

# Itraconazole-induced adrenal insufficiency in a patient with exogenous Cushing's syndrome

Dear Editor,

A 42-year-old farmer presented with multiple, itchy, erythematous plaques of 10-year duration involving the face, upper limbs, and trunk. He had received multidrug therapy for multibacillary leprosy and was prescribed systemic steroids (prednisolone, variably dosed from 10-40 mg per day for 3 months) for a presumed diagnosis of lepra reaction. He had continued self-administering prednisolone intermittently for almost seven years before he presented to us.

General examination revealed features suggestive of exogenous Cushing's syndrome, including facial plethora, striae and fat deposition on the upper back and abdomen. Blood pressure was normal in both standing and supine positions. Dual-energy X-ray absorptiometry scan revealed osteopenia. Biochemical investigations revealed significantly reduced 8 AM adrenocorticotrophic hormone (ACTH, 3.8 pg/ml, normal 7.2-63.3 pg/ml), cortisol (4.97 mol/l, normal 171-536 nmol/l) and almost undetectable dehydroepiandrosterone sulfate (0.01 µg/dl, normal 1.0-4.2 µg/dl). He had impaired fasting glucose (fasting blood glucose 131 mg/dl); the rest of the investigations were normal (Na/K 143/3.7 mmol/l). Considering a diagnosis of exogenous Cushing's with secondary adrenal insufficiency, he was advised to stop the intake of prednisolone and a replacement regimen of hydrocortisone dosed 5, 2.5, and 2.5 mg to be taken at 0800h, 1230h, and 1630h respectively, was initiated. For his cutaneous symptoms, after a series of investigations and clinico-pathological correlation, he was diagnosed with a case of extensive primary cutaneous sporotrichosis, and capsule itraconazole was added at a dosage of 200 mg twice daily to his hydrocortisone regimen.

Within 2 weeks of initiating itraconazole, the patient started having extreme weakness, prostration, loss of appetite, muscle pains, nausea, and dizziness while standing. He reduced the itraconazole dosage to 200 mg once daily, and his symptoms improved slightly. However, the symptoms returned when he increased the itraconazole dosage to 200 mg twice daily. He consulted us again.

Physical examination this time was similar to the previous visit except for a blood pressure of 110/70 mm Hg that reduced to 88/60 mm Hg after standing for two minutes, suggesting new-onset postural hypotension. In addition to a series of blood investigations to rule out other medical conditions, including sepsis, an endocrinology consult was obtained. Adrenal autoantibodies directed against CYP21A2 were undetectable, and electrolytes were normal (Na/K 140/ 4.3 mmol/L). Serum ACTH, cortisol, and dehydroepiandrosterone sulfate were similar to those on the prior visit. It was suggested to increase the dosage of hydrocortisone to 7.5 mg, 5 mg, and 2.5 mg before re-initiating itraconazole at a dosage of 200 mg once a day and gradually increasing it to 200 mg twice a day. The patient felt symptomatically better again, orthostatic hypotension resolved, and we could restart itraconazole at 200 mg once a day.

Itraconazole is one of the most frequently prescribed drugs by Indian dermatologists currently.<sup>1</sup> It is a hepatic microsomal enzyme inhibitor.<sup>2</sup> Itraconazole decreases inhaled budesonide's hepatic metabolism, resulting in an exogenous Cushing-like state and secondary adrenal insufficiency.<sup>3</sup> Metabolism of methylprednisolone and dexamethasone is significantly reduced by itraconazole. However, minimal effect has been seen on the metabolism of prednisolone or hydrocortisone.<sup>4</sup>

Interestingly, azoles also inhibit adrenal and gonadal steroidogenesis.<sup>2,5</sup> This adverse effect is primarily known in the context of ketoconazole; however, itraconazole and posaconazole can also inhibit adrenal steroidogenesis, and the effect can be significant in patients having an underlying secondary adrenal insufficiency. Itraconazole inhibits the side chain cleaving enzyme that catalyzes the first step in steroidogenesis and converts cholesterol into pregnenolone.<sup>6,7</sup> In a steroid-naïve patient, a rise in ACTH would accompany inhibition in cortisol synthesis, as in Addison's disease. However, in the presence of pre-existing secondary adrenal insufficiency (as in our patient), the expected rise in ACTH levels would not occur and hence would not be helpful diagnostically.

**How to cite this article:** Bishnoi A, Narang T, Das L, Chatterjee D, Singh V, Shah S, *et al.*; Itraconazole-induced adrenal insufficiency in a patient with exogenous Cushing's syndrome. *Indian J Dermatol Venereol Leprol.* 2024;90:703. doi: 10.25259/IJDVL\_295\_2023

**Received:** March, 2023 **Accepted:** August, 2023 **Epub Ahead of Print:** November, 2023 **Published:** August, 2024

**DOI:** 10.25259/IJDVL\_295\_2023 **PMID:** 38031683

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To conclude, itraconazole can cause de-novo inhibition of adrenal steroidogenesis and produce a clinical syndrome of adrenal insufficiency, more pronounced in a patient having pre-existing secondary adrenal insufficiency. Knowledge of such scenarios becomes very important in dermatology settings where exogenous Cushing's syndrome with secondary adrenal insufficiency is frequent because of concomitant exogenous or self-administration of both systemic and potent topical corticosteroids. Many patients have chronic recalcitrant dermatophytosis<sup>8,9</sup> with co-existent exogenous Cushing's and secondary adrenal insufficiency due to reasons mentioned above. At presentation, they are usually receiving multiple drugs including steroids and antifungals, many a times in systemic formulations. In such scenario, a caution should be exercised about the enhanced secondary adrenal insufficiency (in the setting of combined corticosteroid-itraconazole usage).<sup>10</sup> Also, patients these days receive itraconazole as a first-line antifungal agent because of widespread resistance to terbinafine. Dermatologists should be aware of the features of adrenal insufficiency in such clinical settings because the underlying secondary adrenal insufficiency may go undiagnosed when patients are started on itraconazole while exogenous steroids are withdrawn abruptly and replacement hydrocortisone is either not initiated or its dose is not increased.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent.

**Financial support and sponsorship:** Nil.

**Conflicts of interest:** There is no conflict of interest.

**Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation:** The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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