

**DRUG-INDUCED HORMONAL HAVOC: A CASE REPORT ON FLUCONAZOLE AND ADRENAL INSUFFICIENCY****Akshara K. R.\*, Dr. Sara Kurien K., Dr. Jency Maria Koshy and Dr. Swetha Reba Mathew**<sup>1</sup>Pharm D. Intern, Nazareth College of Pharmacy, Othara, Thiruvalla.<sup>2</sup>Assistant Professor, Department of Pharmacology, Believers Church Medical College Hospital, Kerala.<sup>3</sup>Professor, Department of General Medicine, Believers Church Medical College Hospital, Kerala.<sup>4</sup>Assistant Professor, Department of Pharmacology, Believers Church Medical College Hospital, Kerala.**\*Corresponding Author: Akshara K. R.**

Pharm D. Intern, Nazareth College of Pharmacy, Othara, Thiruvalla.

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**ABSTRACT**

Fluconazole is a widely used triazole antifungal agent which is available for oral or intravenous use. Studies have shown its activity against infections caused by various fungal species.<sup>[1]</sup> Long-term azole therapy is associated with hepatotoxicity and hormone-related effects, including gynecomastia, alopecia, decreased libido, oligospermia, azoospermia, impotence, hypokalemia, hyponatremia, etc.<sup>[2]</sup> Although rare, there have been case reports that describe an association between Fluconazole and adrenal dysfunction which is an important cause of morbidity and mortality in patients who are critically ill.<sup>[3]</sup> So here we present the case of a 39-year-old male who experienced adrenal insufficiency while on treatment with Fluconazole for the therapeutic management of candida albicans.

**KEYWORDS:** Fluconazole, Adrenal insufficiency, Candida Albicans, Antifungals, Drug induced adrenal dysfunction.

**INTRODUCTION**

Fluconazole is a fluorine-substituted, bis-triazole antifungal agent which is widely used for different types of fungal infections. The mechanism of action, like that of other azoles, involves interruption of the conversion of lanosterol to ergosterol via binding to fungal cytochrome P-450 and subsequent disruption of fungal membranes. Studies have shown its activity against organisms such as *Aspergillus* species, *Candida* species, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, etc.<sup>[4]</sup>

Adrenal insufficiency (AI) is a potentially life-threatening endocrine abnormality that can arise from a primary adrenal disorder, secondary to adrenocorticotrophic hormone deficiency, or by suppression of adrenocorticotrophic hormone by exogenous glucocorticoid or opioid medications. It can also be rarely associated with azole antifungal therapy. Hallmark clinical features of AI include unintentional weight loss, postural hypotension, anorexia, profound fatigue, myalgia, abdominal pain, and hyponatremia.<sup>[5,6]</sup>

Fluconazole generally does not inhibit steroidogenesis, but there are few case reports of adrenal suppression, which raises the possibility that this problem may be currently under-recognized.<sup>[7]</sup> Here we present the case

of a 39-year-old male who experienced adrenal insufficiency while on treatment with Fluconazole for the therapeutic management of candida albicans.

**CASE REPORT**

A 39-year-old male visited the hospital for his fifth session of double J Stenting. He is a known case of Type 2 Diabetes Mellitus (T.Metformin 500 mg), Hypertension (T.Cilacar 10mg), Dyslipidemia (T.Atorvastatin 40 mg) since 5 years, and k/c/o retroviral disease (WHO STAGE-IV for the past 6 years- contracted during a blood transfusion) and is under treatment with T. Tenofovir, T.Lamivudine and T.Dolutegravir. HIV viral load was 8710 copies/ml at the time of HIV detection. He contracted with Tuberculosis 6 months back for which he was on T.Rifampicin. He was referred to the Urology department for further management of right upper ureteric calculus. The patient was admitted for a double J stenting procedure. He subsequently developed a fever spike. Blood cultures from the central line showed candida albicans hence an injection of Fluconazole 400 mg once daily for 5 days was started. He continued to have fever spikes and the Fluconazole dose was hiked to 800 mg once daily for 7 days as the isolate showed only intermediate sensitivity to Fluconazole. Co syntropin stimulation test showed primary adrenal insufficiency which was probably induced by Fluconazole and he was started on the oral

steroid tablet Prednisolone 5 mg once daily for 2 weeks. The patient continued to have fever spikes. Hence anti-fungal was changed to injection Caspofungin after which patient did not have any symptoms.

