

Vincristine-Induced Seizure Potentiated by Itraconazole Following R-CHOP Chemotherapy for Diffuse Large B-Cell Lymphoma

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Abstract: *Objectives:* To report the case of a patient with diffuse large B-cell lymphoma (DLBCL) who developed vincristine (VCR)-induced seizure after R-CHOP chemotherapy.

Case Summary: A 22-year-old boy with DLBCL developed generalized tonic clonic seizures following R-CHOP chemotherapy. After receiving the third cycle of chemotherapy, he developed *Aspergillus* pneumonia; therefore, itraconazole was started 18 days before the administration of cycle 4 of chemotherapy. Seven days after the administration of the fifth doses of vincristine, the patient reported symptoms of gastrointestinal toxicity (abdominal cramps and constipation). Subsequently, he developed three episodes of generalized tonic-clonic seizure which lasted for 2-3 minutes during one day and became unconsciousness. His serum electrolytes were normal with the exception of low serum sodium (128mEq/L). Blood glucose, blood urea nitrogen, the complete blood count, and a cerebrospinal fluid study were also normal. A computed tomography scan of the brain did not show any abnormalities. He had no previous history of convulsion. Occurrence of seizure due to central nervous system invasion of DLBCL was ruled out with a normal cerebrospinal fluid examination, computed tomography scan, and magnetic resonance imaging of the head. Therefore, the patient's neurotoxicity has been attributed to vincristine, the effects of which were likely potentiated by itraconazole therapy.

Discussion: Vincristine is a naturally occurring vinca alkaloid used in various chemotherapy regimens. Neurotoxicity is a known and commonly encountered side effect of vincristine. Peripheral neuropathy is the most common form of vincristine neuropathy whereas central effects are rarer. Enhanced VCR neurotoxicities from drug interactions with several azole antifungals such as itraconazole and voriconazole have been reported. Our case represents a drug possible adverse drug effect based on the Naranjo ADR Probability Scale.

Conclusion: Administration of vincristine in conjunction with azole antifungals should be with caution and after carefully considering the risks and benefits. Also, it is important to rule out other causes of seizure in these patients.

Keywords: Diffuse large B-cell lymphoma (DLBCL), R-CHOP chemotherapy, seizure, itraconazole.

INTRODUCTION

Vincristine is a naturally occurring vinca alkaloid used in various chemotherapy regimens that blocks mitosis by arresting cells in metaphase [1]. Neurotoxicity is a known and commonly encountered side effect of vincristine which is dose-related. Peripheral neuropathy is the most common form of vincristine-induced neuropathy whereas central effects such as seizure are rarer. Seizures have been observed after using both toxic and therapeutic doses of vincristine [1,2]. This adverse effect has been reported to develop earlier

when itraconazole is given concurrently [1]. We report a case of a patient with diffuse large B-cell lymphoma (DLBCL) who developed vincristine-induced seizure after R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisolone).

CASE STUDY

A 22 year old male was admitted to Masih Daneshvari hospital, an educational and university affiliated hospital in pulmonary diseases, and was diagnosed with DLBCL (stage IIBX). The R-CHOP protocol (rituximab 375 mg/m² before chemotherapy, cyclophosphamide 750mg/m² on day 1, vincristine 1.4mg/m² on day 1, doxorubicin 50mg/m² on day 1, and prednisolone 40 mg/m² on days 2-5) was started for the patient and was to be repeated every 3 weeks for 8 cycles. After receiving the third cycle of chemotherapy, the

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patient developed *Aspergillus* pneumonia which was validated with the presence of an air-crescent sign on computed tomography (CT) scan of the lung and later confirmed by biopsy. Itraconazole capsules (200mg two times a day) were started 18 days before the administration of 4th cycle of chemotherapy and continued throughout chemotherapy treatment. He had no complaints until seven days after the administration of the fifth course of vincristine when he experienced gastrointestinal toxicity. Fifty-three days after the initiation of itraconazole, he developed three episodes of generalized tonic-clonic seizure in one day with loss of consciousness. The patient had no previous history of seizure. When admitted to the hospital, his serum electrolytes were normal with the exception of serum sodium which was 128mEq/L but was later corrected to 136mEq/L over four days. Blood glucose, blood urea nitrogen and the complete blood count (CBC) were also normal. A lumbar puncture (LP) was done and cerebrospinal fluid (CSF) study was found to be normal. A CT scan of the brain did not show any abnormalities. Brain magnetic resonance imaging (MRI) revealed bilateral foci of signal hyperintensity on T2W and FLAIR sequences, involving both the white and gray matter of the posterior parietal lobes. These findings are nonspecific and are suggestive of cortical infarcts, ischemic changes, vasculitis or focal cerebritis. Adverse drug reaction may also be considered. Chest X-ray and abdominal and pelvic ultrasonography were also normal. Following the investigation outlined above, phenytoin (100mg three times a day) was administered for prophylaxis.

