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Hallucinations during Voriconazole Therapy

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Abstract

As part of a prospective natural history cohort study of voriconazole toxicity, we describe the characteristics of 12 of 72 voriconazole-treated patients who experienced hallucinations from March 2006 through November 2007. Hallucinations associated with voriconazole use are not uncommon. Doctors should be aware of this complication, and the recipients of the drug should be reassured that the hallucinations are an effect of the drug.

Voriconazole is a triazole antifungal that is often used for the treatment of invasive aspergillosis. Although voriconazole has a favorable safety profile, hepatotoxicity, visual disturbances, photosensitivity, and skin rashes have been observed [1–4]. Altered color sense, photophobia, or blurred vision has occurred in ~30% of patients. Hallucinations and other CNS symptoms, such as confusion, have also occurred in voriconazole-treated patients [2,4,5]. Hallucinations are false sensory perceptions that occur in any of the 5 sensory modalities. The incidence of hallucinations has been reported to be 4.3% [4] and 9% [2] in some large clinical trials, whereas other trials failed to report a single case [1,3,6]. One recent retrospective pharmacovigilance database reported visual hallucinations in 13.3% of patients, although no clear distinction was made between visual changes and hallucinations [7]. Higher voriconazole blood levels have been implicated in hallucinations, but the evidence remains controversial [8,9]. Auditory hallucinations have also been reported [10]. The characteristics and significance of hallucinations have not been elucidated. In this article, which is part of a larger study of voriconazole toxicity, we describe 12 patients who had voriconazole-related hallucinations.

Materials and methods

Seventy-two patients (48 men and 24 women; age, 14–76 years) who were treated with voriconazole at the Mark O. Hatfield National Institutes of Health Clinical Research Center (Bethesda, MD) were observed from March 2006 through November 2007. Voriconazole-related toxicity was recorded prospectively by directly interviewing the patients weekly (or daily in cases of adverse events) for symptoms and by recording concomitant medications. The study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board, and all patients provided informed consent. Voriconazole blood levels were obtained for 6 patients who experienced adverse events, and the measurements were analyzed as described elsewhere [11].

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Patients

Twelve patients developed hallucinations (table 1). A detailed description of the symptoms follows.

Patient 1 complained of blurred vision, changes of colors, and visual hallucinations on the first day of intravenous voriconazole therapy. She saw several unfamiliar, silent people going in and out of her room. This was more intense when her eyes were closed and during the night. The experience was not disturbing. All symptoms disappeared on the fifth day of treatment when the treatment was discontinued.

Patient 2 reported seeing images of beautiful places and landscape during receipt of loading doses of intravenous voriconazole treatment. He saw scenic images that he thought might be Montana or New York City. During the night, he heard gurgling water around him, preventing him from sleeping. Symptoms disappeared on the third day, when intravenous voriconazole treatment was switched to oral voriconazole treatment.

A few hours after intravenous voriconazole treatment initiation, patient 3 began to have the impression that he could move objects with his eyes. He also had the impression that he was being transferred to different hospital wards and even to the intensive care unit during the night. This caused him to have considerable anxiety, and voriconazole treatment was discontinued on day 3. All symptoms resolved shortly after treatment discontinuation.

Patient 4 had experienced hallucinations after receiving voriconazole several months before his second course of treatment. On this second occasion, he developed visual hallucinations at his home 8 days after oral voriconazole treatment was initiated, and the treatment was discontinued. The patient described seeing ugly and unfamiliar faces.

Patient 5 developed both auditory and visual hallucinations. Visual hallucinations consisted of flying objects and a sense of his floating in the room. He also saw Christmas trees flying around the room and saw himself traveling to beautiful places. Auditory symptoms included television commercials and Christmas carols. All symptoms disappeared on the fifth day after discontinuation of voriconazole treatment.

On the first day of treatment, patient 6 saw a figure bending over him when he closed his eyes. The figure looked large and hairy but not threatening, like the character Chewbacca from the *Star Wars* films. That day, the patient also had the impression that his bed was moving around the room, and he saw a gray background when reading. Symptoms resolved on day 4 when voriconazole treatment was stopped.

