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An investigation of visual hallucinations associated with voriconazole administration to patients with hematological malignancies

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Voriconazole (VRCZ) is commonly administered to treat fungal infections in patients with hematological malignancies. Some of these patients experience VRCZ-associated visual hallucinations. We conducted a retrospective survey to investigate the characteristic features of this side effect. Patients with hematological malignancies who were treated with VRCZ for a fungal infection after hospitalization at Ichinomiya municipal hospital between 1 October 2005 and 31 December 2015 were included in this study (n = 103). Fifteen of these (14.6%) reported visual hallucinations that started on day 1-7. Seven of these 15 patients developed this symptom rapidly (day 1 or 2). Three patients had transient symptoms (lasting 2-12 days), 6 patients experienced hallucinations throughout the treatment, and the duration was unknown in 6 patients. Eleven patients experienced visual hallucinations when their eyes were closed (73 %) and these disappeared when they opened their eyes. One patient had visual hallucinations with open eyes, while the state of the eyes was unknown in 3 patients. The patients saw a range of images including people, animals, landscapes, and foods; several reported seeing images like those found in movies. In addition, 9 of 15 patients (60%) with visual hallucinations had visual disturbances. This was a higher proportion than that observed in patients who did not develop hallucinations (17 of 88; 19.3 %; $P < 0.05$). However, we found no significant difference between the blood VCRZ concentrations of patients who developed or did not develop visual hallucinations. This study indicated that most of these patients had visual hallucinations that manifested on eye closure, and they did not progress to serious mental illness. Our findings emphasized the importance of fully explaining the features of this symptom to each patient prior to starting VRCZ administration in order to reduce anxiety. In addition, since VRCZ discontinuation will compromise patient management, therapeutic drug monitoring should be used to increase the likelihood of successful therapy.

1. Introduction

Patients with hematological malignancies sometimes develop invasive fungal infections, either due to the disease or the administration of anticancer drugs and/or immunosuppressive agents. Voriconazole (VRCZ) is a second-generation azole-antifungal agent that is widely used for the prevention and treatment of fungal infections in patients with leukemia. VRCZ is the primary antifungal agent for the treatment of invasive aspergillosis, according to the guideline of the Infectious Diseases Society of America (Freifeld et al. 2011). VRCZ is generally well-tolerated, although some side effects have been reported; these include hepatotoxicity, skin rashes, arrhythmia, bone morrow depression, and visual or neurological disturbances (Imhof et al. 2006; Eiden et al. 2007). Mental disorders account for < 1-5% of the side effects reported during VRCZ treatment. These symptoms include confusion and auditory or visual hallucinations, according to the VFEND® (VRCZ) injection prescribing information in Japan (Pfizer Inc.; revised 12/2015). At Ichinomiya Municipal Hospital, we encountered some patients with hematological malignancies who reported VRCZ-associated visual hallucinations. Some of these patients only experienced this symptom when their eyes were closed. Previous reports described the incidence and the onset time of VRCZ-related visual hallucinations (Dolton et al. 2012; Zonios et al. 2014). However, few studies investigated the detailed features of these visual symptoms (Zonios et al. 2008). To address this, the present study retrospectively surveyed this side effect in order to improve understanding of its characteristic features, incidence, time of onset, and duration.

2. Investigations and results

2.1. Study subjects

Patients with hematological malignancies (n=104) were treated with VRCZ for a fungal infection following hospitalization in the Ichinomiya Municipal Hospital between 1 October 2005 and 31 December 2015. One of these patients was excluded from this evaluation because VRCZ administration was discontinued after one day due to a side effect (rash). A total of 103 patients was therefore included in the present study.

2.2. Patient characteristics

The characteristics of the patients are shown in Table 1. Fifteen of these 103 patients (14.6%) developed visual hallucinations. There were no demographic differences between those who developed visual hallucinations and those who did not report this side effect.

