Case Report

Posaconazole-Vincristine Coadministration Triggers Seizure in a Young Female Adult: A Case Report

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Coadministration of azoles and vincristine has been shown to increase vincristine neurotoxic effects due to the inhibition of cytochrome P450 (CYP) isoform 3A4, for which vincristine is a substrate. Despite the absence of any casual relationship between seizure and coadministration of azoles, few case reports of vincristine-induced seizure have been documented after coadministration of fluconazole or posaconazole in children. In this paper we are reporting the first young female adult who experienced generalized seizure after coadministration of posaconazole and vincristine. The 19-year-old female was diagnosed with acute lymphoblastic leukemia. She started induction phase of Berlin Frankfurt Muenster protocol along with posaconazole 200 mg three times daily as prophylactic antifungal therapy. Five days after the third vincristine dose, she developed generalized seizure accompanied by high blood pressure and SIADH. Her neurological exam/CT scan did not show any abnormality. In conclusion, this study reports a novel finding in the sense that all previous case reports pertaining to posaconazole-vincristine-induced seizure in literature involved children. Physicians should be made aware of this rare possible outcome to closely monitor their patients and take appropriate measures to prevent such possible adverse effect.

1. Introduction

Vincristine (VCR) is widely used in the treatment of acute lymphoblastic leukemia (ALL) [1]. Its antineoplastic effect is attributed to the inhibition of microtubule formation in the miotic spindle causing cell death that may be accompanied by neurological side effects [1, 2]. This neurological toxicity is dependent on both dose and duration of treatment and is characterized by neuropathy, paresthesia, sensory deficits, muscle weakness, and rarely seizures [3]. Vincristine neurotoxic symptoms usually occur within 4 to 10 days of its administration [4] with most symptoms disappearing by about the sixth week after discontinuation of therapy.

Coadministration of azoles (as prophylaxis or treatment of fungal infections) and VCR has been shown to increase VCR neurotoxic effects due to the inhibition of cytochrome P450 (CYP) isoform 3A4, for which VCR is a substrate [1, 5]. Those neurotoxic symptoms usually present as constipation and peripheral neurotoxicity [6, 7]. These symptoms are usually reported after the administration of VCR second dose [1]. Despite the absence of any casual relationship between seizure and coadministration of azoles, few case reports of VCR-induced seizure have been documented after coadministration of fluconazole in an 11-years-old child [8] and coadministration with PSZ in 9- and 4-year-old children [9, 10].

2. Case Presentation

This case report was approved by the Medical Research centre of Hamad Medical Corporation, Doha, Qatar. The 19-year-old South west Asian girl, 40 Kg weight and 153 cm tall, was admitted to Al Amal hospital, Doha, Qatar, on June 16, 2010 and was diagnosed with ALL. The induction phase of Berlin Frankfurt Muenster protocol was started on June 23, 2010. The chemotherapy protocol given consisted of (a) Prednisolone (60 mg/m²) 80 mg orally everyday starting from June 23, 2010, (b) VCR (1.5 mg/m²) 2 mg intravenously (i.v.)
VCR, a vinca alkaloid, exhibits peripheral neurotoxicity that involves autonomic nervous system and may be accompanied by syndrome of inappropriate antidiuretic hormone (SIADH) secretion and high blood pressure [9]. Generalized seizure has been reported to result from the hyponatremia associated with SIADH and mostly occurred in patients with seizure disorders [8, 9]. In a study involving 20 pediatric patients, severe CNS toxicity was detected in patients coadministered azoles but not in those administered VCR alone [14].

Up to the authors’ knowledge, all of the reported seizures suspected to be caused by the coadministration of PSZ and VCR were in pediatric patients [8–10, 14]. This may be due to the fact that VCR clearance in children is known to be faster than that in adults [15]. As such enzyme inhibitors would cause significantly lower VCR clearance in children with much more aggravated side effects [15]. However, in this study, the authors present the first report of PSZ-VCR drug interaction yielding seizure in a young female adult. Our patient did not have any family history of seizure and her CT scan did not suggest any neurological damage. At the time of seizure, the patient suffered from SIADH symptoms and elevated blood pressure similar to the other cases of VCR toxicity [8–10].

The question that rises is what makes this adult patient more prone to this drug interaction. There are several possible theories which could include lower seizure threshold or altered polymorphic expression of CYP3A5 which can play an important role as a determinant of VCR elimination, systemic exposure, and hence neurotoxicity [16]. However no absolute answer to such question can be provided as this is a retrospective study and has the following limitations. First PSZ and VCR are not therapeutically monitored drugs, as such their plasma or blood concentrations were not readily available. Second is the absence of MRI and EEG data and finally the absence of information on the patient’s CYP3A5 allele.

In conclusion, this paper describes a case where a young adult experiences VCR-induced seizure due to PSZ coadministration. This is a novel finding in the sense that all previous case reports pertaining to PSZ-VCR-induced seizure in literature involved children. Physicians should be made aware of this rare possible outcome to closely monitor their patients and take appropriate measures to prevent such possible adverse effect. Thus helping their cancer patients lead better lives.

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