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ID CASES

Elevated Voriconazole Level Associated With Hallucinations and Suicidal Ideation: A Case Report

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Voriconazole, a broad-spectrum antifungal, has been associated with visual and auditory hallucinations. We report the case of patient being treated with voriconazole for pulmonary aspergillosis who developed visual hallucinations and new suicidal ideation with plan. Voriconazole troughs were supratherapeutic (9.0 mcg/mL) and the patient was positive for the CYP2C19*1/*2 allele.

Keywords. aspergilosis; suicidal ideation; supratherapeutic; voriconazole.

Voriconazole, a broad-spectrum triazole antifungal, is first-line therapy for serious fungal infections, including invasive pulmonary aspergillosis. In clinical trials, and subsequent case reports and retrospective analyses, one of the most common adverse events associated with therapy has been visual and auditory hallucinations, but no reports of suicidal ideation with plan have ever been reported [1, 2]. These central nervous system adverse reactions have been associated with elevated voriconazole levels, which could be the result of incorrect dosing, drug-drug interactions, or genetic variance in the ability to metabolize the drug [2]. In this study, we report the first possible case of suicidal ideation with plan related to elevated voriconazole levels in a patient who was found to be an intermediate voriconazole metabolizer.

PATIENT CASE

A 67-year-old white male (79.3 kg) with a history of relapsing polychondritis on chronic prednisone therapy, alcoholic hepatitis, chronic pancreatitis, and chronic obstructive pulmonary disorder presented to the emergency department (ED) for evaluation of fatigue, weakness, and fevers (home medications can be found in Table 1). In the ED, the patient was found have an oxygen saturation of 84% on room air and was initiated on vancomycin, cefepime, metronidazole, and treatment doses of sulfamethoxazole/trimethoprim for possible pneumonia. The patient was noted to have diffuse pulmonary infiltrates, and, because of failure to improve on broad-spectrum therapy, the pulmonary service was consulted and decided to perform a bronchoalveolar lavage (BAL). Cultures from the BAL ultimately grew *Candida albicans* and *Aspergillus fumigatus*. In addition, a galactomannan serum antigen test was obtained, while on antibiotics, and was found to be positive at 4.57 pg/mL (<0.5 pg/mL). It was determined not to obtain a second galactomannan level because the turnaround time would have been 7 days, but because of the culture and initial galactomannan results, voriconazole was initiated at 400 mg orally every 12 hours for 2 doses, then 200 mg orally every 12 hours.

On day 2 of voriconazole therapy, the patient reported having some visual hallucinations, such as seeing "patterns on ceiling" and "seeing people in his room that weren't there"; however, the patient's mental status remained at his baseline. On day 5 of voriconazole therapy, the patient reported having hallucinations and confusion intermittently at night and during the day, which would spontaneously improve. The patient was fully aware of these episodes and knew they were hallucinations. On day 12 of voriconazole therapy, the patient reported new suicidal ideation with a plan of jumping out of his window to his nurse, along with continued mild hallucinations. The patient had previously reported situational depression secondary to his illness but had no formal history of mental disorders and had never previously reported suicidal ideations.

A voriconazole trough level, obtained on day 7, was elevated at 9.0 mcg/mL (therapeutic range, ~2.0–5.0 mcg/mL). Given the supratherapeutic level, visual hallucinations, and new suicidal ideation, which were thought to be secondary to high voriconazole levels, the infectious diseases consult service recommended discontinuing voriconazole; no additional antifungal therapy was initiated due to the belief that *Aspergillus* sp found on BAL represented non-pathogenic colonization. In addition, material from the first BAL was evaluated by pathology and read as "probable infection with *Pneumocystis jiroveci*", and treatment with sulfamethoxazole/trimethoprim was continued for 28 days; the patient's respiratory status continued to improve and eventually returned to baseline.

Before being placed on voriconazole therapy, the patient was initiated on omeprazole for stress ulcer prophylaxis and prednisone treatment was continued. To help explain why this patient experienced elevated levels of voriconazole therapy and adverse reactions, a CYP2C19 genotype was ordered and was

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Table 1. Medications Before Admission

Albuterol/ipratropium 100/20 micrograms 1 puff inhaled every 6 hours for chronic obstructive pulmonary disease (COPD)
Albuterol 90 micrograms 2 puffs inhaled every 6 hours as needed for shortness of breath
Azathioprine 150 milligrams by mouth once daily for relapsing polychondritis
Budesonide/formoterol 80/4.5 micrograms 2 puffs inhaled twice daily for COPD
Creon extended release capsules 48 000 units 3 times a day with meals for chronic pancreatitis
Nifedipine sustained release 30 milligrams once daily for hypertension
Prednisone 40 milligrams once daily for relapsing polychondritis
Sennosides 8.6 milligrams twice daily for constipation
Sulfamethoxazole/trimethoprim 400/80 milligrams once daily for prevention of infection while on immunosuppressive therapy
Tamsulosin 0.4 milligrams once daily for benign prostatic hypertrophy
Tramadol 50 milligrams 1–2 tablets every 6 hours as needed for pain
Valacyclovir 500 milligrams once daily for prevention of infection while on immunosuppressive therapy

found to be positive for the *1/*2 allele. This means the patient carries a single nonfunctional CYP2C19 genetic variant that causes reduced metabolism of some drugs; this patient was likely to be an intermediate metabolizer of voriconazole.

