Painful Peripheral Neuropathy Associated With Voriconazole Use

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Background: Voriconazole is a new antifungal agent that has been recently introduced into clinical practice. We found no published reports of painful peripheral neuropathy associated with its use.

Objective: To describe a unique case of painful peripheral neuropathy associated with voriconazole use.

Setting: University hospital.

Patient: A 43-year-old patient who had undergone liver transplantation received voriconazole for invasive deep sinus aspergillosis and developed intolerable pain in all extremities.

Results: A laboratory workup and electromyographic and nerve conduction studies were performed to exclude other causes of neuropathy in this complicated patient. Results of electromyographic and nerve conduction studies were suggestive of a demyelinating neuropathy. Symptoms and signs of neuropathy disappeared shortly after voriconazole discontinuation, suggesting a possible role in the development of neuropathy. The patient continues to do well 10 months after this event.

Conclusions: To our knowledge, this is the first reported case of voriconazole-associated peripheral neuropathy. Awareness of this association and careful monitoring for neurological signs are necessary for patients receiving voriconazole.

Arch Neurol. 2005;62:144-146

Voriconazole is a new antifungal agent that has been recently introduced into clinical practice. It exhibits good activity against several Candida species, Aspergillus species, and other filamentous fungi. The drug is metabolized in the liver, and dose adjustment is required for patients with hepatic impairment. We report a case of voriconazole-associated peripheral neuropathy in a patient who had undergone liver transplantation and received this drug as part of a therapeutic regimen for invasive extrapulmonary aspergillosis.

REPORT OF A CASE

A 43-year-old white woman underwent liver transplantation for hepatitis C–associated cirrhosis. Her medical history was significant for hypothyroidism and adult-onset diabetes mellitus, both under treatment and well controlled. After surgery, she received cyclosporine, mycophenolate mofetil, and methylprednisolone acetate for immunosuppression. Twenty-six weeks after transplantation, the patient developed left maxillary, ethmoid, and sphenoid sinus infection due to Candida and Aspergillus species, for which she received repeat local surgical debridement and a combination of caspofungin acetate and voriconazole. After 2 weeks of combination therapy, she continued with voriconazole alone, and when the clinical picture permitted, immunosuppression with tacrolimus and mycofenolate was restarted 32 weeks after transplantation, as well as once-weekly liposomal amphotericin B therapy as prophylaxis for a previous Leishmania infection. At that time, she was also receiving metformin hydrochloride and rosiglitazone maleate, recently introduced for diabetes management.

Thirty-eight weeks after transplantation and after 10 weeks of voriconazole use, progressive pain developed in all extremities, gradually becoming intolerable. She complained of continuous, intense, sharp pain over both shins, described as “pins and needles,” as well as numbness and tingling involving both feet, from the toes to the heels, associated with an annoying burning sensation. She could not tolerate...
the sensation of touch and had lost perception of heat. She stated that everything felt unnaturally cold. Symptoms were more intense at the lower parts of the shins, toes, and plantar surface of the feet bilaterally. Similar symptoms, but of lower intensity, were described at the hands (digits) bilaterally. The discomfort was severe, present throughout the day, and disrupting sleep. The patient denied having a history of sensory symptoms; however, we did not have documentation of normal neurological examination findings before the onset of the symptoms. The patient denied any history of industrial or other exposure to heavy metals or pesticides. Physical examination revealed normal muscle strength and slightly reduced but symmetric deep tendon reflexes. Proprioception, vibratory, and pinprick sensation in the feet and toes was diminished. There was no evidence of arthritis, tendinitis, or plantar fasciitis by history and physical examination. We did not find evidence for carpal or tarsal tunnel syndrome, and the Tinel sign was negative, with no tenderness elicited with palpation over the flexor retinaculum.

Results of electromyographic and nerve conduction studies disclosed the presence of severe demyelinating polyneuropathy with significant reduction of the posterior tibial and peroneal nerve conduction velocities. Needle electromyography showed mild denervation of the right anterior tibialis muscle and the orbicularis oris. The peroneal and posterior tibial nerve compound muscle action potentials were of low amplitude, with values of 0.2 and 0.5 mV, respectively, (normal range, 3-30 mV), along with marginally prolonged distal latencies for the same nerves. Motor conduction velocities and F-wave study findings were also consistent with demyelination. Slowed motor conduction velocities were observed bilaterally for the peroneal (36 m/s [lower normal value, 45 m/s]) and the right posterior tibial (27 m/s [lower normal value, 42 m/s]) nerves. The F wave value was 65 milliseconds for the right posterior tibial nerve and 62 milliseconds for the left peroneal nerve. Sensory conduction velocities of the sural nerves bilaterally were normal. Electromyographic evaluation revealed a few fibrillation potentials and a reduced (interference pattern) maximal contraction diagram in the tibialis anterior muscle.