Patient 7 developed visual and auditory hallucinations on the first day of treatment. The patient reported seeing beautiful places and scenery, as if traveling on a train. She also reported seeing furniture moving around her room. Unfamiliar faces came close to her face, as if wanting to kiss her, and she heard loud music coming from outside her room, as if someone were having a party. The hallucinations were increased during the night when her eyes were closed. They disappeared on day 5—1 day after intravenous treatment was switched to oral treatment.

Patient 8 admitted hearing voices give orders to her, as if she was doing something wrong, 6 days after beginning intravenous voriconazole treatment. She also saw people walking in and out of her room during the night as she was trying to sleep and when her eyes were closed. Voriconazole treatment was discontinued because of hepatotoxicity 2 days later, and all symptoms disappeared.

Patient 9 described seeing cockroach-like bugs in his hospital room. He also saw unknown people flying around his room, and at other times, he would see his job office and several coworkers. The symptoms were present in variable intensity for 4 days. Although during the first 2 days, he considered the experience to be funny, the hallucinations later became annoying, and voriconazole treatment was stopped. The patient did not experience auditory hallucinations.

Patient 10 saw scenes as if he were walking around in a house that he did not recognize. This began on the first day that he was treated and continued even when intravenous therapy was changed to oral therapy on the third day. Symptoms disappeared overnight after the drug was stopped on the fifth day. The patient was unable to sleep well, because these scenes appeared when he closed his eyes. He related that he had previously received voriconazole at a different hospital, but the treatment had been stopped when he complained that he saw a man crashing through the door into his room, frightening him.

Patient 11 saw a cat scurrying around his hospital room and hiding under the furniture. His wife's brown hair looked purple, but other colors were normal. Symptoms were present only on the first day, although therapy was continued for 10 days.

Patient 12 thought that the furniture in his hospital room was floating around on his first day of intravenous treatment. The symptoms disappeared on the second day. He was switched to oral treatment 9 days later and was still receiving voriconazole at hospital discharge 20 days after the initiation of treatment.

Results and discussion

Symptoms in 8 patients occurred during receipt of the initial 2 loading doses of intravenous voriconazole (6 mg/kg every 12 h), and symptoms in 2 patients occurred on only the first day when they received 4 mg/kg of voriconazole every 12 h (1 of these patients received intravenous treatment, and the other received oral treatment). Only 2 patients reported symptoms beginning at the end of the first week, one of whom experienced symptoms while taking the oral formulation. Four patients also experienced auditory hallucinations, 3 of whom experienced these hallucinations on the first day of treatment. Although altered color perception or blurring was also observed in patients during this study, only 3 patients had both hallucinations and altered vision. Hallucinations were disturbing for 3 patients, and the remainder described them as being funny or not unpleasant. A recurring feature was that symptoms worsened when the patients' eyes were closed when they tried to sleep, but in all cases, the patient remained oriented, alert, and able to recognize hallucinations as being unreal. Six patients failed to report their hallucinations spontaneously and were hesitant to describe them, perhaps because of embarrassment or because they felt that the symptoms were not important enough to mention. There was no temporal relationship between voriconazole infusion and symptoms.

No connection was found between the hallucinations and the numerous other drugs administered. None of the patients needed specific treatment for the hallucinations. Doses of voriconazole were within the approved range. None of the patients had a history of psychiatric illness or similar symptoms, and all were treated for hematological or other malignancies. For 8 patients, symptoms disappeared shortly after treatment was discontinued. For 2 patients, hallucinations disappeared after treatment was changed from the intravenous formulation to the oral formulation. Two patients had mild hallucinations only on the first day despite continued treatment. There were no residual symptoms or sequelae after voriconazole treatment was stopped.

Although hallucinations were also seen after receipt of the oral formulation, they occurred mainly after receipt of the intravenous formulation. The weight-adjusted voriconazole dose

given to the patients who received the oral formulation was not different from the dose given to the patients who received the intravenous formulation. Moreover, symptoms often disappeared when intravenous treatment was switched to oral treatment. Therefore, it may be reasonable to continue voriconazole treatment with the oral formulation before considering drug discontinuation if the situation is considered to be critical.

