Torsades De Pointes upon Fluconazole Administration in a Patient with Acute Myeloblastic Leukemia

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Prolonged QT syndrome often causes torsades de pointes (Tdp), a potentially lethal arrhythmia. A 55-year-old woman with M4Eo who was receiving consolidation chemotherapy had an episode of prolonged QT and Tdp following fluconazole (FCZ) administration. Intravenous supplementation of magnesium sulfate and multiple attempts at electrophoresis led to recovery from the arrhythmia. FCZ appears to contribute to the development of QT prolongation, in particular with low concentrations of serum potassium or magnesium. Although mechanisms of Tdp development in patients with QT prolongation remain to be determined, it is possible that FCZ administration leads to manifestation of Tdp. Special cautions should be exercised upon the emergence of QT prolongation following FCZ administration. Am. J. Hematol. 81:366–369, 2006. © 2006 Wiley-Liss, Inc.

Key words: torsades de pointes; fluconazole; QT prolongation; acute leukemia

INTRODUCTION

Acquired QT prolongation can be elicited by administration of certain anti-arrhythmics, antihistamines, Ca++ channel blockers, psychotherapeutics, and antibiotics or with electrolyte abnormalities such as hypokalemia and hypomagnesemia, and this cardiac condition potentially leads to life-threatening ventricular arrhythmias, such as ventricular tachycardia or ventricular fibrillation. A few cases of QT prolongation followed by torsades de pointes (Tdp) have been reported upon fluconazole (FCZ) administration [1–4]. We hereby present a patient with acute myeloblastic leukemia (AML) who developed QT prolongation, which triggered Tdp following FCZ administration.

Case

A 55-year-old woman was admitted for gum swelling. Laboratory findings revealed a leukocyte count 12.5 × 10^9/L with leukemic blast cells 47%, hemoglobin level 7.5 g/dl, platelet count 38 × 10^9/L. Bone marrow aspiration showed 69.2% leukemic cells and 6.0% abnormal eosinophils. Cytogenetic study of the bone marrow cells revealed 46,XX,inv16(p13q22), showing that she had AML M4Eo by the FAB classification. Induction chemotherapy consisted of idarubicin and cytarabine. AML97 protocol was begun, resulting in complete remission [5,6]. During the second consolidation therapy with cytarabine, etoposide, daunorubicin, and mercaptopurine, the patient developed a high fever of 38°C and bacteremia with Pseudomonas aeruginosa and was treated with ampicillin sodium sulbactam sodium and amphotericin B and subsequently with tobramycin and cefoperazone sodium sulbactam sodium (Fig. 1). Her high fever was sustained and her chest X-rays subsequently revealed pneumonia and laboratory examinations showed high CRP levels of up to 15 mg/dl and serum β-d-glucan levels of up to 44 pg/ml. Her pneumonia was suspected to be caused by bacterial and fungal superinfection. With no pneumonia improvement and symptomatic aggravation with wheezing, an intravenous injection of aminophylline and 200 mg intravenous FCZ therapy were implemented. Approximately

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8 h following FCZ administration, significant QT prolongation was found on electrocardiogram and short durations of Tdp ensued (Fig. 2a). Lidocaine hydrochloride administration was given with no apparent effects. Episodes of Tdp started to last longer, ranging 30–60 s and resulting in syncope, when an electrical defibrillation was administered. Since Tdp occurred multiple times and were resolved with an electrical defibrillation each time, magnesium sulfate supplementation (8 g/day) was started (Fig. 1). Twenty-four hours later, long-lasting Tdp no longer occurred, although short-lasting, asymptomatic Tdps of up to a few seconds and QTc prolongation of up to 528 ms persisted (Fig. 2b). Administration of FCZ was discontinued after emergence of Tdp. Next-day laboratory data showed Na 146 mEq/L, K 3.0 mEq/L, Ca 8.2 mg/dL, and Mg 2.8 mg/dL. Three days after the first bout, Tdp no longer occurred. Her pneumonia later improved upon recovery of normal leukocytes and the patient was discharged with normal bone marrow profiles and normal complete blood count.

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Fig. 1. Clinical course in the present case with torsades de pointes. Ara-C, cytarabine; ETP, etoposide; DNR, daunorubicin; 6-MP, mercaptopurine; FCZ, fluconazole; MgSO₄, magnesium sulfate; AMPH-B, amphotericin B; S/A, ampicillin sodium sulbactam sodium; S/C, cefoperazone sodium sulbactam sodium; CAZ, ceftazidime; CFPM, cefepime dehydrochloride; TOB, tobramycin; AZT, aztreonam; Tdp, torsades de pointes.

Fig. 2. (a) ECG showing torsades de pointes. The lower line denotes breathing. (b) QT and QTc in the present case. Normal upper limits of QT and QTc are 420 and 440 ms.
DISCUSSION

We present a case report where prolonged QT syndrome is associated with FCZ administration in a patient receiving consolidation chemotherapy for AML (M4Eo). Prolonged QT syndrome, if not adequately treated, often leads to life-threatening arrhythmias such as ventricular tachycardia and ventricular fibrillation. It has recently been reported that anti-leukemic treatment with arsenic trioxide (ATO), a therapeutic agent for acute promyelocytic leukemia, often causes electrocardiographic QT prolongation [7]. However, QT prolongation has not been well reported in subjects with leukemia under therapy not involving ATO. Although underlying inherited prolonged QT syndrome has been reported in patients with Tdp, our patient has no familial history of QT prolongation syndrome and Tdp. The cause for the prolonged QT syndrome seen in the present patient can be multifactorial: (i) abnormalities in serum electrolytes, (ii) possible myocardial damages from prior anti-leukemic therapy, and (iii) certain medications. In this patient, serum potassium levels were within normal limits (3.4 mEq/L) before the emergence of QT elongation (Fig. 1). Although no magnesium levels were determined prior to Tdp, magnesium sulfate administration appeared to be effective upon the Tdp, suggesting that the patient had low magnesium levels before her Tdp. No abnormality was found on electrocardiogram before this consolidation chemotherapy. Aminophylline is known to cause low potassium levels and this effect could have been further augmented by the FCZ inhibition of CYP 3A4 that metabolizes aminophylline, thereby potentially increasing the serum aminophylline concentration, which might have triggered prolonged QT syndrome [8]. Lidocaine is known to exacerbate or has proarrhythmic effects before given magnesium sulfate, it might have been concerned with deterioration of Tdp. FCZ administration also appears to be associated with QT prolongation syndrome, although how FCZ causes QT elongation is as yet unknown [1–4].

While the exact mechanism(s) of the emergence of Tdp is still unknown, drugs that prolong action potential duration, induce early afterdepolarizations and ectopic beats, and increase dispersion of ventricular repolarization have the propensity to cause Tdp [9]. In this regard, it is not known whether FCZ has such pharmacological properties; however, in all of the four recently reported cases of Tdp associated with FCZ administration [1–4] (Table I), prodromal QT prolongation following FCZ administration had occurred before Tdp. It is of note that for as yet unknown reasons, more female than male individuals sustain Tdp, and indeed, all these reported cases were female and so is the present case.

It is noteworthy that a number of chemotherapeutics for acute leukemia induce gastrointestinal adverse effects, resulting in electrolyte abnormalities, and a variety of infections during chemotherapy aggravate the vulnerability of patients to cardiac abnormalities causing QT prolongation syndrome. Thus, when a triazole antifungal agent such as FCZ is administered and electrocardiographic QT prolongation ensues, special cautions should be exercised and proper treatment should be administered to block the emergence of life-threatening Tdp.

REFERENCES