Laboratory findings revealed anemia (hematocrit, 33%), leukopenia (white blood cell count, 3×10^9/L), mild thrombocytopenia (platelet count, 110×10^3/µL), a normal erythrocyte sedimentation rate, and normal liver function test results except for elevated γ-glutamyl transpeptidase (323 U/L [normal values, <35 U/L]) and serum alkaline phosphatase (119 U/L [normal values, <92 U/L]). Cytomegalovirus DNA test results were negative in the peripheral blood. Electrolyte values were normal, as well as urea and creatinine levels. Immunologic tests included evaluation of C-reactive protein, antinuclear antibodies, rheumatoid factor, antineutrophilic cytoplasmic antibodies, hepatitis C, human immunodeficiency virus, cryoglobulins, and serum protein electrophoresis, with immunofixation showing all normal results. We found normal thyroid hormone levels (she was receiving therapy) and a normal hemoglobin A1c (HbA1c) level. Because of increasing serum γ-glutamyl transpeptidase levels and the potential association of neuropathy and the liver function test abnormalities with the recently introduced rosiglitazone treatment, this was discontinued as soon as the first symptoms were reported. Results of a repeated liver biopsy disclosed no evidence of acute rejection. However, moderate to severe (Ishak classification, stage 4) fibrosis and grade 10 necroinflammation, compatible with recurrent hepatitis C in the transplanted liver, were present.

Clinically, the patient felt worse. The sharp pain and burning sensation progressively spread over her entire body. Symptoms were intense, especially around the wrists, forearms, shoulders, dorsocervical area, abdomen, thighs, and lower legs. At that point, in addition to voriconazole, she was receiving tacrolimus (appropriate serum levels), mycophenolate, metformin, levothiroxine sodium, and amlodipine besylate for hypertension. Prescribed citalopram hydrobromide provided some relief, but the pain sensation was still present. Because of the incapacitating pain and after a repeated computed tomographic scan failed to reveal any findings of sinusitis, it was decided to discontinue the voriconazole treatment. Her clinical symptoms improved rapidly within approximately 2 weeks, and while all other medications were kept constant, the incapacitating pain disappeared. Neurological examination findings were markedly improved for proprioception, vibratory, and pinprick sensation, with slightly decreased symmetric tendon reflexes. She continues to do well 10 months after this event under close medical monitoring.

**COMMENT**

Painful sensory neuropathy can be attributed to several causes. Our patient's neuropathy was accompanied by abnormal nerve conduction, with electromyography results showing significant abnormalities, but laboratory findings were unremarkable. In addition, decreased position and vibratory sensation were found during the clinical examination. This makes the presence of pure small-fiber disease unlikely. According to several studies, the diagnosis of small-fiber painful sensory neuropathy represents the most common type of painful sensory neuropathy in patients older than 50 years.

Our patient's peripheral neuropathy could be related to the presence of diabetes mellitus. Patients with diabetes mellitus often experience painful sensory changes associated with reduced tendon reflexes and reduced distal sensation. Results of nerve conduction and electromyographic studies are usually abnormal, revealing axonal neuropathy rather than a demyelinating process. However, because most lesions in polyneuropathy consist of a mixture of myelin involvement and axonal loss, one usually sees a combination of changes. Results of the electromyographic and nerve conduction studies in our patient disclosed evidence of a mixed injury, with predominating demyelinating findings. However, features associated with mild axonal loss were also observed. These were secondary to the main process or could be attributed to another entity, such as the presence of diabetes mellitus. On the other hand, diabetic neuropathy can occasionally mimic the presentation and findings of the small-fiber painful sensory neuropathy subtype. In the case under discussion, diabetes mellitus was well controlled during the entire course of the patient's illness, as evidenced...
by the normal HbA1c and blood glucose levels and by the absence of autonomic neuropathy, often a part of diabetic neuropathy. Moreover, the patient had no evidence of sensory changes before the events presented, and physical examination failed to disclose any neurological abnormalities before the onset of pain and numbness. The presence of diabetes mellitus had a significant confounding effect in this case; however, the clinical response was indicative that the demyelination seen was probably associated with medication use.

