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Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study.

Tomson T[1], Battino D[2], Bonizzoni E[2], Craig J[2], Lindhout D[2], Perucca E[2], Sabers A[2], Thomas SV[2], Vajda F[2]; EURAP Study Group.

Collaborators (42)

Finnell R, Robert-Gnansia E, Pantaleoni C, Schmidt B, Brodie MJ, Kamga BM, Gargantini L, Prato L, Cirillo S, Nardini G, Specchio LM, van Puijenbroek E, Nakken KO, Schmitz B, Ferri MM, Zarubova J, Kuba R, Milovanović M, Russell A, Kälviäinen R, Luef G, Ohtani H, Safcák V,Tettenborn B, Kurthen M, Mameniskiene R, De Marinis A, Neufeld M, Özkara Ç, Kinay D, Čebular B, Kiteva-Trencevska G, Lai CW, Yu HY, Cabral-Lim L, Toidze O, Kasradze S, Kochen S, Vitezic D, Jedrzejczak J, Kwan P, Baulac M.

Author information

- [1]From the Department of Clinical Neuroscience (T.T.), Karolinska Institutet, Stockholm, Sweden; Epilepsy Center (D.B.), Department of Neurophysiology and Experimental Epileptology, IRCCS Neurological Institute Carlo Besta Foundation, Milan; Department of Clinical Science and Community (E.B.), Section of Medical Statistics and Biometry G.A. Maccacaro, Faculty of Medicine and Surgery, University of Milan, Italy; Belfast Health and Social Care Trust (J.C.), Belfast, Ireland; Department of Medical Genetics (D.L.), University Medical Center Utrecht; SEIN-Epilepsy Institute in the Netherlands Foundation (D.L.), Hoofddorp, the Netherlands; Department of Internal Medicine and Therapeutics (E.P.), University of Pavia, and Clinical Trial Center, C. Mondino National Neurological Institute, Pavia, Italy; The Epilepsy Clinic (A.S.), Department of Neurology, Rigshospitalet University State Hospital, Copenhagen, Denmark; Department of Neurology (S.V.T.), Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala State, India; and Departments of Medicine and Neurology (F.V.), University of Melbourne, Royal Melbourne Hospital, Australia. torbjorn.tomson@karolinska.se.
- [2]From the Department of Clinical Neuroscience (T.T.), Karolinska Institutet, Stockholm, Sweden; Epilepsy Center (D.B.), Department of Neurophysiology and Experimental Epileptology, IRCCS Neurological Institute Carlo Besta Foundation, Milan; Department of Clinical Science and Community (E.B.), Section of Medical Statistics and Biometry G.A. Maccacaro, Faculty of Medicine and Surgery, University of Milan, Italy; Belfast Health and Social Care Trust (J.C.), Belfast, Ireland; Department of Medical Genetics (D.L.), University Medical Center Utrecht; SEIN-Epilepsy Institute in the Netherlands Foundation (D.L.), Hoofddorp, the Netherlands; Department of Internal Medicine and Therapeutics (E.P.), University of Pavia, and Clinical Trial Center, C. Mondino National Neurological Institute, Pavia, Italy; The Epilepsy Clinic (A.S.), Department of Neurology, Rigshospitalet University State Hospital, Copenhagen, Denmark; Department of Neurology (S.V.T.), Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala State, India; and Departments of Medicine and Neurology (F.V.), University of Melbourne, Royal Melbourne Hospital, Australia.

Abstract

OBJECTIVE:

To assess the risk of major congenital malformations (MCMs) in association with maternal use of valproic acid (VPA) in monotherapy or adjunctive therapy, and its relationship with dose.

METHODS:

The analysis was based on prospectively acquired data from EURAP, a registry enrolling women treated with antiepileptic drugs (AEDs) in early pregnancy, in which the primary outcome is presence of MCMs at 1 year after birth. Exposure was defined as type and dose of AEDs at time of conception. A comparison was made among 3 exposure types: (1) VPA monotherapy (n = 1,224); (2) VPA combined with lamotrigine (LTG) (n = 159); and (3) VPA combined with another AED but not LTG (n = 205).

RESULTS:

The frequency of MCMs at 1 year after birth was 10.0% for VPA monotherapy, 11.3% for exposures to VPA and LTG, and 11.7% for exposures to VPA + another (non-LTG) AED. Regardless of exposure group, the frequency of MCMs increased with dose of VPA, being highest at doses ≥1,500 mg/d (24.0% for monotherapy, 31.0% for VPA + LTG, and 19.2% for VPA + other AEDs), and was similar across treatment groups at the

lowest VPA dose level of <700 mg/d (5.9% for monotherapy, 7.0% for VPA + LTG, and 5.4% for VPA + other AEDs).

CONCLUSIONS:
The risk of MCMs associated with VPA exposure increases with increasing VPA dose, both in the presence and in the absence of one concomitant AED, and appears to be related primarily to the dose of VPA.