2.3. VRCZ-associated visual hallucinations

The detailed symptoms of the 15 patients (14.6%) who developed VRCZ-associated visual hallucinations are shown in Table 2. The onset of visual hallucinations was reported on days 1-7 of VRCZ treatment. Seven of these patients developed early symptoms (day 1-2). In 3 patients, the visual hallucinations were transient and lasted between 2-12 days, while 6 patients had this symptom until the completion of treatment; the duration was unknown for the

Table 1: Demographic characteristics of the patients

	Patients with visual hallucinations	Patients without visual hallucinations	*P*
Total number of patients	n = 15	n = 88	
Gender; male/female	9/6	56/32	0.984[a)]
Age; mean (range)	69.3 (52-78)	70.7 (35–92)	0.637[c)]
Disease	AML 5 ALL 1 CLL 1 MDS 5 MM 1 NHL 2 Chemotherapy 12	AML 19 ALL 3 CLL 1 MDS 29 MM 10 NHL 26 Chemotherapy 63	0.332[b)]
Therapy	Immunosuppressive agent 0 Conservative treatment 3	Immunosuppressive agent 3 Conservative treatment 22	0.848[b)]
Serum creatinine (mg/dL); mean ± SD	0.69 ± 0.16	0.76 ± 0.40	0.492[c)]
AST (U/L); mean ± SD	22.0 ± 12.9	40.9 ± 107.3	0.501[c)]
ALT (U/L); mean ± SD	36.1 ± 52.9	38.9 ± 64.0	0.875[c)]
T-bil (mg/dL); mean ± SD	0.8 ± 0.4	0.9 ± 0.7 (n = 87)	0.714[c)]
Drugs interacting with VRCZ	 Omeprazole 1 Rabeprazole 5 Prednisolone 3 Dexamethasone 1	Phenytoin 1 Omeprazole 9 Rabeprazole 19 Prednisolone 11 Dexamethasone 3 Methylprednisolone 1	–
Voriconazole initial dose (mg/day); mean ± SD	576.0 ± 139.4	525.0 ± 138.6	0.195[c)]
Voriconazole maintenance dose (mg/day); mean ± SD	382.7 ± 75.8	345.9 ± 89.8	0.141[c)]

SD, standard deviation
AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome;
MM, multiple myeloma; NHL, non-Hodgkin's lymphoma
AST, asparate transaminase; ALT, alanine transaminase; T-bil, total bilirubin
a) Chi square test, b) Fisher's exact test, c) *t* -test

Table 2: Characteristics of 15 patients who experienced visual hallucinations during voriconazole treatment

Patient No.	Disease	Sex	Age	VRCZ initial dose (mg/day)	VRCZ maintenance dose (mg/day)	Onset time	Duration of symptoms, days	Details of symptoms	Eyes open or closed at onset	Visual disturbances	Plasma VRCZ trough level (μg/mL)
1	AML	F	71	500 IV	400 IV	day 7	until the completion of therapy	The patient saw strange images like dried fish	closed	blurred vision color blindness (yellow)	4.76
2	NHL	M	63	800 PO	400 PO	day 2	until the completion of therapy	The patients saw a lot of hair scattered on the table	open	diplopia	2.85
3	MDS	M	70	700 IV	400 IV	day 2	2 days	The patient saw clear figures of children and animals. He did not experience this in the daytime or with open eyes	closed	color blindness (yellow) photophobia	–
4	MDS	F	70	600 IV	400 IV for 14 days, then 200 IV	day 3	until the completion of therapy	After waking and going to the toilet, various scenes and animals appeared when the patient closed her eyes	closed	photophobia	8.7
5	MDS	M	78	400 PO	400 PO	day 1	until the completion of therapy	The patient saw beautiful scenery when he closed his eyes. However, he understood that it was not real because he could not touch it. When I was interviewing him, he said that 'I see a beautiful white lady and a ballon in front of a green forest, when I close my eyes now. However, no scary thing is visible'	closed	–	5.5
6	NHL	M	70	400 IV	200 IV	day 2	unknown	The patient saw strange things and shrimp	unknown	–	–

