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CASE REPORT

Coma probably induced by lorazepam–valproate interaction

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Both valproate (VPA) and lorazepam (LZP) are primarily cleared from the body by glucuronidation. Concomitant administration of VPA has been reported to reduce the elimination of LZP. However, it remains unknown whether this drug interaction is clinically significant. We report a patient with epilepsy who showed that VPA–LZP interaction could result in severe encephalopathy such as coma.

Key words: coma; drug interaction; lorazepam; valproic acid.

INTRODUCTION

Valproate (VPA) encephalopathy is rare but has been reported[1]. It is usually associated with hyperammonemia. Recently, it was reported that VPA reduces plasma clearance and increases plasma concentrations of lorazepam (LZP)[2,3]. However, it remains unclear whether this drug interaction can cause clinically significant drug toxicity such as coma. We report a patient with epilepsy who developed coma probably due to LZP–VPA interaction.

CASE REPORT

A 36-year-old woman with medically intractable seizures was referred to our center for epilepsy surgery. Her seizures developed at the age of 27 years. The risk factors for seizure were absent. General and neurologic examinations were normal. A brain MRI demonstrated a left hippocampal atrophy. Prolonged video-EEG monitoring revealed left temporal interictal spikes and ictal EEG seizure onset in the left temporal lobe. Her seizure semiology was compatible with temporal lobe seizures. She underwent a standard anterior temporal lobectomy on the 6th March 2000. The pathology report confirmed hippocampal sclerosis.

She had a normal postoperative recovery and complained of headaches. VPA (1000 mg/day), PHT (300 mg/day), and CBZ (400 mg/day) were re-administered postoperatively. On the 8th March at 11:00 PM, the first complex partial seizure (CPS) developed after surgery. Intravenous LZP (2 mg) was administered at that time. On the 9th March, several CPS recurred. Intravenous LZP (2 mg) was injected at 6:00 PM and 9:30 PM. The patient was awake but slightly drowsy during the intervening periods between seizures. After the last injection at 9:30 PM, she became unconscious and unresponsive. On the 10th March, the patient's mental status was deep stupor to semi-coma. Deep tendon reflexes were hyperactive in all extremities and Babinski's sign was present bilaterally without focal neurological deficits. Brain CT and MRI scans provided no evidence for an acute structural lesion. EEG monitoring for 1 day

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revealed generalized theta to delta slowing without epileptiform discharges. She was transferred to the intensive care unit. Blood cell count, serum chemistry, electrolyte and urinalysis were normal. The serum levels for VPA, PHT, and CBZ were 58.9, 18.1, and 3.0 mg L^{-1}, respectively. The serum levels for ammonia were between 31 and 75 μmol L^{-1}. On the 11th March, she remained in semi-coma and was intubated. At that time VPA was discontinued. Over the next 2 days she gradually improved and displayed a normal mental status with no focal neurological deficits. She was discharged taking PHT 300 mg/day, CBZ 400 mg/day, and clobazam 30 mg/day. She has remained seizure-free for 12 months after discharge.

DISCUSSION

Our patient, who was taking VPA, developed coma after the injection of a total of 6 mg LZP during a period of 24 hours. She remained in a coma for between 48 and 72 hours. At that time we did not find any possible causes of inducing coma. EEG monitoring for 1 day did not show evidence of non-convulsive status epilepticus. The possibility of acute structural or metabolic abnormalities was excluded by the imaging and routine blood test. The normal serum ammonia level excluded VPA-induced hyperammonemic encephalopathy. The generalized slowing on EEG and bilateral Babinski's sign were suggestive of diffuse encephalopathy. Based on the exclusion and prompt recovery after the withdrawal of VPA, it was most likely that the elevated plasma concentration of LZP due to LZP–VPA interaction induced her coma, although this was not documented.

Recent evidence has shown that VPA inhibits the elimination of drugs metabolized by glucuronide conjugation[4,5]. It is well known that VPA reduces the elimination of lamotrigine, which is principally cleared by glucuronidation[4]. Similar to lamotrigine, LZP is also cleared from the body primarily by glucuronidation. Recently, two studies[2,3] confirmed LZP–VPA drug interaction. However, it remains less well understood how clinically significant this interaction is. Anderson *et al.*[2] reported that intersubject variability of this drug interaction was wide. Our case serves to emphasize that co-administration of LZP with VPA may cause significant drug toxicity, including coma, and clinicians should pay attention to the possibility of this drug interaction.

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