

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) or Hyponatraemia Associated with Valproic Acid Four Case Reports from the Netherlands and a Case/Non-Case Analysis of Vigibase

Erna Beers,¹ Eugene P. van Puijenbroek,¹ Imke H. Bartelink,² Carolien M.J. van der Linden³ and Paul A.F. Jansen⁴ ¹ Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands ² Department of Pharmacy, University Medical Centre Utrecht, Utrecht, the Netherlands ³ Geriatric Department, Catharina Hospital, Eindhoven, the Netherlands ⁴ Geriatric Department, University Medical Centre Utrecht, Utrecht, the Netherlands

Abstract

Background: The Netherlands Pharmacovigilance Centre Lareb received four cases of severe symptomatic hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with valproic acid use, in which a causal relationship was suspected. This study describes these cases and gives support for this association from Vigibase, the adverse drug reaction (ADR) database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre.

Methods: Cases of hyponatraemia in valproic acid users are described. In a case/non-case analysis, the strength of the association between reported cases of hyponatraemia and the use of valproic acid in Vigibase was established by calculating a reporting odds ratio, adjusted for possible confounding by concomitant medication.

Results: Four females aged 57, 67, 71 and 88 years developed symptomatic hyponatraemia or SIADH after starting valproic acid. Despite concomitant medication or co-morbidity, a causal relationship was plausible. In Vigibase, valproic acid is disproportionately associated with hyponatraemia and SIADH (corrected reporting odds ratio 1.83 [95% CI 1.61, 2.08]).

Discussion: Based on the described cases and the reports from Vigibase, a causal relationship between valproic acid use and hyponatraemia or SIADH can be suspected. The mechanism by which valproic acid could cause hyponatraemia or SIADH has not been fully elucidated. Valproic acid use could lead to reduced sensitivity of hypothalamic osmoreceptors. It also might directly affect tubular cell function, thereby leading to SIADH. It might be expected that a combination of effects on the osmoreceptors and a lack of compensation of the salt-water unbalance by the nephrons causes SIADH in some patients using valproic acid. It could be a dose- or concentration-related adverse effect.

Conclusion: In this report, severe symptomatic hyponatraemia and SIADH have been associated with the use of valproic acid. With this study, not only is the number of published cases doubled, but also the data from Vigibase strongly support the association. Since hyponatraemia and SIADH have a high morbidity, health professionals should be aware of this potential ADR.

For more information, please contact info@lareb.nl