## DISCUSSION

Azole antifungals are considered the first-line agents in the prophylaxis and treatment of invasive fungal infections. Among them, Fluconazole therapy is considered to be generally safe, efficacious, and easy to administer in the treatment of various systemic mycoses.<sup>[7]</sup> The drug is hydrophilic, rapidly absorbed after oral administration, and penetrates well into body fluids and tissues, including the CSF. It is mainly excreted without conversion through urine. It has an elimination half-life of approximately 30 hours, which allows for its once-daily dosing.<sup>[1]</sup>

Fluconazole therapy is often used for prolonged periods of time (12 days). Long-term use of azoles is associated with hepatotoxicity and hormone-related effects like gynecomastia, decreased libido, alopecia, oligospermia, azoospermia, sexual impotence, hypokalemia, hyponatremia, and rarely adrenal insufficiency. Sufficient information and early detection of adverse events caused by azoles, thereby reducing the dose or discontinuation of the drug can usually reverse these adverse events.<sup>[2]</sup>

Adrenal insufficiency (AI) is a condition which is characterized by a deficiency of adrenal cortisol production. Primary AI (PAI) is rare and is caused directly by adrenal failure. Secondary AI (SAI) is more frequently seen and is usually caused by diseases affecting the pituitary gland, whereas in tertiary AI (TAI), the affected area is the Hypothalamus. The most prevalent form is TAI, caused by exogenous glucocorticoid use. Symptoms of AI are usually non-specific, often overlooked or misdiagnosed, and are related to the lack of cortisol, adrenal androgen precursors, and aldosterone (especially in PAI). Diagnosis of AI is based on the measurement of the adrenal corticosteroid hormones, their regulatory peptide hormones, and stimulation tests. The goal of therapy is to establish a hormone replacement regimen that closely mimics the physiological diurnal cortisol secretion pattern, which is tailored to the patient's daily requirements.<sup>[8]</sup>

The signs and symptoms of primary adrenal insufficiency result from the deficiency of all adrenocortical hormones, but they can also include signs of other autoimmune conditions. In secondary or tertiary adrenal insufficiency, the clinical features result from glucocorticoid deficiency only, but manifestations of the primary pathological disorder can also be present in these cases. The diagnostic criteria, even though well established, can be challenging, especially in patients with secondary (SAI) or tertiary (TAI) adrenal insufficiency.<sup>[9]</sup> Detection of adrenal insufficiency is

often delayed because the initial presentation is often non-specific; physicians must be aware of this to avoid adrenal crisis.<sup>[10]</sup>

In conclusion, The patients who are on azole antifungal therapy should be regularly monitored as they are at an increased risk of developing AI. It can become fatal if not detected and managed early. Here in this case report, this immunosuppressant patient was on long-term. Fluconazole therapy for candida albicans, which may have been the contributory factor for drug induced adrenal dysfunction.

In conclusion, by assessing the cause using the Naranjo Scale, a score of 6 was determined, indicating that the adverse drug reaction is probable and preventable. Given that only 74 cases have been reported in VigAccess, it is evident that there is significant underreporting of such incidents. Therefore, this case report is particularly relevant as it contributes to the existing body of knowledge and highlights the need for increased awareness and reporting of similar cases.

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## Abbreviations

**AI:** Adrenal insufficiency

**CSF:** CerebroSpinal Fluid

**PAI:** Primary Adrenal insufficiency

**SAI:** Secondary Adrenal insufficiency

**TAI:** Tertiary Adrenal insufficiency

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