Acute Adrenal Failure Associated With Fluconazole After Administration of High-Dose Cyclophosphamide

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A 63-year-old man received high-dose cyclophosphamide for peripheral blood stem-cell (PBSC) harvest. He received 200 mg fluconazole. On day 3, atrial fibrillation developed with blood pressure declining to 78 mmHg. The rapid adrenocorticotropin (ACTH) test showed blunted adrenal responses. He was suspected as having adrenal failure, and fluconazole was discontinued. The rapid ACTH test became normal on Day 14, and PBSCs were successfully harvested. To clarify the association between adrenal failure and fluconazole, we resumed 400 mg fluconazole on Day 16 and repeated the test on Day 21, which showed blunted adrenal responses. This case demonstrates that prophylactic use of fluconazole can cause adrenal insufficiency. Am. J. Hematol. 66:303–305, 2001.

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INTRODUCTION

Fungal infection is a potentially fatal complication in the case of patients undergoing high-dose cytotoxic chemotherapy, leading to high morbidity and high mortality. Early diagnosis and prompt initiation of antifungal treatment are frequently difficult, and prevention of fungal infection is of great importance.

The introduction of fluconazole has had a dramatic effect on the prevention and treatment of fungal infections in these patients, and several controlled studies have shown that it is highly effective for the prevention of fungal infection [1,2]. In a prospective, randomized, placebo-controlled trial, fluconazole at a dosage of 400 mg/day was shown to significantly reduce fungal colonization, superficial and hematogenous candidiasis, and mortality [2]. Because fluconazole is well absorbed from the gastrointestinal tract, and there is little associated toxicity [3], this anti-fungal agent is now widely used in chemoprophylaxis in cases involving a risk of opportunistic mycoses.

We agree that fluconazole is a relatively safe drug for patients undergoing high-dose cytotoxic chemotherapy. However, we recently encountered a patient who developed life-threatening acute adrenal failure associated with fluconazole. A detailed description of this case provides important information regarding the possible association between fluconazole prophylaxis and adrenal insufficiency after high-dose therapy including hematopoietic stem-cell transplantation.

CASE REPORT

A 63-year-old man was admitted to our hospital due to multiple myeloma in December 1999. He responded to two courses of VAD therapy [4], and the multiple myeloma was diagnosed as being in partial remission. During the VAD therapy, he developed candidial enterocolitis and received intravenous administration of amphotericin B. Renal function was impaired with the administration of amphotericin B.

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To harvest peripheral blood stem cells, he received 2 g/m^2 of cyclophosphamide for two consecutive days in April 2000 [4]. Because he had a history of candidial enterocolitis and hemorrhoid, he received tosfloxacine and 200 mg of FCZ for prevention of bacterial infection and fungal infection, respectively. Trimethoprim/sulfamethoxizole was also administered as prophylaxis against *Pneumocystis carinii* infection.

On Day 3, he complained of heart palpitations and nausea, and he went into shock with his blood pressure declining to 78 mmHg. Atrial fibrillation was detected on an electrocardiogram. His body weight decreased from 51.1 to 49.0 kg. Blood tests were almost normal. Serum levels of potassium and sodium were 3.6 and 131 mEq/l, respectively. We supposed that high-dose cyclophosphamide might have caused cardiac damage, leading to atrial fibrillation. However, an echocardiogram showed normal motion of the cardiac walls, and cardiac effusion was not detected. The atrial fibrillation did not respond to antiarrhythmic agents, and finally electric cardioversion was required.

On the basis of the clinical findings in this case, adrenal failure was suspected. We supposed that fluconazole might have the potential to inhibit the synthesis of cortisol, although adrenal insufficiency is rarely reported in the case of patients receiving fluconazole [5]. We therefore performed a rapid adrenocorticotropin (ACTH) test on Day 8, and this revealed mild suppression of cortisol secretion (Fig. 1). The procedures of the rapid ACTH test have been reported previously [6]. We discontinued fluconazole and initiated intravenous administration of amphotericin B at a dose of 10 mg/day was administered also until PBSCH. On day 15, 6.0 × 10^6 CD34-positive cells were successfully harvested without recurrence of atrial fibrillation or adrenal insufficiency. We repeated the rapid ACTH test on Day 14, and it showed a normal adrenal response (Fig. 1).

Because he had a history of candidial enterocolitis and he had developed renal dysfunction associated with amphotericin B, FCZ was essential for safe and successful transplantation. To clarify the association between adrenal failure and fluconazole, we resumed administration of fluconazole at 400 mg/day after obtaining informed consent, and repeated the rapid ACTH test on Day 21. Hydrocortisone, 20 mg/day, was administered for supplementation of cortisol between Day 16 and Day 21. He did not develop overt adrenal failure, but the rapid ACTH test showed marked suppression of cortisol levels (Fig. 1). He was finally diagnosed as having adrenal insufficiency caused by fluconazole.

He received autologous PBSCT in May 2000 with FCZ prophylaxis and supplementation of corticosteroid. He did not develop adrenal failure, and autologous PBSCT was successful.

**DISCUSSION**

Introduction of ketoconazole into medical practice in the early 1970s initiated a new era of antifungal therapy. The availability of an orally absorbed drug with low toxicity permitted outpatient therapy in cases of deep mycosis and long-term prophylaxis of fungal infection. Considering the toxicity of the conventional amphotericin B, the introduction of ketoconazole seemed to be quite attractive. However, some endocrinological disorders have been reported in the case of patients receiving ketoconazole. These include menstrual irregularities, gynecomastia, azoospermia, adrenal insufficiency, hypertension, and fluid retention [7]. Because ketoconazole inhibits steroid biosynthesis in patients, as it does in fungi, by inhibiting cytochrome P450-dependent enzyme synthesis, it is reasonable that ketoconazole is associated with a variety of hormonal disorders and that a daily dose of 800 mg of ketoconazole has been used to suppress plasma cortisol levels in patients with Cushing’s disease [8]. Subsequently, newer azole antifungals have replaced ketoconazole because of improved efficacy, minimal hormonal effects, and the possibility of intravenous administration.

FCZ is a newer triazole with a high specificity for fungal cytochrome P450, and this triazole appears to have fewer adverse effects than does ketoconazole. To our knowledge, fatal adverse effects have not been reported except for hepatic failure [9] and Stevens-Johnson syndrome [10]. Most physicians believe that fluconazole can be used safely in the treatment and prophylaxis of fungal infection. However, this case demonstrates that
fluconazole can cause severe damage to the adrenal gland leading to adrenal shock, while its exact mechanism and the risk factors involved remain unknown. The repeated rapid ACTH tests revealed that fluconazole suppressed cortisol secretion in a dose-dependent manner in this patient and showed the existence of an association between adrenal failure and fluconazole.

Although the adrenal toxicity was reversible upon discontinuation of fluconazole, the fact that fluconazole can cause adrenal insufficiency is quite significant for patients receiving high-dose cytotoxic chemotherapy. As shown in this patient, it seems to be difficult to differentiate the adrenal insufficiency associated with fluconazole from the so-called “regimen-related toxicity” associated with high-dose chemoradiotherapy. Unless we fully recognize the possibility that fluconazole can induce adrenal insufficiency, it may be overlooked or misdiagnosed as a complication of the high-dose cytotoxic chemotherapy. Considering the widespread use of fluconazole in prophylaxis of fungal infection, adrenal failure associated with fluconazole should be included in the list of complications after high-dose cytotoxic chemotherapy.

REFERENCES


