CASE REPORT

Reversible acute adrenal insufficiency caused by fluconazole in a critically ill patient

S G Santhana Krishnan, R K Cobbs

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A 38 year old man with history of obstructive sleep apnea and polycythaemia presented with hypercapnic respiratory failure that required intubation. He developed fever with infiltrates on chest radiography that required empiric antifungal therapy with fluconazole along with broad spectrum antibiotics. He developed acute adrenal insufficiency that recovered after fluconazole was stopped. It is believed that this complication of adrenal suppression attributable to fluconazole is underrecognised and it may be prudent to monitor all critically ill patients who are given fluconazole for this complication.

Azole antifungal therapy has been in use for nearly a quarter of century when ketoconazole was first introduced. They are generally safe, efficacious, and easy to give orally in treatment of various systemic mycoses.¹ Ketoconazole is reported in daily dose exceeding 400 mg to reversibly inhibit synthesis of testosterone and cortisol leading to various endocrine disturbances including adrenal insufficiency.² Even though fluconazole does not generally inhibit steroidogenesis, there are rare reports³⁻⁵ of adrenal suppression, raising the possibility that this problem is currently underrecognised. We report a patient who developed reversible adrenal suppression on fluconazole.

CASE REPORT

A 38 year old obese man with medical history significant for obstructive sleep apnea and secondary polycythaemia presented to emergency room with complaints of cough for three days before admission with greenish expectoration. His drug treatment included hydrochlorothiazide, lopressor, and aspirin. He denied taking corticosteroids recently. He was found to be in hypercapnic respiratory failure that required intubation. Chest radiography was normal.

He was given ampicillin and sulbactam and azithromycin intravenously for pneumonia. Pulmonary embolus and acute coronary syndrome were ruled out. He developed fever on second day of admission. As fever persisted after 48 hours with new infiltrates on chest radiography, antibiotics were changed to vancomycin and imipenam. Trimethoprim-sulfamethoxazole was added to cover for *Pneumocystis carinii*. A cosyntropin test done on day 4 of admission as a part of an ongoing study showed a peak cortisol concentration of 663 nmol/l. This was consistent with normally functioning adrenals.

Later, fluconazole 400 mg intravenous once a day was started empirically as he remained febrile. Two days after starting fluconazole sodium decreased to 113 and potassium increased to 5.6. Cosyntropin test was repeated. Basal cortisol was 45 nmol/l with a peak of 375 nmol/l, at 60 minutes consistent with adrenal insufficiency.⁶ Hydrocortisone 100 mg intravenously every eight hours was started.

Computed tomography of adrenals was negative for haemorrhage. He became afebrile and fluconazole was stopped after nine days together with other antibiotics. All cultures remained negative. He was extubated and had an uneventful recovery. Repeat cosyntropin test done 10 days after stopping fluconazole showed a basal cortisol of 38 nmol/l, with a peak of 662 nmol/l, at 60 minutes. This was indicative of the adrenals recovering from suppression.

DISCUSSION

Azole antifungal agents are classified as imidazole (miconazole, ketoconazole) or triazole (itraconazole and fluconazole) according to whether they contain two or three nitrogen atoms, respectively, in five member azole ring. They mainly act by inhibiting ergosterol synthesis through interaction with C 14 α demethylase, an enzyme dependent on cytochrome P 450 that is necessary for conversion of lanosterol to ergosterol. Triazoles have greater affinity for fungal cytochrome P 450 compared with mammalian cytochrome P 450 making it less toxic to mammalian cell, albeit, retaining this potential at higher than recommended doses.¹ This dose dependent inhibition of mammalian cytochrome P 450 has been shown in animal studies.⁷

Michaelis *et al*⁸ studied basal cortisol and adrenocorticotrophic hormone (ACTH) levels in 11 patients admitted to intensive care unit who were receiving antimycotic treatment using either fluconazole (n = 6) or combination of amphotericin B and flucytosine (n = 5) for 14 days, both during and seven days after stopping treatment. These were compared with eight patients who had same baseline criteria as the other 11 patients, but did not need antimycotic treatment. It was found that basal ACTH, basal cortisol and cortisol level after ACTH stimulation were within normal range in all three groups.

In our review of English language literature we came across three reports of four cases of adrenal cortical insufficiency in patients who were critically ill and treated with fluconazole.³⁻⁵ Albert *et al* reported two cases of reversible adrenal insufficiency in patients admitted to intensive care units 24–48 hours after starting fluconazole

Learning points

- Adrenal insufficiency is a rare complication of fluconazole therapy.
- It is more likely to occur in patients who are critically ill.
- This responds to stress dose corticosteroids
- Adrenal suppression recovers on stopping fluconazole.

Abbreviations: ACTH, adrenocorticotrophic hormone; CT, computed tomography; ICU, intensive care unit

(800 mg intravenous first dose followed by 400 mg intravenously daily).⁴ Adrenal function returned to normal on repeat ACTH stimulation testing 11 days and 5 days respectively after stopping fluconazole. In a report by Shibata *et al*, a patient who was taking fluconazole 200 mg/day after high dose cyclophosphamide for peripheral blood stem cell harvest developed signs of adrenal insufficiency on day 3 with hypotension.⁵ Fluconazole was stopped and ACTH stimulation test returned to normal on day 14. This temporal effect of fluconazole was confirmed by rechallenging the patient with 400 mg/day from day 16 with blunted adrenal response to ACTH stimulation test on day 21.

It is probable that this complication is underrecognised as many of the patients who are critically ill and need fluconazole tend to get corticosteroid replacement to cover for possible adrenal insufficiency and immunosuppression as in patients after transplant.

Our patient had a normal baseline adrenal cortical function as evidenced by cosyntropin test before starting fluconazole. Thirty six hours after starting fluconazole he developed electrolyte abnormalities consistent with adrenal insufficiency that was confirmed by cosyntropin test. This adrenal suppression resolved 10 days after stopping fluconazole.

The electrolyte abnormalities corrected with stress dose hydrocortisone without any obvious deleterious clinical outcome. This reversible adrenal suppression had temporal relation to fluconazole treatment. It is highly probable that this complication of adrenal suppression attributable to fluconazole is underrecognised. Also, this could pose diagnostic challenge in patients receiving fluconazole for treatment of fungal infections like cryptococcosis, where the infection could by itself lead to adrenal insufficiency. As adrenal suppression has occurred even with lower doses of 200 mg/day, we recommend that all critically ill patients given fluconazole be monitored closely for possible signs of adrenal cortical suppression. If unrecognized, it could have

potentially serious consequence. Currently data on adrenal insufficiency associated with fluconazole use are limited, but we believe that it may be safe to continue fluconazole along with stress dose corticosteroids in patients who develop this complication as in our case.

Authors' affiliations

R K Cobbs, S G Santhana Krishnan, Department of Internal Medicine, Metropolitan Hospital Center, New York, USA

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Correspondence to: Dr S G S Krishnan, 410 Lakeville Road, Suite 105, Long Island Jewish Medical Center, New Hyde Park, NY 11042, USA; sgskrishnan@hotmail.com

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