Case Report

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Angio-oedema as an unusual tolerable side effect of voriconazole therapy

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Voriconazole (VRC) has not previously been reported to cause angio-oedema. Here, we report a case of angio-oedema associated with VRC therapy. A 37-year-old woman with relapsing invasive vertebral aspergillosis received intravenous VRC and developed angio-oedema 10 days after starting therapy. This condition rapidly diminished after administration of intravenous antihistaminics and did not necessitate cessation of VRC treatment. The treatment was continued for 6 months without recurrence of the symptoms. After 18 months, the patient was in good health. To our knowledge, this is the first report of an angio-oedema associated with VRC.

Introduction

Voriconazole (VRC) is a new extended-spectrum second-generation triazole antifungal agent that is fungicidal against moulds including *Aspergillus* spp., in contrast to other azoles considered fungistatic agents (Mouas *et al.*, 2005; Pfaller *et al.*, 2002; Kirkpatrick *et al.*, 2000; Murphy *et al.*, 1997). VRC has demonstrated comparable *in vitro* activity to, or better *in vitro* activity than, itraconazole and amphotericin B (AmB) against filamentous and dimorphic fungi including *Aspergillus* spp. (Ghannoum & Kuhn, 2002). Therefore, VRC is useful for first-line and salvage therapy of invasive aspergillosis (IA) (Perfect *et al.*, 2003; Denning *et al.*, 2002; Herbrecht *et al.*, 2002).

VRC is safe and well tolerated. The chief adverse effects observed include transient visual disturbance, hepatotoxicity and skin reactions (Ghannoum & Kuhn, 2002). To our knowledge, angio-oedema has not been reported as a side effect of VRC before. Angio-oedema, formerly called angioneurotic oedema, is an uncomfortable temporary swelling in the face. It may occur as an adverse reaction to some medicines as well as to some foods. In this paper, we report a case of vertebral *Aspergillus* osteomyelitis in a patient who developed angio-oedema during VRC treatment which did not lead to discontinuation of the drug. Another striking feature of this patient is that vertebral osteomyelitis progressed despite surgery and prolonged treatment with liposomal AmB (L-AmB), but responded when antifungal treatment was switched to VRC.

Case report

A 37-year-old woman was admitted to the Neurosurgery Clinics in October 2002 with a 9-month history of

increasing low back pain. She had no fever or sweats. There had been no trauma or surgical intervention. She had been treated for pulmonary tuberculosis in 1990. In her physical examination, there were no remarkable findings. Laboratory examination revealed an erythrocyte sedimentation rate (ESR) of 118 mm h⁻¹, haemoglobin 8.4 g dl⁻¹, leukocytes 6800 mm⁻³, thrombocytes 403 000 mm⁻³ and C-reactive protein (CRP) level of 139 mg l⁻¹ (reference range <5 mg l⁻¹). HIV and *Brucella* standard agglutination tests were all negative. An MRI scan of the lumbar spine revealed the presence of a 5 cm diameter mass in the fourth lumbar vertebra and a paraspinal soft-tissue mass. The patient underwent laminectomy and spinal fusion. Pathological examination of surgical biopsy specimens revealed chronic granulomatous inflammation with abscess formation and fungal hyphae. Gram staining and acid-fast staining of the abscess material were negative. Culture of the abscess material grew *Aspergillus fumigatus*. The patient was transferred to the Infectious Disease Clinics of the hospital and antifungal therapy was initiated with L-AmB (1 mg kg⁻¹ once per day i.v.). After an 8-week course of intravenous L-AmB, therapy was switched to oral itraconazole (200 mg b.i.d.). At that time, the patient was diagnosed as having chronic granulomatous disease by the oxidative burst test. The patient eventually improved, the ESR decreased to 55 mm h⁻¹ and the CRP level was 31 mg l⁻¹, and she was discharged home after 3 months of therapy. Three months later, she was in good health and stopped oral itraconazole therapy by herself. However, the patient was readmitted to hospital 5 months after stopping therapy because of her low back pain again. She was treated with a 4-month course of L-AmB followed by oral itraconazole therapy. Her medical condition gradually improved and treatment was stopped 6 months later.

The patient was admitted to another hospital 2 years after her first admission with recurrence of symptoms and

Abbreviations: AmB, amphotericin B; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IA, invasive aspergillosis; VRC, voriconazole.

elevation of the ESR (98 mm h^{-1}) and CRP (110 mg l^{-1}). Antifungal therapy was initiated with caspofungin ($50 \text{ mg i.v. once per day}$) and continued irregularly for 3 months, so the patient did not improve. A month after stopping caspofungin she was admitted to our hospital and VRC (loading dose of $6 \text{ mg kg}^{-1} \text{ q.12 h}$ on day 1, followed by $4 \text{ mg kg}^{-1} \text{ q.12 h}$) was initiated as antifungal therapy. By day 10 of VRC therapy, she developed a sore throat followed by dyspnoea and swelling of the lips and tongue. On physical examination, swollen lips and tenderness of the pharynx were noted. No rash was seen. This condition was diagnosed as an angio-oedema caused by VRC, and the symptoms gradually diminished over 2 days after administration of intravenous antihistaminics. The symptoms did not recur and did not necessitate cessation of VRC treatment. She had not eaten allergenic foods or anything out of the ordinary and not taken any other drugs. She had not previously experienced angio-oedema. Laboratory examination revealed complement 3 (C3) 105 mg dl^{-1} (reference range $90\text{--}200$) and C4 32 mg dl^{-1} (reference range $20\text{--}50$). Anti-nuclear antibody was negative. After a month of VRC treatment, her symptoms continued to improve. The ESR and CRP had decreased to 94 mm h^{-1} and 8 mg l^{-1} , respectively. She was discharged home by switching intravenous therapy to oral therapy and followed as an outpatient. The treatment was continued for 6 months until the patient improved, the ESR decreased to 66 mm h^{-1} , the CRP level was 13 mg l^{-1} and an MRI scan showed improvement. After 18 months, the patient was in good health.

