FOR HEALTHCARE PROVIDERS: INFORMATION ABOUT VALPROIC ACID

Valproic acid (VPA) is an anti-seizure drug (ASD) that is used to treat epilepsy. VPA is administered orally or via injection. Sodium valproate and divalproex sodium are other forms of the ASD, but VPA is the pharmacologically active component and will be used in this summary to represent all forms of this medication. VPA is used to treat different seizure types, including generalized tonic-clonic, absence, and myoclonic seizures, as well as epilepsy syndromes (e.g. Dravet, Lennox-Gastaut)[1].

Effects of VPA on child development

VPA is a known teratogen and is associated with an increased risk of major congenital malformations (MCMs) when taken during the prenatal period[2,3]. These MCMs include spina bifida, atrial septal defect, hypospadias, and face and skull malformations.

The prevalence of MCMs in children exposed to VPA in utero is 10.93% and the risk of MCMs is 2-7 times greater than other widely used ASDs[3].

VPA is also recognized as a neurobehavioural teratogen and likely crosses the placenta in potentially clinically important amounts[3]. Exposure in utero is associated with an increased risk of neurodevelopmental impairments, including poorer school performance, lower IQ in school aged children, and an increased risk of autism spectrum disorder[4,5]. It is important that women or girls have a discussion with their health care provider before discontinuing VPA.

Additional risks

Treatment with VPA may increase the risk of osteoporosis later in life since it has been shown to reduce bone mineral density[6].

RECOMMENDATIONS[1,2]

- Whenever possible, VPA should be avoided in women of child bearing potential.
- Women with epilepsy taking VPA should be counselled on the risks of malformations and possible neurodevelopmental impairments in an unborn child and given information about alternative ASDs.
- Physicians should specifically discuss the risk of continued use of VPA to the unborn child, being aware that higher doses of VPA (more than 800 mg/day) and polytherapy are associated with greater risk.
- Both teratogenicity and efficacy need to be considered. Risks and benefits need to be carefully weighed in women with generalized epilepsies, such as juvenile myoclonic epilepsies, for which VPA has the best evidence of efficacy.
- When used in women of childbearing potential, VPA should be prescribed at the lowest effective dose, not exceeding 500-600 mg/day when possible.
- For women on VPA who are already pregnant, withdrawal can be considered if risks are acceptable and if VPA is not needed to maintain seizure control.

VPA Dosing Recommendations[7,8]

	Initial Dose	Administration and Titration	Usual Maintenance Dose
For children	10 mg/kg/day	• Given 2-3x/day • 5-10 mg/kg/day every 7 days	30-60 mg/kg/day
For adults	500 mg/day	• Given 2-4x/day • 250 mg/day every 7 days	500-4000 mg/day

References

(1) National Institute for Health and Clinical Excellence (NICE). (2012). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). (Clinical Guideline 137). Found at: http://guidance.nice.org.uk/CG137.

(2) Tomson, T., Marson, A., Boon, P., Canevini, M.P., Covanis, A., Gaily, E., Kalviainen, R., Trinka, E. (2015) Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia. 56(7):1006-1019.

(3) Weston, J., Bromley, R., Jackson, C.F., Adab, N., Clayton-Smith, J., Greenhalgh, J., Hounsome, J., McKay, A.J., Tudur Smith, C., Marson, A.G. (2016). Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews. 7;11:CD010224.

(4) Bromley, R., Weston, J., Adab, N., Greenhalgh, J., Sanniti, A., McKay, A.J., Tudur Smith, C., & Marson, A.G. (2014) Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database of Systematic Reviews, Issue 10. Art. No.:CD010236.

(5) Elkjær, L.S., Bech, B.H., Sun, Y., Laursen, T.M., & Christensen, J. (2018) Association Between Prenatal Valproate Exposure and Performance on Standardized Language and Mathematics Tests in School-aged Children. JAMA Neurology 1;75(6):663-671.

(6) Petty, S.J., O'Brien, T.J., Wark, J.D. (2007) Anti-epileptic medication and bone health. Osteoporosis International, 18,129–142.

(7) Abou-Khalil, B.W. (2019). Update on Antiepileptic Drugs. Continuum (Minneap Minn);25(2):508-536.

(8) Perucca, E., Dulac, O., Shorvon, S. et al. (2001). Harnessing the Clinical Potential of Antiepileptic Drug Therapy. CNS Drugs 15, 609–621.

EPLINK
THE EPILEPSY RESEARCH PROGRAM OF THE ONTARIO BRAIN INSTITUTE

More information and the complete set of guidelines can be found at: ontarioepilepsyguidelines.ca