Patient No.	Disease	Sex	Age	VRCZ initial dose (mg/day)	VRCZ maintenance dose (mg/day)	Onset time	Duration of symptoms, days	Details of symptoms	Eyes open or closed at onset	Visual disturbances	Plasma VRCZ trough level (μg/mL)
7	MDS	M	70	600 PO	500 IV	day 1	3 days	The first day, the patient saw people at around 10 pm, when he closed his eyes. The next day, he saw food. However, these disappeared when he opened his eyes	closed	photophobia blurred vision	2.73
8	AML	M	52	760 IV	500 IV for 17 days, then 400 PO	day 5	12 days	When the patient closed his eyes, he saw scenes as though he was watching a video	closed	photophobia	–
9	CLL	F	71	480 IV	320 IV for 8 days, then 400 PO	day 4	until the completion of therapy	The patient saw a nice landscape, such as the roofs of houses under a blue sky. When she closed her eyes, she stood in a place like a theater and could move through it. The scene then changed and a forest appeared. She was surrounded by greenery. The scene kept changing in this manner	closed	–	–
10	AML	F	74	600 IV	400 IV	day 4	unknown	The patient could not sleep because she saw that two unknown people had invaded the toilet in her room. In addition, someone was running above her head all night	unknown	–	7.2
11	ALL	M	70	400 PO	400 PO	day 2	unknown	The patient saw strange images like those in a movie	closed	color blindness (orange)	–
12	MM	F	64	400 PO	400 PO	day 2	unknown	When the patient closed his eyes, he saw animals or total darkness. This symptom appeared during the day or night, but it disappeared when he opened his eyes	closed	–	–
13	MDS	M	69	600 IV	300 IV	day 4	until the completion of therapy	The patient saw ants	unknown	blurred vision	–
14	AML	F	71	600 IV	300 IV	day 4	unknown	The patient saw various scenes like those in a movie when she closed her eyes	closed	blurred vision	–
15	AML	M	77	800 IV	520 IV	-	unknown	The patient saw scenes like those in a movie when he closed his eyes	closed	–	–

AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non- Hodgkin's lymphoma; VRCZ, voriconazole
IV, intravenous; PO, orally

remaining 6 patients. Our study of the features of this side effect on onset indicated that 11 patients experienced the hallucinations on eye closure and 1 patient experienced them with open eyes; the features were unknown in the remaining 3 patients. For the 11 patients who developed visual hallucinations on eye closure, the symptoms disappeared when they opened their eyes. The visual hallucinations included images of people, animals, landscapes, foods, balloons, or a feeling of watching scenes from a movie.

2.4. Relationship between the visual hallucinations, visual disturbances, and blood concentrations of VRCZ

The relationship between the visual hallucinations and blood concentrations of VRCZ is shown Fig. 1. Blood concentrations of VRCZ had been determined in 6 of the 15 patients who developed visual hallucinations, showing a mean trough level of 5.40±2.37 μg/mL. Blood concentrations of VRCZ had been determined in 25 of the 88 patients who did not develop visual hallucinations, showing a mean trough level of 4.26±2.41 μg/mL. There was no significant difference between these two groups. Fig. 2 shows the relationship between visual hallucination and other visual disturbances (blurred vision, color blindness, or photophobia). Nine of the 15 patients (60.0%) who developed visual hallucinations had other visual disturbances. This represented a higher proportion than that observed in patients who did not report visual hallucinations, where 17 out of 88 patients (19.3 %) had other visual disturbances ($P < 0.05$).

3. Discussion

This study of VRCZ-associated visual hallucinations revealed their incidence, time of onset, and duration, as well as their features and relationship to visual disturbances.

Fever, hypoxia, severe metabolic disturbances, liver failure, renal failure, neurological disease, temporal lobe epilepsy, and cerebral tumors have been reported to cause visual disturbances and hallucinations (Raftery et al. 2014). However, these features were not present in the patients who developed visual hallucinations in the present study, with the exception of one patient (No. 2 in Table 2). Therefore, these visual hallucinations were thought to represent a side effect of VRCZ administration.