Discussion

IA is a major infectious complication in immunocompromised patients (Kohli & Hadley, 2005). Infection is most commonly acquired through inhalation of *Aspergillus* spores. Dissemination from a primary pulmonary focus can occur through haematogenous spread (Kohli & Hadley, 2005; Gunsilius *et al.*, 1999). Bone infections in patients with IA are rare (Denning, 1998); in a review of the literature, only 38 (1.8%) of 2121 cases of IA had bone involvement (Denning & Stevens, 1990). However, in patients with chronic granulomatous disease, osteomyelitis is not uncommon, and *Aspergillus* species are the second most common causative pathogens, causing 22% of cases (Winkelstein *et al.*, 2000). Although AmB has long been the drug of choice, the suboptimal responses and toxicity associated with this drug may limit its use and efficacy (Bates *et al.*, 2001; Wingard *et al.*, 1999; Denning & Stevens, 1990). Furthermore, penetration of AmB into bone tissues is poor (Stevens *et al.*, 2000). In contrast, newer azole agents, such as VRC, have excellent *in vitro* activity against *Aspergillus*, good bone penetration and less toxicity (Mouas *et al.*, 2005; Kohli & Hadley, 2005; Stratov *et al.*, 2003; Perez-Gomez *et al.*, 1998). In a large randomized study, VRC was found to be more effective than AmB in treating IA, in terms of response rate, survival

rate and safety (Herbrecht *et al.*, 2002). VRC has become the new recommended primary therapy for most patients with IA. The optimum duration of therapy for IA, especially bone aspergillosis, has not been established. Depending on the patient's clinical and radiological responses, treatment usually lasts several months (Denning, 1998). In a previous report, cases of bone aspergillosis, most of which were in patients experiencing treatment failure with other antifungals, had a response rate to VRC of 55% and patients received a median duration of VRC treatment of 180 days (Mouas *et al.*, 2005).

VRC is generally well tolerated. However, treatment with VRC does carry some risk of toxicity. The most common side effect is a reversible disturbance of vision, occurring in 23–35% of patients and most frequently during the first week of therapy (Ghannoum & Kuhn, 2002). Visual disturbances include altered colour discrimination, blurred vision, the appearance of bright spots and wavy lines, and photophobia. In general, these visual disturbances are transient and reversible, mostly resolving within 1 h. In clinical trials, visual changes rarely necessitate discontinuation of the drug (Johnson & Kauffman, 2003; Ghannoum & Kuhn, 2002; Purkins *et al.*, 2002; Lazarus *et al.*, 2002; Walsh *et al.*, 2002a, b; Ally *et al.*, 2001).

Skin reactions are the second most common adverse effect noted with VRC therapy. Two types of skin reactions have been noted: rash and photosensitivity. From 6 to 25% of patients experience some form of rash. Rashes noted include facial and generalized erythema, exanthem and dermatitis. Most of these are mild and constitute no major problem. However, severe reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, have been reported in a very small number of patients. Photosensitivity occurs at a much lower level than a rash (between 1 and 2%), and is more frequently observed in patients receiving more than 12 consecutive weeks of VRC therapy (Johnson & Kauffman, 2003; Ghannoum & Kuhn, 2002; Denning & Griffiths, 2001).

The other adverse effect is hepatotoxicity. In a study by Ghannoum & Kuhn (2002), 12 and 21% of subjects had abnormal ALT and total bilirubin levels, respectively. Although most patients have asymptomatic elevation of liver enzyme levels, several patients with severe life-threatening hepatitis have been described. The risk of developing hepatitis appears to increase with increased serum VRC levels and resolves with discontinuation of the drug (Johnson & Kauffman, 2003). Other less commonly noted side effects include headache, nausea and vomiting, diarrhoea, abdominal pain, visual hallucinations and cardiac arrhythmias. Visual hallucinations occurred at a rate of 5% in one clinical trial (Walsh *et al.*, 2002b).

A new side effect which has not been reported before is angio-oedema. Our patient developed angio-oedema 10 days after starting VRC therapy. As the reaction was described after 10 days of VRC treatment and did not recur

during the long therapy with VRC, a Jarisch–Herxheimer reaction, which is a transient inflammatory reaction caused by organisms dying off and releasing toxins into the body, might be considered. It is manifested by fever, chills, headache, myalgias and skin lesions. However, our patient did not present such symptoms. She had an appearance of angio-oedema. Angio-oedema is an uncomfortable temporary swelling, particularly in the lips and other parts of the mouth and throat, the eyelids, the genitals, and the hands and feet. It may be life-threatening if swelling in the mouth or throat makes it difficult to breathe and usually settles in a few days. It may result from allergy to certain foods such as shrimps or strawberries or as an adverse reaction to some medicines, such as ACE inhibitors, beta-blockers, aspirin and other antiinflammatory agents. There was nothing causing angio-oedema other than VRC in our patient, no history of previously experienced angio-oedema and no family history. There was no other known disease apart from chronic granulomatous disease. However, there is no known relationship between angio-oedema and chronic granulomatous disease in the medical literature. Therefore, the only causal relationship was with VRC. Our patient developed angio-oedema, which was transient and did not lead to discontinuation of the drug and she had no further episodes of angio-oedema.

In conclusion, we present, to our knowledge, the first reported case of angio-oedema associated with VRC. We believe that angio-oedema should be added to the list of adverse reactions associated with VRC.

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