Valproic Acid
Sodium Valproate
Use in Pregnancy
**Introduction**

Valproic acid (VPA), di-n-propylacetic acid, was first synthetized in 1882 by Burton and used as a solvent for pre-clinical testing of lipophilic drugs (1). Its pharmacological activity was not realised until 1962 when Pierre Eymard used VPA to dissolve several newly synthesised khelline derivatives (1). As part of the study Eymard and his colleagues evaluated anticonvulsant properties of these new entities in pentylenetrazole seizure test. They found that the solvent alone- VPA exerted an anticonvulsant effect (1). The discovery was followed by pre-clinical tests focusing on anticonvulsant activity of valproate in rabbits and mice and five years later, in 1967, the drug was approved for the treatment of epileptic seizures in France. It later became marketed in other countries worldwide and used in several types of epilepsy. In the United Kingdom VPA was first licensed in 1975 (2).
Mode of action

The mechanism of action of VPA is not fully understood but it is clear that the drug acts through several molecular mechanisms. The drug is shown to increase GABA levels in the brain and at high concentrations inhibits nerve terminal GABA-T inhibiting GABA degradation (3). Blockage of voltage-dependant Na+ channels appears to play a role in activity against partial seizures. Also blockage of glutaminergic mechanisms may contribute to anticonvulsant activity, although the available data is still inconsistent (3). VPA also acts directly on mitochondria impairing cellular energy metabolism (4).

VPA is effective against absence seizures, myoclonic and generalized tonic-clonic attacks (3). It does not cause sedation but this feature is absent when VPA is used in combination with phenobarbital (3). Semisodium valproate (Depakote®) is licensed for the management of psychiatric conditions such as bipolar disorder or schizophrenia. In some countries the drug is indicated for the prevention of migraine.
Risks associated with valproate products

The adverse effects of VPA include nausea, vomiting, abdominal pain and heartburn which are dose related. It is therefore recommended to titrate valproate slowly to achieve prescribed doses (3). The drug may also cause reversible weight gain, increased appetite and alopecia. Patients under the age of 2, those taking multiple medication are at higher risks of developing hepatotoxicity within 4 months from starting valproate and therefore monitoring of liver functions is recommended, especially at the beginning of the therapy (3).

VPA was initially considered safe with only minor adverse reactions (5). The first report of the effects associated with the VPA use during pregnancy was published in 1980 by Dalens. In 1984 Di Liberti proposed the term ‘Foetal Valproate Syndrome’ (FVS) to describe teratogenic effects caused by VPA (4). Since then more reports emerged which described minor and major anomalies including neurodevelopmental and cognitive problems (4). Although VPA is commonly prescribed in Europe there is a lack of prospective cohort studies and the available case series and retrospective studies are not free of bias. This impedes the interpretation of the studies as it was noted in Conchrane review in 2004 (6).
Evidence of teratogenic effects of valproate

The risk of congenital malformations following prenatal exposure to VPA is estimated to be 6-9% in comparison to 2-3% in the general population (4). Foetal Valproate Syndrome includes neural tube defects, congenital heart defects, orofacial clefts, craniosynostosis, limb and genitourinary defects (4). The face of affected children may also show distinctive features such as: broad forehead, thin arched eyebrows, epicanthic folds, coloboma of the iris, infraorbital grooves, flat nasal bridge and long and smooth philtrum with a thin upper lip (4). Minor to moderate mental retardation with low IQ score are also noticed in FVS. Severe retardation requiring supervision in adult life is less frequent (4). Global developmental delay is observed in severely affected children. It is characterized by a delay in comprehension and expression of speech, poor muscle tone and co-ordination and poor execution of the daily activities (dressing up, handwriting, swimming and toilet training). Additionally, children affected by FVS may display the features of autistic spectrum disorder and childhood autism. The occurrence of these conditions is three and five times higher than in the general population, respectively (7, 8). It is considered that disruption of early embryonal serotoninergic neuronal development could be responsible for this disorder (4). There are a few hypothesis of the FVS aetiology. Most of them refer to genetic factors and teratogenic effects of enzymes involved in valproate metabolism (epoxide hydrolase), folate antagonism or enzymes directly inhibited by valproates (histone deacetylase HDAC inhibition) (4). Continued over...
Currently, alteration of gene expression as a consequence HDAC inhibition appears to be most plausible (5). VPA is well absorbed when administered orally (bioavailability 80%) and passes the placenta by passive diffusion. Notably, the foetal drug concentration has been found to be higher than maternal (3, 4). The risk of FVS is greater at doses exceeding 1000mg/day and a dose reduction should be considered in pregnant women when the therapy change is not an option (4). Additionally, 4mg/day of folic acid is advisable in the pre-conception period and during the first trimester (4).

Dysmorphic features together with developmental delay have been also described with other antiepileptic drugs including phenytoin and carbamazepine (2). However, according to a study conducted in the UK by Adab et al., 40% of children exposed to VPA during pregnancy required additional educational needs in comparison to 8.2% and 13.6% of children exposed to carbamazepine and phenytoin, respectively (2). Similarly, more children exposed to VPA displayed moderate to severe dysmorphic features (44%) in comparison to children exposed to carbamazepine (9.2%) (2). Decrease in verbal intelligence and autism and autistic spectrum disorder have only been reported with exposure to VPA (4). Adab et al. advocate the use of lamotrigine or carbamazepine in generalised epilepsy starting from the pre-conceptual period (2). Even though these drugs appear to carry lower risks of malformations, the treatment decision has to be individualised and potential withdrawal implications have to be taken into consideration. It is also advisable to attempt a monotherapy as a safer option (5).
Current recommendations

The recent PRAC recommendation is consistent with the current state of knowledge. The prescribers and patients have been advised to avoid VPA in girls and women who are pregnant or can become pregnant if other alternatives are clinically acceptable. Monotherapy, dose adjustments and high dose folic acids should be considered if substitute drugs are not effective or not tolerated. All therapeutic decisions should be discussed with patients and all risks clearly communicated.
References


