Abstract. – Torsade de pointes (TdP) is a life-threatening arrhythmia that can result from long QT syndrome. Drug-induced QT prolongation is a potentially dangerous adverse effect of some drug combinations. A 34-year-old woman with history of nephrotic syndrome and rheumatic mitral valve disease was admitted to our Hospital because of high fever. The patient continued to be febrile until antifungal treatment was switched to voriconazole. The electrocardiogram demonstrated sinus tachycardia and a prolonged QTc interval of 580 ms. Patient was resuscitated with electrical cardioversion and had an emergent temporary pacemaker placed. We recommend careful monitoring for QTc prolongation and arrhythmia in patients who are receiving voriconazole, particularly those who have significant electrolyte disturbances.

Key Words: Voriconazole, QTc prolongation, Torsades de pointes.

Introduction

Torsade de pointes (TdP) are a life-threatening arrhythmia that can result from long QT syndrome. Many agents and medical conditions can cause acquired long QT syndrome¹. Azoles may cause prolongation of the QT interval either directly or by inhibiting the hepatic metabolism of other QT-prolonging agents². Voriconazole is extensively metabolized by the liver, via the cytochrome P450 pathway, by the isoenzymes CYP2C19, CYP2C9, and to a less degree by CYP3A4³. We report a rare case of voriconazole-associated torsade de pointes (TdP) ventricular tachycardia followed by QT interval prolongation that occurred with a small dose of voriconazole in a patient with nephrotic syndrome.

Case Report

A 34-year-old woman with a 6 year history of nephrotic syndrome was admitted to the intensive care unit (ICU), due to high fever. Her medical history was including uneventful rheumatic mitral valve disease in addition to nephrotic syndrome. Her family history showed no cases of cardiac arrhythmia or sudden deaths. She presented with a fever (temperature, 39°C), blood pressure of 110/70 mmHg, a regular heart rate (96 beats per minute), and no other abnormalities. Laboratory studies were notable for potassium 3.5 mmol/L (RV: 3.5-5.5), magnesium 1.2 mg/L (RV: 1.3-2.1), calcium 7.4 mg/dL (RV: 8.4-10.2), albumin 2.3 mg/dL (RV: 3.5-5), WBC 13.700 cells/mm³, neutrophils 77%, CRP 18.5 mg/dL, and 66 mm/h. Echocardiography was performed during the course of treatment because the patient’s unstable state. Rheumatic mitral valve and a moderate mitral regurgitation were found. Three days later, while she was still febrile, blood samples for culture were obtained, and an empiric treatment with piperacillin-tazobactam and amikacin was started. Five days after the beginning of the chemotherapy, vancomycin and systemic amphotericin B were added to her regimen. The patient continued to be febrile, and because of the dissemination of her infection, the antifungal treatment was switched to voriconazole [200 mg 2 × 1. given intravenously (i.v.) for 4 days]. Therapy with i.v. voriconazole with dose later adjusted according to her renal function was started. An ECG showed sinus tachycardia at a rate of 105, with
QTc prolongation and torsade de pointes ventricular tachycardia in a small dose voriconazole therapy

Figure 1. Electrocardiogram (ECGs) recorded on day 4 of voriconazole treatment showing sinus tachycardia (heart rate, 105 beats per minute) and QTc prolongation to 580 ms.

Discussion

Antifungal agents of the azoles have been described as potentially arrhythmogenic drugs. Cases of arrhythmia that develop after treatment with itraconazole, fluconazole or ketoconazole, alone have been reported, as well2-6. QT interval prolongation and TdP were described as adverse effects of treatment with azole family in combination with other arrhythmogenic drugs2. Female gender is the most frequently associated risk factor for TdP2. Voriconazole is a potent blocker of the P450 system, leading to increased hemetic concentrations of drug scarcely metabolized by this system2.

In the literature, a few cases of nonsustained, polymorphic ventricular tachycardia with QTc interval prolongation associated with voriconazole have been reported, involving a 15-year-old girl with acute lymphoblastic leukemia and a 14-year-old girl with acute myeloid leukaemia. In the first patient mentioned above8, the first episode of QTc prolongation followed by torsade de pointes was noted after 3 weeks of voriconazole treatment. She developed asymptomatic bradycardia, QT interval prolongation and nonsustained, polymorphic ventricular tachycardia. In addition voriconazole level and metabolism were within expected normal values in that patient.

Another case of bradycardia with QTc interval prolongation associated with voriconazole has been reported: a 14-year-old girl with acute myeloid leukemia and a suspected mucormucosis infection was treated with intravenous voriconazole9.

In those cases the duration of the voriconazole treatment was 3 weeks. However, in our case the duration of voriconazole treatment was only 4 days. In our patient the first episode of QTc prolongation followed by TdP was noted after 4 days of voriconazole treatment, when she had a combination of several risk factors. In this patient predisposing factors identified were: i.v. voriconazole, female gender, drug-interaction and hypomagnesaemia, antifungal azoles and amphotericin B treatment.

Polymorphic ventricular tachycardia and QTc prolongation were dose independent and recurred upon rechallenge with a very small voriconazole dose in the absence of other known proarrhythmogenic agents, thus suggesting a causal relationship with voriconazole exposure.
In this case we suggest that voriconazole may induce QTc prolongation and polymorphic ventricular tachycardia independent of duration and dose, in the absence of other arrhythmogenic factors. Physicians must be aware of multi-drug interactions potentiating QTc prolongation and leading to torsade de pointes ventricular tachycardia. Patients receiving voriconazole should be followed carefully for potential drug interactions and electrolyte imbalance to minimize the possibility of proarrhythmia.

References


7) MAKKAR RR, FROMM BS, STEINMAN RT, MEISSNER MD, LEHMANN MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993; 270: 2590-2597.
