Misuses of valproic acid: an evaluation on clinical records from the Emergency Department of Galliera - Hospital in Genoa

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A research was carried out using the "PIESSE" program on patients recovered in the Emergency Department of the Galliera Hospital of Genoa. By using the key words "valproic acid", "valproate" and "sodium valproate", 39 records were identified in the period from 2008 to 2013. Records referred to both epileptic patients and those suffering from bipolar disorders or psychoses. Our data reveal that the cases of underdosing are much more than those of overdosing, being 28 (71.8%) the subjects admitted for valproic acid (VA) underdosing versus 11 cases (28.2%) of overdosing. Among patients with VA plasma concentration <50 mg/l (underdosed), 20 out or 28 (71.4%) were epileptic. Despite the literature, our case records show a frequency of underdosing almost three times higher than overdosing. For patients with a diagnosis of "epilepsy", a recent clinical trial shows dosages of VA within the therapeutic range in 45.69% of patients undergoing chronic therapy with VA (1). In our study 71.4% of epileptic patients had a VA therapeutic range below 50 mg/l. In other studies a lack of adherence to the treatment was shown to vary between 30-50% (2). Generally, in subjects with bipolar or psychotic disorders the main cause of underdosing is the decision of patient to stop the therapy without consulting his/her physician, very often complaining of some adverse event. About 15% of patients treated for epilepsy in our study are foreign, coming from abroad and the underdosage is due to a wrong comprehension of the posology or to the change of the name and dosage of the drug used. Our study revealed a poor compliance, both in patients with epilepsy and in patients with bipolar disorders. The most compliant patients were those with a diagnosis of "Bipolar Disorder" (20.5% underdosing vs. 51.3% of the total of 39 patients). This is an indication for the effective support by the referring mental health centres and psychiatrists. In the subjects with overdosing of VA, a progressive evolution of the acute treatment was noted. The use of levocarnitine and high-flow hemodyalisis has been recently confirmed (3-4). Early dosing or plasmatic concentrations of VA in Emergency Departments could permit to distinguish the cases of lack of adherence to treatment from the cases in which the drug is ineffective. Early diagnosis accelerates the continuation of the correct treatment and, in the case of underdosing, it permit to re-evaluate the neurologic/psychiatric treatment. Besides, in conclusion: intravenous L-carnitine administration could increase the beta-oxidation of VA leading to a decrease in hepatotoxicity and a decrease in ammonia levels in patients with VA overdose; there have been multiple reports on therapeutic use of L-carnitine for acute VA toxicity as well as prophylactic supplementation during VA treatment; the determined dosage is an IV loading dose of L-carnitine 100 mg/kg (up to 3 g) over an hour and a continuous IV infusion of L-carnitine 50 mg/kg tid, until the patient recovers clinically or side effects occur due L-carnitine, for patients with impaired consciousness. Saliva can be an appropriate monitoring fluid to detect VA inefficacy or toxicity as it is highly correlated with free drug. So it becomes not only a noninvasive, cheap, and easy to obtain fluid, but also a useful tool to detect therapeutic failure or undesirable effects. Ammonia levels in blood depend on VA and 4-ene-VA (metabolites of valproic acid) concentrations, so during VA treatment ammonia in blood should be measured.

References

1) Sharma S, et al. Am J Ther. 2009; 16: 11-6
2) Jones RM, et al. Seizure. 2006; 15: 504-8
3) Felker D, et al. Expert Rev. Clin. Pharmacol. 2014; 7: 211–218.
4)Temel V., et al. Case Reports in Emergency Medicine. 2013.