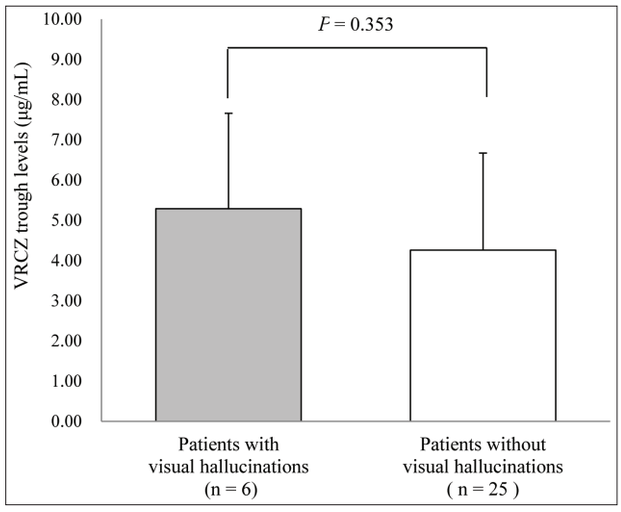

Fig. 1: Comparison of the mean trough plasma voriconazole (VRCZ) levels in patients with and without visual hallucinations.
The shaded region represents the mean trough levels in patients with visual hallucinations, while the unshaded region represents the mean trough levels in patients without visual hallucinations. *P* value, unpaired *t*-test.

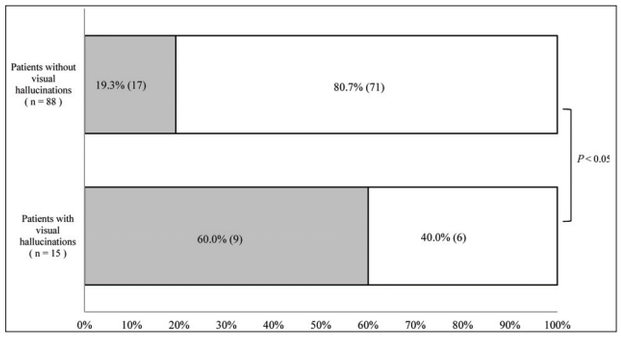

Fig. 2: The level of visual disturbances in patients with and without visual hallucinations. The shaded region represents the percentage with visual disturbances, while the unshaded region represents the percentage with no visual disturbances. *P* value, *Chi* square test.

The prescribing information for injectable VRCZ in the USA (VFEND®; Pfizer Inc., revised 02/2015) indicates that the incidence of hallucinations is 2.4%. In this study, we confirmed the presence of visual hallucinations in 15 of 103 (14.6%) patients, an incidence that was similar to the report [16 of 95 patients (16.8%)] by Zonios et al. (2014). In the present study, only one patient experienced both auditory and visual hallucinations. Zonios et al. (2014) reported that 5 of 16 patients experienced both visual and auditory hallucinations. Dolton et al. (2012) also reported that neurotoxic adverse events (visual and auditory hallucinations) occurred in 21 of 201 (10.5%) patients.

With respect to the time of onset, Zonios et al. (2014) reported that the hallucinations developed within a week. This was consistent with the present study, where this side effect was observed from day 1-2 in 7 of 15 patients.

With respect to duration, three patients had transient symptoms (lasting 2-12 days), 6 patients experienced hallucinations throughout the treatment, and the duration was unknown in 6 patients in this study. Zonios et al. (2008) also reported both transient and more persistent durations.

In the present study, we confirmed that visual hallucinations only appeared during eye closure in 11 of the 12 patients where this information was available. The patient who developed visual hallucinations with open eyes had a recurrence of non-Hodgkin's lymphoma, which affected the central nervous system, and he had diplopia and dysarthria before starting VRCZ. Therefore, his visual hallucinations may not have been induced by VRCZ. The visual hallucinations on eye closure in 11 patients involved unknown people, animals, landscapes, foods, a balloon, and a feeling of watching a movie. In the only case series report to describe the visual hallucinations in detail, Zonios et al. (2008) reported the following symptoms: several unfamiliar people entering and leaving the patient's room, the appearance of a figure resembling a character from the *Star Wars* films, images of beautiful places and landscapes, furniture that moved and floated around the patient's room, images of the patient's own house, etc. Moreover, in some patients, these symptoms intensified when they tried to sleep or closed their eyes, whereas the present study found that this symptom only appeared in 11 of the patients when they closed their eyes, and disappeared when they opened their eyes. In the present study, 9 of 15 patients (60%) with visual hallucinations also had visual disturbances, a higher prevalence than that observed in patients who did not develop hallucinations (17 of 88; 19.3%; $P < 0.05$). VRCZ-associated visual disturbances have been reported to relate to the plasma drug concentration, whereby the odds ratio for visual disturbances increased by 4.7% for every 1-μg/mL increase in plasma VRCZ concentration (Tan et al. 2006). Hallucinations commonly occur in association with visual disturbances (Imataki et al. 2008), but the relationship between visual disturbances and VRCZ-associated hallucinations has not yet been fully elucidated. VRCZ accumulates at high concentrations in cerebrospinal fluid and cerebral tissue (Imataki et al. 2008; Pasqualotto et al. 2010). Moreover, some reports have indicated that the plasma concentrations of VRCZ correlated with elevated liver enzyme activities, as well as visual and neurological disturbances (Boyd et al. 2004; Imhof et al. 2006). Therefore, Imataki et al. (2008) suggested that high plasma concentrations of VRCZ may affect the retina and the central nervous system.