Hepatitis C–related painful peripheral neuropathy is usually, but not always, associated with the presence of peripheral nerve vasculitis, cryoglobulinemia, multifocal symptoms of disease, and abnormal nerve conduction and electromyographic findings revealing multiple mononeuropathy; however, hepatitis C–associated polyneuropathy is also commonly seen. Cytomegalovirus and other viruses can cause a neuropathy in an immunocompromised individual. In our patient, we do not have cerebrospinal fluid findings to suggest this possibility, and cytomegalovirus DNA test results were negative; however, one should always consider these possibilities in an immunocompromised individual. An acute inflammatory demyelinating polyradiculoneuropathy (ie, Guillain-Barré syndrome) is another possibility that would improve spontaneously over time. Moreover, in this case, there was no clinical or serological evidence of connective tissue disease or vasculitis, and serologic test results did not suggest gammopathy. However, it is possible that the diagnoses of diabetes mellitus and hepatitis C may have contributed to the underlying neuropathy in our patient.

Peripheral neuropathy is a significant adverse effect of several medications and has been associated with the use of the traditional deoxycholate formulation of amphotericin B. Dysesthesias have been less commonly described with the liposomal amphotericin B formulation that our patient was receiving weekly for leishmaniasis prophylaxis at the time of the development of the neuropathy. However, none of the medications the patient was receiving has peripheral neuropathy as a major adverse effect. For tacrolimus, mycophenolate, and amlo-dipine, paresthesias and neuropathy are referred to in the corresponding prescribing information, and it is well known that antifungal triazole agents may increase the levels of tacrolimus. However, there was no evidence of toxic tacrolimus levels during the voriconazole administration in our patient. After the initiation of voriconazole therapy (10 weeks before the onset of the patient’s symptoms), tacrolimus levels were monitored routinely because of the expected interaction, and to maintain the levels well within the therapeutic range, the dosage was appropriately decreased to as low as 1 mg every fifth day from the initial few weeks of voriconazole therapy, before the onset of the patient’s symptoms. After the discontinuation of voriconazole, the tacrolimus dosage was gradually increased to maintain therapeutic levels without recurrence of the neuropathy. Moreover, one would expect onset of some symptoms of disease during the course of tacrolimus therapy before or after the voriconazole therapy because the tacrolimus levels often fluctuate. It was only after voriconazole discontinuation that the symptoms of the patient improved.

We realize the complexity of the case and that other factors may have played a role in the development of a demyelinating neuropathy in this immunocompromised patient with diabetes mellitus and recurrent hepatitis C. A search of the literature revealed no other similar reports of voriconazole-related peripheral neuropathy. In the full US prescribing information for voriconazole (in the section describing less common [<1% of all voriconazole-treated patients] adverse events), neuropathy is mentioned as an adverse effect.

To our knowledge, our case is the first published report of voriconazole-associated severe peripheral neuropathy. It occurred in a complicated immunocompromised patient, and it is possible that other factors, in addition to voriconazole, may have contributed to its appearance in this particular case. However, the neuropathy disappeared after discontinuation of the drug. The adverse event has been reported to our country’s National Pharmaceutical Organization. In this case, it was a diagnosis of exclusion and could only be made after adequate evaluation for all other types of demyelinating neuropathy was performed. Physicians treating patients with voriconazole should be aware of this association and closely monitor their patients for this potentially incapacitating and serious adverse effect.

Accepted for Publication: February 9, 2004.
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Author Contributions: Study concept and design (Tsiodras, Zafiropoulou, Kanta, Demponeras, and Manesis); acquisition of data (Tsiodras, Zafiropoulou, Kanta, Demponeras, Karandreas, and Manesis); analysis and interpretation of data (Tsiodras and Karandreas); drafting of the manuscript (Tsiodras, Zafiropoulou, Kanta, Demponeras, and Manesis); critical revision of the manuscript for important intellectual content (Tsiodras, Zafiropoulou, Kanta, Demponeras, Karandreas, and Manesis); administrative, technical, and material support (Tsiodras); study supervision (Tsiodras, Zafiropoulou, Kanta, Demponeras, Karandreas, and Manesis).

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