

Valproic Acid and Midazolam Infusion for Post-Traumatic Seizures in Patients with Severe Traumatic Brain Injury Yirui Sun MD PhD; Jian Yu MD; qiang yuan; Jin Hu

Introduction

Post-traumatic seizures have been documented to occur frequently after traumatic brain injury, with a significant proportion demonstrated to be non-convulsive. To summarize the incidence of post-traumatic seizures and proportions of convulsive and non-convulsive seizures. To determine efficiency of valproic acid and midazolam as first line anticonvulsants in the prophylactic and rapid control of seizure attacks.

Methods

A retrospective investigation was conducted from 2011 to 2016 on patients with severe traumatic brain injury. Continuous electroencephalograph (cEEG) monitoring was applied for seizure determination and treatment evaluation. Valproic acid (VPA) and midazolam (MDZ) infusion were used in prophylactic treatment and rapid control of seizures, respectively. Mortality, length of ICU/Hospital stay, Glasgow outcome scales were compared among the groups.

Learning Objectives Continuous

electroencephalograph is essential to detect post-traumatic seizures in severe TBI patients. Non-convulsive seizures showed significant impact on patient outcomes. Valproic acid and midazolam infusion could successfully control approximately 40% of seizure attacks, while nearly 10% would turn into refractory seizures.

Results

After analysing 455 cases of severe TBI, we have detected 92 (20.22%) cases with posttraumatic seizures. The majority of first post-traumatic seizures were detected within 3 days after injury, which could be related to low VPA plasma concentrations. MDZ infusion could rapidly end epileptic activity in 39.13% of seizure patients, though 10.87% turned into refractory seizures. Non-convulsive seizures accounted for 44.57% of all posttraumatic seizures and 9.01% of all patients with severe TBI. Compared to convulsive ones, Non-convulsive seizures had greater impact on outcomes.

Conclusions

Post-traumatic seizures is a major complication for severe TBI. cEEG monitoring is recommended to identify nonconvulsive seizures that had great impacts on outcomes. With VPA infusion as prophylactic antiseizure therapies, MDZ is effective as first line anti-seizure medications.

References

1. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. The New England journal of medicine. 1998;338(1):20-4. 2.Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. Journal of neurosurgery. 1999;91(5):750-60. 3.Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch L1, Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743-8. 4. Jordan KG. Continuous EEG and evoked potential monitoring in the neuroscience intensive care unit. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 1993;10(4):445-75. 5.Vespa PM, Nenov V, Nuwer MR. Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 1999;16(1):1-13.

References (Continued)

6.Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35(12):2830-6. 7.Vespa P, Prins M, Ronne-Engstrom E, Caron M, Shalmon E, Hovda DA, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. Journal of neurosurgery. 1998;89(6):971-82. 8.Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2016.

9.Chadwick DW. Concentration-effect relationships of valproic acid. Clinical pharmacokinetics. 1985;10(2):155-63. 10.AAAM. Abbreviated Injury Scale (AIS) 2005 Manual. 1 ed. Gennarelli TA, Wodzin E, editors: Association for the Advancement of Automotive Medicine; 2005.

11.Demetriades D, Kuncir E, Murray J, Velmahos GC, Rhee P, Chan L. Mortality prediction of head Abbreviated Injury Score and Glasgow Coma Scale: analysis of 7,764 head injuries. Journal of the American College of Surgeons. 2004;199(2):216-22. 12.Zehtabchi S, Soghoian S, Liu Y, Carmody K, Shah L, Whittaker B, et al. The association of coagulopathy and traumatic brain injury in patients with isolated head injury. Resuscitation. 2008;76(1):52-6. 13. Alvarez M, Nava JM, Rue M, Quintana S. Mortality prediction in head trauma patients: performance of Glasgow Coma Score and general severity systems. Crit Care Med. 1998;26(1):142-8. 14.Brain Trauma F, American Association of Neurological S, Congress of Neurological S. Guidelines for the management of severe traumatic brain injury. Journal of neurotrauma. 2007;24 Suppl 1:S1-106. 15.Noai M, Soraoka H, Kajiwara A, Tanamachi Y, Oniki K, Nakagawa K, et al. Cytochrome P450 2C19 polymorphisms and valproic acid-induced weight gain. Acta neurologica Scandinavica. 2016;133(3):216-23. 16.Ebner T, Burchell B. Substrate specificities of two stably expressed human

liver UDP-glucuronosyltransferases of the UGT1 gene family. Drug metabolism and disposition: the biological fate of chemicals. 1993;21(1):50-5.

17.Jin C, Miners JO, Lillywhite KJ, Mackenzie PI. Complementary deoxyribonucleic acid cloning and expression of a human liver uridine diphosphate-glucuronosyltransferase glucuronidating carboxylic acid-containing drugs. The Journal of pharmacology and experimental therapeutics. 1993;264(1):475-9.

18.Chung JY, Cho JY, Yu KS, Kim JR, Lim KS, Sohn DR, et al. Pharmacokinetic and pharmacodynamic interaction of lorazepam and valproic acid in relation to UGT2B7 genetic polymorphism in healthy subjects. Clinical pharmacology and therapeutics. 2008;83(4):595-600.

19.Klotz U. The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. Clinical pharmacokinetics. 2007;46(4):271-9.

20.Loscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009;50(1):1-23.

21.Kiang TK, Ho PC, Anari MR, Tong V, Abbott FS, Chang TK. Contribution of CYP2C9, CYP2A6, and CYP2B6 to valproic acid metabolism in hepatic microsomes from individuals with the CYP2C9*1/*1 genotype. Toxicological sciences : an official journal of the Society of Toxicology. 2006;94(2):261-71.

22.Innocenti F, Liu W, Fackenthal D, Ramirez J, Chen P, Ye X, et al. Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene. Pharmacogenetics and genomics. 2008;18(8):683-97.

23.Nagar S, Zalatoris JJ, Blanchard RL. Human UGT1A6 pharmacogenetics: identification of a novel SNP, characterization of allele frequencies and functional analysis of recombinant allozymes in human liver tissue and in cultured cells. Pharmacogenetics. 2004;14(8):487-99. 24.Ibarra M, Vazquez M, Fagiolino P, Derendorf H. Sex related differences on valproic acid pharmacokinetics after oral single dose. Journal of pharmacokinetics and pharmacodynamics. 2013;40(4):479-86. 25.Birnbaum AK, Ahn JE, Brundage RC, Hardie NA, Conway JM, Leppik IE. Population pharmacokinetics of valproic acid concentrations in elderly nursing home residents. Therapeutic drug monitoring. 2007;29(5):571-5.

[Default Poster]