Voriconazole trough blood levels on the day of treatment discontinuation or just before a change from intravenous to oral treatment in 6 of the patients were 6.38, 7.66, 5.67, 5.24, 5.79, and 1.97 μg/mL; most of these levels were within the top 19% of voriconazole level measurements (>5 μg/mL) reported in previous studies [12]. In addition, the mean trough voriconazole level (±SD) in 170 samples from the 72 patients was 2.45 ± 2.39 μg/mL. The levels cited above for patients who experienced hallucinations were not measurements from the time when symptoms began, but symptoms were present when these levels were measured. These findings suggest that there may be an increased risk of hallucinations in patients with greater-than-the-mean voriconazole levels.

The incidence of hallucinations in our study was 16.6%, which is significantly higher than that found in previous studies. This can be attributed to the prospective collection of data directed at adverse events and to the systematic observation of the patients with use of a predefined clinical research form. Our population consisted of patients with hematological and other malignancies, because this population frequently receives voriconazole treatment. Whether hallucinations would occur in patients who are less ill is unknown.

Hallucinations associated with voriconazole therapy can often be overlooked by physicians who focus on the patient's serious illness and who do not inquire about what might be considered extraneous adverse events. Patients should be cautioned about the possibility of adverse events before starting voriconazole therapy and should avoid driving if treated as outpatients. Our experience has revealed that patients with hallucinations appreciate being reassured that the hallucinations are not a sign of mental illness.

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Table 1

Characteristics of 12 patients who experienced hallucinations after receiving voriconazole treatment

Patient	Age, years	Sex	Race	Voriconazole treatment[a]		Underlying disease	Day when symptoms first occurred	Type of hallucination	Duration of symptoms, days	Action taken
				First dose, mg/kg	Later dose, mg/kg					
1	33	F	White	6.12 IV	4.05 IV	Breast cancer, Allo HSCT	1	Visual	5	Treatment stopped on day 5
2	68	M	White	6.09 IV	4.14 IV	MDS, Allo HSCT, GVHD	1	Visual and auditory	3	Treatment switched from IV to PO (3.8 mg/kg twice daily) on day 3
3	46	M	White	6.22 IV	4.10 IV	Melanoma	1	Visual	3	Treatment stopped on day 3
4	61	M	White	2.94 PO	2.94 PO	Myelofibrosis, Allo HSCT, GVHD	8	Visual	2–3	Treatment stopped on day 10
5	62	M	White	6.07 IV	4.05 IV	Melanoma	1	Visual and auditory	5	Treatment stopped on day 5
6	61	M	White	6.64 IV	4.43 IV	CMML, Allo HSCT	1	Visual	4	Treatment stopped on day 4
7	50	F	White	6.19 IV	4.13 IV	NHL, Allo HSCT, GVHD	1	Visual and auditory	5	Treatment switched from IV to PO (2.22 mg/kg twice daily) on day 4
8	38	F	Hispanic	6.32 IV	3.46 IV	ALL, Allo HSCT	6	Visual and auditory	2	Treatment stopped on day 7 (also because of hepatotoxicity)
9	39	M	Asian	5.76 IV	3.85 IV	AML, Allo HSCT, GVHD	1	Visual	4	Treatment stopped on day 4
10	36	M	White	6.38 IV	4.28 IV	APML, Allo HSCT	1	Visual	5	Treatment stopped on day 5
11	53	M	White	4.37 PO	4.37 PO	AML	1	Visual	1	Treatment continued for 10 days
12	40	M	Hispanic	4.16 IV	4.16 IV for 9 days, then 3.97 PO	MDS, Allo HSCT	1	Visual	1	Treatment continued for >2 weeks

NOTE. Allo HSCT, allogeneic hemopoietic stem cell transplantation; APML, acute promyelocytic leukemia; CMML, chronic myelomonocytic leukemia; GVHD, graft-versus-host disease; IV, intravenous; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PO, per os.

[a] All doses were given every 12 h.

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