DISCUSSION

Auditory and visual hallucinations secondary to voriconazole toxicity have been widely reported in the literature; however, this is the first report of hallucinations complicated by suicidal ideation with plan in a patient receiving voriconazole [1–3]. Clinical trials of voriconazole report an incidence of visual disturbances of 0% to 9%, whereas smaller analyses report rates of 16.6% or greater [2, 4]. Hallucinations have been described with both intravenous and oral administration of voriconazole [2]. Furthermore, these hallucinations have been correlated with increased drug exposure, as determined by serum trough levels. One analysis showed that hallucinations occurred in 32% of patients with serum concentrations >5 mg/L compared with 1.2% of patients with serum concentrations ≤5 mg/L ($P < .01$) [5]. Another analysis found that the hazard ratio for neurologic adverse events due to voriconazole was 2.27 (95% confidence interval, 1.45–3.56; $P < .001$) with every 0.1 μg/mL increase in serum concentration [6]. Because increased voriconazole serum concentrations result in increased incidence of neurologic adverse events, external variables that may have contributed to supratherapeutic voriconazole concentrations in our patient must be explored. These variables include voriconazole metabolism, dose, and drug-drug interactions.

Voriconazole displays nonlinear kinetics due to saturable metabolism. Voriconazole is metabolized through hepatic cytochrome P450 (CYP450) enzymes, primarily CYP2C19, with limited metabolism through CYP3A4 and CYP2C9 [7, 8]. CYP2C19 is known to have genetic polymorphisms that can result in either increased or decreased voriconazole metabolism. Two clinically significant loss of function (LoF) alleles have been described, CYP2C19*2 and CYP2C19*3, with a prevalence in whites of 15% and <1%, respectively [7]. The most common genetic polymorphism observed in CYP2C19 is the gain of function (GoF) allele CYP2C19*17, with a prevalence of 22% in whites [7]. Patients expressing homozygous LoF CYP2C19 alleles have voriconazole exposure 3- to 4-fold higher than wild-type (CYP2C19*1) patients, and patients with heterozygous LoF CYP2C19 alleles have voriconazole exposure 1.5- to 2-fold higher than wild-type patients [1, 9]. In contrast, a single GoF allele results in a 50% decrease in voriconazole exposure, which is further decreased with homozygous GoF alleles [9]. One analysis found a significant increase in serum concentration between patients with CYP2C19*2/*2 and CYP2C19*1/*1 ($P = .006$); however, the difference in serum concentrations between CYP2C19*1/*2 patients and CYP2C19*1/*1 was not significant [7].

Voriconazole is commonly dosed at 6 milligram per kilogram per dose for 2 doses and then decreased to 3 to 4 milligram per kilogram per dose twice daily [4, 10]. In clinical trials, a standardized oral dose of 200 mg twice daily was used for conversion to oral therapy [4, 11]. The average weight of the population in one clinical trial of voriconazole was 70.4 kg, for which the 200 mg twice daily adheres to the 3 to 4 mg/kg per dose recommendation [4]. An analysis of voriconazole dose and trough levels found that these 2 variables were poorly correlated due interpatient variability [12]. Rather, a relationship between voriconazole dose, CYP2C19 genotype, and voriconazole trough level has been described in a population pharmacokinetic model. The model revealed that patients with a single CYP2C19*17 GoF allele would likely require doses of at least 300 mg twice daily to achieve serum concentrations ≥2 mg/L. Furthermore, the model predicted that 29%–39% of patients receiving 200 mg twice daily with at least 1 CYP2C19*2 allele, like the patient described in the above report, would be at risk of serum concentration ≥5 mg/L [8].

Voriconazole inhibits the fungal CYP450 enzyme 14-α demethylase, which is essential for the conversion of lanosterol to ergosterol. Although voriconazole targets a fungal CYP450 enzyme, cross inhibition of human CYP450 enzymes occurs, resulting in the potential for many drug-drug interactions. Proton pump inhibitors, especially omeprazole, have been previously described to increase voriconazole exposure through competitive inhibition of CYP2C19 [5, 8]. Phenytoin, rifampin, St. John's wort, and glucocorticoids have all been associated with decreased voriconazole exposure through induction of CYP2C19 and CYP3A4 [5, 8].

CONCLUSIONS

A case report of a 43-year-old Indian woman shares a similar presentation to the patient reported here, with the exception of suicidal ideation. This woman experienced voriconazole induced hallucinations with a serum concentration of 7.8 mg/L while receiving 200 mg twice daily. The patient was heterozygous

for CYP2C19*2 and receiving chronic immunosuppression with prednisone and taking daily esomeprazole, similar to the current patient [13]. Our patient expressed a single CYP2C19*2 allele, received a voriconazole dose of 200 mg twice daily (2.52 mg/kg per dose), and was concurrently receiving omeprazole and prednisone. Despite the large interpatient variability of voriconazole, our patient's voriconazole trough of 9.0 mg/L was unexpectedly elevated given the relatively low dose and single LoF allele. Furthermore, omeprazole is known to increase voriconazole exposure, but prednisone has been associated with decreased voriconazole exposure [5, 8]. Both patients developed supratherapeutic voriconazole troughs while receiving omeprazole and prednisone therapy concurrently; it seems possible that the CYP2C19 genotype, which was the same for both patients, and the proton pump inhibitor had a greater effect on voriconazole levels than did chronic prednisone therapy. The use of therapeutic drug monitoring and CYP2C19 genotyping in patients with symptoms of voriconazole toxicity is further warranted, and it seems feasible to consider suicidal ideation as a possible manifestation or complication of toxicity.

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