According to the Naranjo ADR probability scale, a probable relationship between generalized tonic-clonic seizure and vincristine therapy was indicated.

DISCUSSION

Here we report a case of neurotoxicity in a 22 year old male on treatment with R-CHOP chemotherapy and itraconazole. Our patient presented with peripheral neurologic symptoms and gastrointestinal toxicity in addition to central neurotoxicity, with seizure possibly secondary to moderate VCR induced hyponatremia enhanced following co-administration with itraconazole.

Convulsion following the use of vincristine has been reported several times in the literature [3-6]. The exact underlying mechanism by which vincristine induces seizure is unknown. Generalized seizure has been reported in association with hyponatremia secondary to VCR-induced syndrome of inappropriate antidiuretic hormone (SIADH). Seizure appears to be more frequent in patients with a previous history of seizure disorder [2]. It has been proposed that vincristine acts on hypothalamic nuclei and stimulates the release of antidiuretic hormones which may result in convulsions [3]. The rate of SIADH attributed to vincristine is very low with a reported frequency of 1.3 per 100000 patients treated with vincristine. Usually SIADH occurs between 4 and 10 days after vincristine administration and improves within 1 week of starting symptomatic treatment. The severity and frequency of SIADH depends on the frequency and doses of vincristine administered [1]. Our patient experienced seizure 14 days after the administration of fifth doses of vincristine. Gastrointestinal toxicity had been developed after 7 days and more delayed central

symptom that occurred after 14 days may be related to previous hyponatremia that had not been recognized. Eiden *et al.* also, reported a case of posaconazole-induced vincristine central neurotoxicity which happened 14 days after injection of vincristine [7].

Also, it seems that vincristine exerts a direct neurotoxic effect on the central nervous system. This hypothesis is based on the finding of neuronal lesions in the medulla, pons, and cerebellum at autopsy in patients with ALL treated with vincristine. These changes resemble those induced in animals by the drug [3, 6].

Recently Moriyama *et al.* reviewed adverse interactions between antifungal azoles and vincristine. They reported seizures as a complication of vincristine therapy that occurred in nearly 23% of patients (n = 8) in their review. Hyponatremia has considered a plausible explanation for seizure activity in five of these patients, whereas direct neurotoxicity appeared to explain seizures in the other three patients [8].

Enhanced vincristine neurotoxicities from drug interaction with several azole antifungals has been reported [4, 7]. However, data with itraconazole is limited primarily to case reports [9-11]. The most likely explanation of this interaction is inhibition of CYP450 3A4 isoenzyme by azole antifungals. Indeed, vincristine is a major substrate of this isoenzyme and therefore, the magnitude of this interaction is significant. The vincristine dose may need to be adjusted or suspended when azoles are used concurrently. Another explanation is that vincristine is also a substrate of P-glycoprotein which effluxes vincristine out of the cells. Both posaconazole and itraconazole can inhibit P-glycoprotein efflux of vincristine resulting in increasing vincristine serum concentrations [2, 9]. Since the half-life of vinca alkaloids is 24-48 hours, the time course of the interaction is almost 5-7 days [11]. It has been suggested that neurologic side effects of vincristine can develop as soon as two weeks after itraconazole is given [2]. Jeng *et al.* reported vincristine neurotoxicity 3-4 weeks after the combination treatment with itraconazole and vincristine [12].

Reports of severe neurotoxicity with the combination of vincristine and antifungal azoles should be continued because there is a lack of appreciation of this adverse drug interaction. For example, although potentiation of vincristine neurotoxicity by itraconazole was first described by Murphy and colleagues in 1995, case reports and case series of this severe drug interaction with itraconazole continue to be reported [8]. Five cases of VCR neurotoxicity enhanced by oral itraconazole have been reported for first time by Takahashi *et al.* [13].

CONCLUSION

In conclusion, the physicians should be aware of the possible drug interactions between vincristine and azole antifungals and closely monitor for the earliest appearance of the neural symptoms so as to take timely and appropriate measures to decrease the risk of central neurotoxicity. Rule out other causes of seizure in these patients and consulting an infectious diseases physician and clinical pharmacist to use a non-azole antifungal agent is recommended.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

Declared none.

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