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Case Report

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Significant drug interaction between voriconazole and dexamethasone: A case report

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Abstract

Background: Voriconazole is extensively metabolized by the CYP450 isoenzymes 2C19 and 3A4 and to a lesser extent by CYP2C9; therefore, any medication that affects this pathway can alter its plasma concentration. Treatment failure can probably occur if subtherapeutic levels are achieved.

Case description: A 32-year-old woman who suffered from acute lymphoblastic leukemia was admitted and received treatment with vincristine and dexamethasone. After several days, to control her fever, based on two consecutive positive serum galactomannan test results, voriconazole as an antifungal agent was added to *Aspergillus* infection treatment. Through the first week after voriconazole initiation, its plasma concentrations were subtherapeutic. The most suspicious medication for interaction was dexamethasone, which can induce CYP450 isoenzymes and reduce plasma concentration.

Conclusion: As a result of the narrow therapeutic window of voriconazole and the relationship between efficacy and plasma concentration of azoles, therapeutic drug monitoring of voriconazole in patients receiving a high dose of glucocorticoids is recommended, in order to achieve optimal response to treatment and toxicity reduction. Further studies regarding the interaction between voriconazole and dexamethasone to prevent clinically relevant interactions should be considered.

Keywords

Voriconazole, dexamethasone, drug interaction, therapeutic drug monitoring, acute lymphoblastic leukemia

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Introduction

Voriconazole as a triazole antifungal agent is frequently used for the prevention and treatment of invasive fungal infections in patients undergoing chemotherapy.[1] The drug is widely metabolized by the CYP450 isoenzymes 2C19 and 3A4 and to a lesser extent by CYP2C9. Therefore, multiple drugs affecting these pathways may alter voriconazole plasma concentration by drug–drug interactions.[2] Due to the narrow therapeutic window of voriconazole, the maintenance of plasma concentration in the therapeutic range (1–5.5 mcg/ml) is necessary to prevent treatment failure and adverse effects.[3] Recent studies have demonstrated that the subtherapeutic plasma concentration of voriconazole is associated with treatment failure, hence it is reasonable to monitor its plasma concentration, especially when the drug is administered concomitantly with other drugs which affect its plasma concentration.[4,5] Although it has been demonstrated that rifampin, rifabutin, phenytoin, carbamazepine, barbiturates,

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ritonavir, and efavirenz can markedly reduce the plasma concentration of voriconazole, there is limited data regarding voriconazole interactions with dexamethasone.[5] Due to the wide administration of both voriconazole and dexamethasone in patients with acute lymphoblastic leukemia (ALL), it is necessary to understand the onset and severity of this interaction. This paper reports one major drug interaction between intravenous voriconazole and intravenous dexamethasone in a patient who suffered from ALL.

Case description

A 32-year-old, 50 kg Iranian woman diagnosed with ALL was referred to the Hematology-Oncology Research Center and Stem Cell Transplantation of Shariati Hospital which is affiliated to the Tehran University of Medical Sciences, Tehran, Iran, for treatment by chemotherapy. The chemotherapy regimen consisted of dexamethasone 8 mg given intravenously twice daily and vincristine 2 mg intravenously every seven days. Eleven days after the initiation of the chemotherapy cycle, the patient developed neutropenic fever and broad-spectrum antimicrobial therapy with piperacillin–tazobactam (4.5 g every 6 h) plus vancomycin (1 g every 12 h) was promptly implemented. Despite treatment with appropriate empiric antibiotic therapy, the patient remained febrile for four days. Based on two consecutive positive serum galactomannan test results (galactomannan indexes = 0.8 and 1), voriconazole was started for treatment of probable *Aspergillus* infection. Based on practice guideline for the management of aspergillosis,[6] voriconazole (VFEND®) was administered 6 mg/kg (300 mg) intravenously twice daily for two initial doses, followed by 4 mg/kg (200 mg) intravenously every 12 h. The trough plasma concentration of voriconazole was determined four days after initiating treatment with voriconazole just before the next dose in a steady state which was 0.5 mcg/ml. Voriconazole plasma concentrations were measured by high performance liquid chromatography technique using the method described by Khoschsorur et al.[7] The plasma concentration of voriconazole was drawn two days later to confirm the true low concentration of voriconazole and the level was subtherapeutic again (0.8 mcg/ml). All other medications of the patient were checked to find probable interactions which can affect the plasma concentration of voriconazole. The patient's drug list is presented in Table 1. Among drugs which were ordered for our patient, only dexamethasone had the potential ability to decrease the plasma concentration of voriconazole. The genotyping of CYP2C19 polymorphism was performed by Sanger's sequencing assay. Polymerase chain reaction was conducted in a thermocycler (Eppendorf, Hamburg, Germany) using a method published by Al-Jenoobi et al.[8] The patient was an intermediate metabolizer due to carrying the CYP2C19*1*2 genotype.

Table 1. The patient's medications list.

Medications	Dose	Route of administration
Vincristine	2 mg weekly	IV
Dexamethasone	8 mg BD	IV
(MTX, cytarabine, and hydrocortisone)	Every four days	IT
Piperacillin-tazobactam	4.5 g QID	IV
Vancomycin	1 g BD	IV
Ciprofloxacin	500 mg BD	Orally
Voriconazole	200 mg BD	IV
Acyclovir	200 mg BD	Orally
Pantoprazole	40 mg daily	Orally

BD: twice daily; IT: intrathecal; IV: intravenous; MTX: methotrexate; TDS: three times daily; QID: four times daily.

