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Voriconazole-induced bradycardia without QT interval prolongation: a possible non-concentration-dependent adverse effect

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Dear Editor,

Voriconazole is commonly used for prophylaxis and treatment of invasive aspergillosis and to improve the survival of mechanically ventilated hematology patients with invasive pulmonary aspergillosis (IPA) [1]. Cardiac adverse effects can occur, but only cases of tachycardia have been described with voriconazole. Here, we report the cases of three patients admitted to the Intensive Care Unit (ICU) with suspected voriconazole-induced bradycardia.

A 63-year-old woman was admitted for pneumonia (*Escherichia coli*) with septic shock. She had prolonged neutropenia due to chemotherapy for a diffuse large-cell lymphoma. On day 7, an IPA was suspected, and antifungal therapy with voriconazole was started. Two days following the initiation of voriconazole therapy, we observed multiple episodes of spontaneous bradycardia (20–25 beats/min) and a QTc up to 0.40 s. As voriconazole was the only change in the patient's therapeutic regimen, we discontinued the administration of voriconazole and switched her to caspofungin. Normalization of the heart rate occurred during the next day and continued until discharge from the ICU.

A 52-year-old woman with chemotherapy-induced myelosuppression was administered voriconazole (400 mg twice per day) for suspected IPA. The diagnosis was confirmed by a computed tomography scan, increased bronchoalveolar lavage antigens and positive test result of sputum for *Aspergillus fumigatus*. After 4 days of voriconazole therapy, the patient developed arrhythmias followed by sinus bradycardia (QTc = 0.38 s) that required atropine. The replacement of voriconazole with caspofungin was followed by resolution of bradycardia.

A 78-year-old man was admitted to the ICU for acute respiratory failure after abdominal surgery. One month later IPA due to *Aspergillus fumicatus* was diagnosed. Voriconazole therapy was initiated (400 mg twice per day). He also received propofol, remifentanil, haloperidol, nefopam, piperacillin–tazobactam and gabapentine. Three days later, however, the patient experienced several episodes of spontaneous and extreme bradycardia with complete atrioventricular block and a QTc up to 0.36 s on the electrocardiogram (Fig. 1), requiring the administration of isoprenaline. The serum potassium level was 3.6 mmol/L. Voriconazole was administrated intravenously at 300 mg twice per day for 1 week. Plasma voriconazole concentrations (as determined by high-performance liquid chromatography) were 2.86, 3.08 and 3.20 mg/L on the first 3 days following the initiation of therapy, respectively (normal range 1–5.5 mg/L) [2]. We replaced voriconazole with caspofungin, and the patient recovered a sinus cardiac rhythm after 12 h, which he maintained up to discharge from the ICU without any new episodes.

In these three patients, severe episodes of bradycardia were not associated with QTc prolongation, torsades de pointes or ventricular tachycardia. All patients were treated

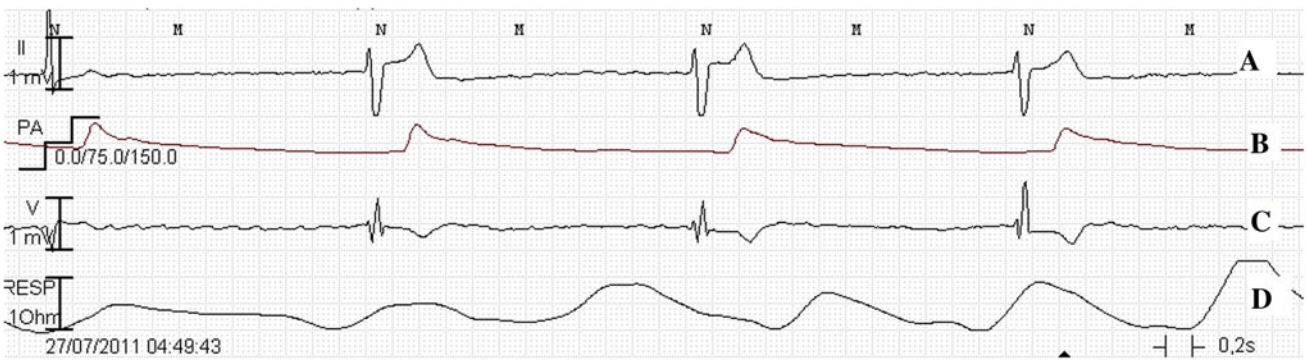

Fig. 1 *A*, *C* Electrocardiogram recording (*lead II and V*) showing a heart rate of 25 beats per minute and a corrected QT [QTc] of 0.36 s, *B* blood pressure analysis, *D* respiratory electrical resistance signal

with atropine or isoprenaline without any other basic life support requirement. The episodes occurred in ICU patients who had possibly received numerous arrhythmogenic drugs. The cardiac event was concentration independent in one patient. Prolongation of the QTc interval has been described as an adverse event following treatment with azole in combination with other arrhythmogenic drugs [3], but without any bradycardia. One case report describing a young patient with non-concentration-dependent QTc prolongation together with initial bradycardia followed by torsades de pointes after 3 weeks of voriconazole treatment (with rechallenge) has been published [4]. The mechanisms underlying bradycardia or QTc prolongation following voriconazole exposure are unknown. One possibility is blockage of cardiac ion potassium rapid-channels and HERG [5].

In conclusion, these cases suggest that voriconazole can induce early bradycardia without QTc prolongation, which in one of the cases reported here was independent of dose and concentration. Physicians should be aware that the QT interval and the heart rate must be monitored in patients receiving long-term treatment with voriconazole, especially when voriconazole is given in combination with other arrhythmogenic drugs.

Conflicts of interest None.

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