, 1970s and 1980s a number of case reports were published in the medical and scientific literature (Lawrence 1963, Meadow 1970, Hill *et al* 1974, Hanson *et al* 1976) which described children who had been exposed to one or more anti-convulsant drug and had one or more major birth defect. These case reports described children who had been born with a range of defects including spina bifida, cleft palate, heart defects and limb malformations. Some of the children in these case reports were also reported to have intellectual disabilities, neurodevelopmental delay or a learning disability whilst others were too young for this to be known. Birth defects occur for a number of reasons and individual case reports are not enough to show that the malformation in that child was likely to have been caused by exposure in the womb to the anti-convulsant. However, a number of case reports indicating the same type of defect in children suggests that closer investigation is required (Dalens 1980, Ardinger *et al* 1988), with the latest research in 2013 (Bromley *et al*) showing cause for concern due to the growing numbers of children with

neurodevelopmental problems and diagnosed ASDs where the mother has taken valproate during pregnancy.

Group studies: birth defects

Investigations into groups of children who have been exposed to a particular type of anti-convulsant provide a more reliable insight into the risks associated with exposure. Early studies conducted in France and the UK demonstrated that there was a potential increased risk of birth defects to children exposed to anti-convulsant medications (Winter *et al* 1987). Particular research in the 1970s and 1980s raised questions about the risks associated with phenobarbital (Luminal), phenytoin (Epanutin) and primidone (Mysoline) exposure (Hanson *et al* 1976, Dalens *et al* 1980, Ardinger *et al* 1988). Following the onset of use of sodium valproate (Epilim) concerns were also raised about the potential association between exposure in the womb to sodium valproate and spina bifida as well as other malformations (Oakeshott & Hunt 1989). Research in the 1990s delineated differences between anti-convulsants and the birth defects they were associated with. Older anti-epileptic drugs such as phenytoin (Epanutin), phenobarbital (Luminal) and primidone (Mysoline) were noted to be associated with cleft palate and/or lip and heart defects, whilst sodium valproate and, to a lesser extent, carbamazepine were noted to be associated with an increased risk of spina bifida. The largest risk for having a child with a birth defect has been demonstrated to be associated with the use of sodium valproate (Epilim) (Clayton-Smith & Donnai 1995). As well as the type of anti-convulsant, the dose taken has also been demonstrated by research to be key to the level of risk conveyed to the developing foetus. For example, the risk of having a child with a malformation or experiencing learning disabilities is higher when the dose of sodium valproate is over 1000mg daily (Clayton-Smith & Donnai 1995).

More recently, large registers of pregnancies both nationally and internationally have increased our understanding about the level of risk with each of the anti-convulsants. The largest of these is the EURAP (International Registry of Antiepileptic Drugs and Pregnancy) study whose recent research studied 3909 of women with epilepsy and their children (Tomson *et al* 2011). This study found that in comparison to children exposed to low doses of lamotrigine (less than 300mg daily) a high dose of carbamazepine (Tegretol) (above 1000mg daily) was associated with a fourfold increase in risk. High doses (greater than 1500mg daily) of sodium valproate (Epilim) were associated with a 16 times increase in risk and high doses (greater than 150mg daily) of phenobarbital (Luminal) were associated with an eightfold increase in risk. Lower doses of all three of these anti-convulsants were still associated with increased risks in comparison to lower dose lamotrigine but the risks were substantially smaller.

A key finding across all research published is that *whatever the level of risk* ***not*** *every child is affected* following prenatal exposure to anti-convulsants. Answering why some children are affected whilst others are not is complex and is likely to be linked to variations in exposure (eg amount of drug that passes into the placenta), how the mother and/or the foetus metabolises the drug and the genetic makeup of the foetus.

Group studies: neurodevelopmental outcome/learning disability

Exposure in the womb to anti-convulsant drugs has also been associated with an increased risk to the developing brain which leads to what historically was termed 'mental retardation' (Committee on Safety of Medicines 1983). This term has been replaced with the term 'learning disability' in the UK and refers to someone who experiences difficulties in acquiring knowledge and skills to the level expected for their age. More recently research has turned its attention to the cognitive and behavioural abilities of children exposed to anti-convulsants in the womb.

Similar to the findings relating to birth defects the type and dose of an anti-convulsant are important when assessing the level of risk to the developing child. There is less research into this risk but our current level of knowledge suggests that exposure to sodium valproate (Epilim) when the dose is above 1000mg daily carries the highest level of risk. Exposure at this level of sodium valproate has been reported to be associated with increased need for educational support and performance in IQ tests below the majority of children's peers.

There is also evidence that children exposed to sodium valproate are at an increased risk of experiencing social communication difficulties and being diagnosed with ASDs (Bromley *et al* 2008).

The research for carbamazepine (Tegretol) has been conflicting, but the majority of studies fail to find evidence that children exposed to carbamazepine experience a higher incidence of learning disability. However, children who have been diagnosed with the physical symptoms associated with prenatal exposure and have a diagnosis of fetal carbamazepine syndrome

may be more likely to experience learning difficulties (Gaily *et al* 2004).

New anti-convulsants

It takes a long time to collect data to investigate the longer-term health and development of children exposed in the womb and therefore we are currently without adequate information about a number of anti-epileptic drugs including levetiracetam, topiramate, zonisamide, lamotrigine and neurontin.

