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Valproate and high dosage of zotepine induced acute delirium: a case report

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Zotepine, one of the second generation antipsychotics, is widely used in the treatment of schizophrenia and bipolar disorder in Asia and Europe. Within the dosage range of 50–450 mg, a significant reduction of positive as well as negative symptoms was noted in patients with schizophrenia. Delirium is characterized by an alteration of consciousness with reduced ability to focus, sustain and shift attention. It is associated with increased morbidity and mortality, persistent functional and cognitive decline, a longer hospital stay, higher rates of nursing home placement and increased healthcare costs. Antipsychotics are used for delirium management. There are several case reports on second generation antipsychotic-induced delirium, but no related report on zotepine-induced delirium. Herein, we present the case of a male patient who developed delirium after a high-dosage prescription of zotepine.

Case report

A 40-year-old man diagnosed with schizophrenia was admitted to our acute ward 2 months ago due to outside wandering, reference delusion, persecutory delusion, delusion of being monitored, poor sleep and irritable mood. He had a history of gout and hypertension. There was no specific finding in the initial physical and laboratory survey during this hospitalization. Due to his irritable mood, we prescribed valproate 1000 mg daily, beginning in the early period of this hospitalization. We also prescribed aripiprazole 20 mg daily for 10 days, then quetiapine XR 750 mg

daily for 2 weeks, but there was only a limited effect on his psychotic symptoms and signs. Then, we changed our antipsychotic to zotepine directly, at a starting dosage of 200 mg daily. He stated that there was no specific adverse effect of the zotepine. Delusion of persecution, delusion of being monitored, delusion of reference and irritability decreased after changing the medication to zotepine. We increased the dosage to our target of 350 mg daily 3 weeks after the antipsychotic shift. Valproate 1000 mg daily was also continued. Unfortunately, he presented with disorientation as to time, person and place, poor attention, confused state, fluctuation of consciousness, visual hallucination and disturbed behaviour at night, beginning on the second day of zotepine 350 mg daily prescription. We checked his physical condition and did a laboratory survey. There was no specific finding, including complete blood count, differential count for white blood cells, alanine aminotransferase, amylase, lipase, uric acid, electrolytes, C-reactive protein, blood glucose and electrocardiogram. However, we found his creatinine level had increased to 1.5 mg dl^{-1}. His valproic acid level was 103.9 µg ml^{-1}. Mild tachycardia was also noted. A decrease in the preload volume was found. We then supplied 0.9% normal saline 1500 ml and decreased the dosage of zotepine to 250 mg daily. His delirium subsided 2 days later, but he could not remember what had happened in the past 2 days. We increased the dosage of zotepine again due to recurrent delusions of persecution and auditory hallucination. Delirium presented again on the second day of treatment with zotepine 350 mg daily. There was no specific finding on the brain magnetic resonance imaging after our survey. His valproic acid level was 90.6 µg ml^{-1}. However, his delirium subsided immediately after decreasing the zotepine dosage. The Naranjo adverse drug reaction probability scale of this case is eight points, which is categorized as probable in the probability category of the scale.

Delirium has been associated with a number of atypical antipsychotics, including quetiapine, risperidone and clozapine, in case reports. The interesting aspect of the relationship between delirium and quetiapine is that several studies have shown quetiapine to have the potential to more quickly reduce the severity of delirium [1, 2]. However, there have been several case reports on quetiapine-related delirium in recent years [3–6]. Anticholinergic effect and combination with other medications were supposed to be the factors resulting in delirium. Elderly patients treated with olanzapine have been reported to develop delirium [7, 8]. Olanzapine intoxication and combination with other medications were also reported to lead to the development of delirium [9]. Central cholinergic antagonism at high doses was considered the reason for the delirium. Clozapine has also been reported to be implicated in the development of delirium [10, 11]. Delirium was found in 10% of clozapine-treated inpatients,

particularly older patients exposed to other central anticholinergics [11]. Delirium was inconsistently recognized clinically in milder cases and was associated with increased length of stay and higher costs, and an inferior clinical outcome [11]. There was also one case report of delirium related to risperidone [12].

The effects of zotepine are mediated through antagonist activity at the dopamine and serotonin receptors. Zotepine has a high affinity for the D_1 and D_2 receptors, and also affects the 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors. In addition, it has noradrenaline reuptake inhibition properties, α_1-adrenoceptor antagonist properties, and histamine H_1 receptor antagonist properties [13–15]. Zotepine has only moderate affinity for cholinoceptors. This receptor-blocking profile could explain the rare occurrence or the mild manifestation of extrapyramidal motor disturbances in the clinical use of zotepine [16]. High-dosage zotepine was highly suspected of inducing anticholinergic delirium. Besides, a decrease in preload volume might result in an elevated zotepine blood level. After tapering the dosage of zotepine and supplying normal saline, the delirium subsided immediately.

Valproic acid is another risk factor related to delirium [17, 18], although the mechanism is still controversial. Also, valproic acid is a broad-spectrum inhibitor of drug metabolism, especially CPY3A4 and CPY2D6. Metabolism of zotepine is mediated mainly by CPY3A4, and CPY2D6 and CPY1A2 also play important roles. Valproic acid prescription might result in increased plasma levels of zotepine, which could increase the risk of delirium.

Competing Interests

There are no competing interests to declare.

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