LETTER TO THE EDITOR

Therapeutic drug monitoring of free fraction valproic acid in patients with hypoalbuminaemia

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Dear Editor,

Valproic acid (VPA) is the most frequently reported anticonvulsant causing unintentional and intentional intoxications.[1] Symptoms of VPA toxicity include central nervous system dysfunction, ranging in severity from mild drowsiness to coma or fatal cerebral oedema. Long-term or high-dose VPA therapy may mediate hepatotoxicity.[2,3] We describe a patient with hypoalbuminaemia and a serious VPA intoxication due to high free fraction of VPA, with normal total blood VPA levels.

A 53-year-old man presented with weight loss (15 kg in 6 months), vomiting, and hyperglycaemia for two weeks. He had a history of epilepsy and chronic alcohol abuse, resulting in liver cirrhosis, and diabetes mellitus type 2. Physical examination was unremarkable. Laboratory results included hyponatraemia (120 mmol/l), hypokalaemia (3.0 mmol/l), hypocalcaemia (1.62 mmol/l), hyperglycaemia (18.3 mmol/l), hypoalbuminaemia (2.1 g/dl) and severe anaemia (haemoglobin 3.8 mmol/l). All other relevant laboratory tests were normal. At home he was treated with subcutaneous insulin once daily, VPA 600 mg four times a day and esomeprazole 40 mg. Based on his history, and spontaneously increased bleeding tendency (prothrombin time 27.3 sec), he was diagnosed with acute on chronic hepatic failure and was given blood transfusion, rehydration therapy, 10 mg vitamin K and thiamine 100 mg once daily. Gastroscopy showed severe oesophageal ulceration and grade II oesophageal varices, but no signs of active bleeding. On the second day of admission he developed respiratory distress and decline of consciousness (E1M5V1), without signs of cerebral bleeding. He was admitted to the intensive care unit for respiratory support and haemodynamic stabilisation. Laboratory results showed liver failure with an ammonium level of 165 mmol/l. Serum total VPA trough concentration was 62 mg/l (normal 50-100 mg/l), with an increased free fraction of 17 mg/l (normal 5-15 mg/l). VPA administration was stopped immediately, but that same day he developed multiorgan failure and died. The cause of death was attributed to a combination of acute on chronic hepatic failure and VPA toxicity.

Intoxication of VPA might be difficult to recognise in critically ill patients due to different pharmacokinetics, pharmacodynamics and their critical illness. This case report suggests that monitoring of unbound drug concentrations of VPA can be helpful in identifying unrecognised concentration-related adverse effects. Awareness of the pharmacokinetic relationship and adverse effects of VPA will aid clinicians to guarantee therapeutic action and prevent overdose. In parallel to the recommendations for phenytoin we would like to recommend routine measurement of VPA free fraction in patients with hypoalbuminaemia.

REFERENCES

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