Visual hallucinations on eye closure can be caused by other factors besides adverse drug effects. Yoshimura et al. (2012) reported two cases of visual hallucinations during eye closure after meningioma excision. Their report suggested that the pathogenesis of visual hallucinations may involve an alteration of cerebral blood flow, based on the results of a single photon emission computed tomography analysis. Increased luxury perfusion in the visual brain area following tumor excision may also be associated with the generation of visual hallucinations. In addition, in patients who have visual hallucinations without a visual field defect, the interruption of visual stimulation by closing the eyes may be the cause of the phenomenon. There are no reports of links between VRCZ-related visual hallucinations and altered cerebral blood flow. This issue would be worth investigating in future studies. Zonios et al. (2014) reported that the average plasma VRCZ level in 14 of 16 patients with hallucinations (4.53 μg/mL) was significantly higher than that observed in 78 patients without hallucinations (2.52 μg/mL; $P = 0.04$). Dolton et al. (2012) reported that neurotoxic adverse events (visual and auditory hallucinations) occurred more frequently in patients with plasma VRCZ concentrations > 5 μg/mL (10/31 patients [32%]), as compared to those with VRCZ concentrations ≤ 5 μg/mL (2/170 patients [1.2%]) ($P < 0.01$). However, in the present study, we found no significant difference between the blood VCRZ concentrations of patients who developed or did not develop visual hallucinations. This may reflect the incomplete data relating to the blood VRCZ concentrations in the present study.

Boyd et al. (2004) mentioned that few measured plasma VRCZ concentrations exceeded 6 μg/mL in patients receiving oral VRCZ therapy, indicating that the "first-pass" effect partially protected against the accumulation of this compound and any associated concentration-related toxicity. Zonios et al. (2008) reported that switching from intravenous VRCZ administration to oral administration in 3 of 12 patients with hallucinations resulted in a resolution of these symptoms in 2 of these patients. However, in the present study, some patients receiving oral VRCZ developed visual hallucinations. In addition, the visual hallucinations persisted throughout the treatment for some patients, while they were transient in others. Therefore, clinical management should initially include checking the extent of the symptoms and the blood VRCZ concentrations, prior to considering a change of administration route and/or dose, as appropriate.

VRCZ pharmacokinetic variability is well-known and depends on numerous factors such as patient body-weight, protein binding, or food and drug interactions (Theuretzbacher et al. 2006). In addition, therapeutic drug monitoring (TDM) is very important for ensuring efficacy and safety; this is usually recommended to achieve a therapeutic range between 1 and 5.5 μg/mL (Park et al. 2012). Dolton et al. (2012) reported that increasing patient age, increasing daily dose, and concomitant administration with any proton pump inhibitor (omeprazole, pantoprazole, esomeprazole, or rabeprazole) were associated with significantly increased VRCZ concentrations; factors associated with reduced VRCZ concentrations included oral administration of VRCZ (as compared to intravenous administration), increasing patient weight, and co-administration with rifampin, phenytoin, or a glucocorticoid such as prednisone/prednisolone, methylprednisolone, or dexamethasone. During chemotherapy for hematologic malignancies, pharmacists must pay attention to potential drug interactions because glucocorticoids are often employed as part of the therapy, while proton pump inhibitors may be used as a preventative measure. Nevertheless, 45 people had been treated with agents that interacted with VRCZ in the present study, and 33 of these patients had not received TDM. In addition, the cytochrome P450 2C19 (CYP2C19) genetic polymorphism is known to affect VRCZ metabolism, with a higher frequency of poor metabolizers in Asian populations (12-23%) than in Caucasians (1-6%) (Desta et al. 2002). Since identification of this genetic polymorphism is not currently an insurance requirement for the administration of VRCZ, it is difficult to check this routinely. For these reasons, there is a need to strengthen TDM of VRCZ by pharmacists.