A small amount of research has been conducted (Shallcross *et al* 2011) which fails to find an association between levetiracetam or lamotrigine and reduced learning ability in children exposed in the womb, although this research mainly comes from a single research group and replication in other cohorts is required before conclusions can be made.

Sodium valproate

The drug sodium valproate (Epilim) is manufactured by the pharmaceutical company Sanofi Aventis, amongst others, and has been prescribed in the UK since the 1970s. Despite its efficaciousness for certain types of seizures, research has demonstrated that it carries a higher level of risk to the exposed foetus. The first case reporting the effects of sodium valproate during pregnancy appeared in 1981. This grew to be a hot topic within the medical profession in the 1980s with numerous reports appearing in medical journals (Dalens *et al* 1980).

Since IN-FACT's last survey into the amount of information given concerning valproate, in particular in pregnancy, it has become apparent that the majority of information available to give to women of childbearing age or pregnant women is insufficient, and mums-to-be are not being given the chance to make an informed choice.

IN-FACT, together with our parental support group Fetal Anti-Convulsant Syndrome Association (FACSA) hope to change this, ensuring that all women, no matter what condition they might be prescribed an anti-convulsant drug for — epilepsy, bipolar disorder, migraines, or as a pain relief — must always be given all the relevant information possible so that they can make an informed choice.

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***Please note that the comments that follow after the references are the author's own.**

References

Adab N, Jacoby A, Smith D *et al* (2001). Additional educational needs in children born to mothers with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry* 70(1):15-21.

Ardinger HH, Atkin JF, Blackston RD *et al* (1988). Verification of the fetal anticonvulsant syndrome. *American Journal of Medical Genetics* 29(1):171-85. ***The first group case series of children exposed prenatally to sodium valproate highlighting potential characteristics of the syndrome.***

Bialer (2012). Neurological & psychiatric conditions: why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia* 53(Sppl 7):26-33.

Bromley R, Mawer G, Clayton-Smith J *et al* (2008). Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 71(23):1923-4. ***The first prospective study to demonstrate an increased prevalence of autistic spectrum disorders in children exposed to sodium valproate.***

Bromley RL, Mawer G, Briggs M *et al* (2013). The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *Journal of Neurology, Neurosurgery and Psychiatry* 84(6):637-43.

Clayton-Smith J, Donnai D (1995). Fetal valproate syndrome. *Journal of Medical Genetics* 32(9):724-7. **The first paper to state that there definitely was a fetal valproate syndrome.**

Committee on Safety of Medicines (1983). Sodium valproate (Epilim) and congenital abnormalities. *Current Problems* 9:1-2. London: HMSO. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2024416.pdf [Accessed 29 October 2013].

Dalens B, Raynaud EJ, Gaulme J (1980). Teratogenicity of valproic acid. *Journal of Pediatrics* 97(2):332-3. ***The first report of an infant with major congenital malformations thought to be linked to exposure to sodium valproate.***

Gaily E, Kantola-Sorsa E, Hiilesmaa V *et al* (2004). Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 62(1):28-32. ***This large and well designed study found that the IQ of children exposed to carbamazepine was not significantly different from a group of unexposed children.***

Hanson JW, Myrianthopoulous NC, Harvey MA *et al* (1976). Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis of the fetal hydantoin syndrome. *Journal of Pediatrics* 89(4):662-8. ***The first paper to identify that intellectual abilities may be lower in children with fetal hydantoin syndrome.***

Hill RM, Verniaud WM, Horning MG *et al* (1974). Infants exposed in utero to antiepileptic drugs: a prospective study. *American Journal of Diseases of Children* 127(5):645-53. ***The first prospective study to investigate this issue.***

Lawrence A (1963). Anti-epileptic drugs and the foetus. *British Medical Journal* 2(1267). ***Possibly the first report of problems in a child where an antiepileptic drug is considered the cause.***

Man SL, Petersen I, Thompson M *et al* (2012). Antiepileptic drugs during pregnancy in primary care: a UK population based study. *PLoS One* 7(12):1-6.

Meador K, Baker GA, Browning N *et al* (2009). Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *New England Journal of Medicine* 360(16):1597-605.

Meadow SR (1970). Congenital abnormalities and anticonvulsant drugs. *Proceedings of the Royal Society of Medicine* 63(4):48-9. ***The first group study into the incidence of major malformations.***

Oakeshotte P, Hunt GM (1989). Valproate and spina bifida. *British Medical Journal* 298(6683):1300-1.

Samrén EB, van Duijn CM, Koch S *et al* (1997). Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 38(9):981-90. ***This collaboration of a number of different research groups highlights the importance of the dose of the drug.***

Shallcross R, Bromley RL, Irwin B *et al* (2011). Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 76(4):383-9. ***The first study to investigate the rate of developmental delay in a group of children exposed to levetiracetam.***

Tomson T, Battino D, Bonizzoni E *et al* (2011). Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurology* 10(7):609-17. ***The largest study to date which shows level of risk by dose of antiepileptic drug.***

Winter RM *et al* (1987). Increased risk of birth defects : fetal valproate syndrome: Is there a recognisable phenotype? *Journal of Medical Genetics* 24(11):692-5.

Williams J. MIDIRS Midwifery Digest, vol 23, December 2013, no 4, pp 462–464.