As a result of persistent fever despite therapy with voriconazole, two consecutive low concentrations of voriconazole and suspicion of other severe concomitant fungal infections (especially refractory candidiasis), voriconazole was replaced with liposomal amphotericin B.

Discussion

Since voriconazole acts as a major substrate of multiple CYP450 isoenzymes including CYP2C19, CYP2C9, and CYP3A4, the coadministration of drugs that induce their activity may affect the plasma concentration of voriconazole.[2] Recent studies have demonstrated that the low plasma concentration of voriconazole contributed to treatment failure; therefore, concomitant drugs with potential induction interaction must be considered in medication regimen.[4] Dexamethasone as a glucocorticoid has been widely used in hematologic malignancy and has the potential to induce isoenzymes CYP3A4 strongly but CYP2C9 and CYP2C19 moderately;[9,10] furthermore, it is a substrate of CYP3A4.[11] The recognition of glucocorticoid receptor binding sites in the in vitro study of the promoter region of the CYP2C19 gene and upregulation of CYP2C19 in response to dexamethasone indicates how glucocorticoids can induce CYP2C19.[11,12]

There are limited data regarding the interaction between voriconazole and dexamethasone. For the first time, Dolton et al. in their multicenter retrospective study on 201 patients reported that coadministration with glucocorticoids (prednisolone, methylprednisolone, or dexamethasone) is associated with significantly reduced plasma concentration of voriconazole. They found that dexamethasone and

Table 2. Drug Interaction Probability Scale (DIPS).[15]

Question	Yes	No	Unknown or nonapplicable
1. Are there previous credible reports of this interaction in humans?	+1	−1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	−1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	−1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?	+1	−2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	−1	0
7. Are there reasonable alternative causes for the event?	−1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from previous question)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	−1	0

methylprednisolone have a greater impact on the plasma concentration of voriconazole compared with prednisolone.[13] Similarly, Cojutti et al.[14] in their retrospective study, observed a significant decrease in voriconazole plasma concentrations in hematologic patients cotreated with glucocorticoids (methylprednisolone or dexamethasone). Recently, Wallace et al.[11] reported multiple subtherapeutic plasma concentrations of voriconazole in one patient with a fungal brain abscess treated with both voriconazole and dexamethasone. They observed a substantial increase in the plasma concentration of voriconazole when the dexamethasone dose was reduced gradually. As in guidelines, measurement of voriconazole plasma level should be done through the first week of treatment,[14] we observed two sequential subtherapeutic plasma concentrations of voriconazole (lower than 1 mcg/ml) in our patient despite a standard dose of intravenous voriconazole. Among the medications prescribed for the patient, only dexamethasone had the potential to decrease the plasma concentration of voriconazole. Conversely, the administration of pantoprazole for stress ulcer prophylaxis had the potential to inhibit the metabolism of voriconazole via CYP450 2C19 and 3A4 and increase the plasma level of azole.[13] Surprisingly, combination therapy with a high dose of dexamethasone and pantoprazole resulted in a subtherapeutic plasma concentration of voriconazole. It has been demonstrated that the oral route of administration and higher patient's weight are other risk factors associated with decreased voriconazole concentration which was not presented by the patient.[13] Genetic polymorphisms in the cytochrome P450 2C19, as a primary elimination pathway of voriconazole, is another factor influencing trough plasma concentration. Ultrarapid metabolizers are at an increased risk of achieving lower plasma concentration compared with other genotypes.[15] It was found that the patient was an intermediate metabolizer, therefore the low concentrations of voriconazole were not attributed to CYP2C19 polymorphism.

Drug Interaction Probability Scale (DIPS) investigates the presumption of drug interaction. The DIPS scoring system consists of four levels for probability prediction based on 10 questions, if the total score was <2: Doubtful, 2–4: Possible, 5–8: Probable, >8: Highly Probable, so as it has been shown in Table 2, the case score was 6, indicating that this interaction was probable.[16]

As recommended in guidelines, measurement of voriconazole plasma level should be done through the first week of treatment.[14] Due to less induction effects of prednisolone than dexamethasone on isoenzymes CYP3A4, we can also suggest prednisolone as an option in patients receiving voriconazole.[17]

Conclusions

Although it appears that the magnitude of interaction between voriconazole and stronger CYP inducers such

as rifampin and phenytoin is greater than the extent of interaction between voriconazole and glucocorticoid,[13] therapeutic drug monitoring of voriconazole should be considered in patients receiving a high dose of glucocorticoids, in order to achieve optimal response to treatment and toxicity reduction.

Due to the narrow therapeutic window of voriconazole and the relationship between efficacy and plasma concentration of azole, further studies are recommended regarding the interaction between voriconazole and dexamethasone to prevent clinically relevant interactions.

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Declaration of Conflicting Interests

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Ethical Approval

All procedures performed in this study involving human participant were in accordance with the ethical standards of the Ethical Committee of Tehran University of Medical Sciences and the 1975 Helsinki Declaration.

Informed Consent

Informed consent was obtained from a participant who included in the study.

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