Zonios et al. (2014) reported that administration was discontinued for 10 of 16 patients with hallucinations, and the VRCZ dose was reduced in 6 of 16 patients with hallucinations. Dolton et al. (2012) reported that VRCZ cessation or dose reduction was applied in all patients with neurotoxic side effects. In the present study, only one of the patients with visual hallucinations had their treatment discontinued or changed. This may have been due to the information provided to the patients. Based on our first experience of a patient with visual hallucinations on eye closure, pharmacists were instructed to explain the following during the medication consultation: 'VRCZ-associated visual hallucinations may occur in some patients in a transient manner during therapy, but will disappear spontaneously after the end of treatment. Thus, you do not need to worry about it'. However, one patient (No. 12 in Table 2) was referred for a psychiatric evaluation by the attending physician, who had no prior experience of a patient with VRCZ-associated visual hallucinations. The psychiatrist did not consider this patient to be mentally ill, and instructed the attending physician to follow him up. Clinical decision-makers should consider discontinuation of VRCZ in cases where mental disorders such as disorientation, coma, and convulsions are observed; however, treatment can be continued (with the patient's agreement) if the only complaint is of visual hallucinations on eye closure and the VRCZ blood concentration is within the normal range.

This study had the limitation of being a retrospective study. There is a possibility that medical staff were not aware of every patient who developed visual hallucinations because this issue was not discussed. In addition, blood VRCZ concentrations were not measured in every patient.

In conclusion, our findings characterized VRCZ-associated visual hallucinations observed during therapy for fungal infections in patients with hematological malignancies. It is important that pharmacists fully explain the potential for visual disturbances (blurred vision, color blindness, or photophobia), as well as the features of visual hallucinations, prior to starting VRCZ administration; this will alleviate patient anxiety. In addition, VRCZ therapy discontinuation will interfere with its therapeutic effects and the clinical aim should therefore be to continue this therapy with the support of TDM.

4. Experimental

4.1. Subjects

The study subjects were patients with hematological malignancies who had been treated with VRCZ for a fungal infection after hospitalization at Ichinomiya municipal hospital between 1 October 2005 and 31 December 2015.

4.2. Data collection and evaluation

This retrospective study collected the following data, which were recorded at the time of VRCZ therapy initiation, from electronic medical records: age, sex, disease, central nervous system complications, serum creatinine levels (sCr), aspartate transaminase (AST) activity, alanine transaminase (ALT) activity, total bilirubin levels (T-bil), concomitant agents affecting blood VRCZ concentrations, and the initial and maintenance doses of VRCZ. We investigated the incidence of VRCZ-associated visual hallucinations, the time of onset, duration of symptoms, and the features of this symptom. In addition, we evaluated the blood trough levels of VRCZ in patients who developed and patients who did not develop visual hallucinations, and analyzed the relationship between visual hallucinations and visual disorders (blurred vision, color change, and photophobia).

4.3. Statistical analysis

The *t*-test, Chi square test, and Fisher's exact test were used to compare data between patients who developed, and patients who did not develop, visual hallucinations. All analyses were conducted using EZR software (version 1.0, CHUGAI-IGAKUSYA, Japan). All *P* values of less than 0.05 were considered statistically significant.

4.4. Ethical considerations

The analysis and publication of the results of this study were conducted in accordance with the appropriate handling of personal information and with the approval of the clinical research review committee at Ichinomiya Municipal Hospital.

Conflict of interest: There are no conflicts of interest to declare.

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