

Fluconazole and Osilodrostat Linked to Adrenal Crisis in EAS

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Patients presenting with weakness after antifungal use may be experiencing adrenal insufficiency, a serious complication. A recent case report highlights this clinical dilemma, detailing adrenal crisis precipitated by fluconazole in a patient with ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) also receiving osilodrostat. Clinicians should consider adrenal insufficiency in patients on similar regimens who develop unexplained weakness.^{1,2,3}

KEY TAKEAWAYS

- ° The Pivot: Fluconazole, when co-administered with osilodrostat, may precipitate adrenal crisis in patients with ectopic ACTH syndrome.
- ° The Data: A patient with EAS and cryptococcal infection developed adrenal crisis while on fluconazole and osilodrostat.
- ° The Action: Monitor adrenal function closely in patients with EAS receiving fluconazole, particularly if also on osilodrostat.

Ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) presents a diagnostic and therapeutic challenge, especially when the primary tumor cannot be localized.^{1,2,3} Management often involves pharmacological interventions to control hypercortisolism.^{1,2,3}

Case Report: Adrenal Crisis with Fluconazole and Osilodrostat

A case report described a patient with EAS and a concomitant pituitary tumor who developed adrenal crisis.^{1,2,3} This patient was receiving osilodrostat for EAS and fluconazole for a cryptococcal infection.^{1,2,3} The adrenal crisis occurred prior to planned bilateral adrenalectomy.^{1,2,3}

The patient's clinical presentation included weakness, which is a common symptom of adrenal insufficiency.³ The co-administration of osilodrostat, a steroidogenesis inhibitor, and fluconazole, an antifungal known to inhibit cytochrome P450 enzymes, is implicated in precipitating the adrenal crisis.^{1,2,3} Fluconazole can inhibit CYP3A4, which is involved in the metabolism of various steroids and drugs, potentially altering the pharmacokinetics of osilodrostat or endogenous corticosteroids.^{1,2,3} Osilodrostat itself reduces cortisol synthesis by inhibiting 11 β hydroxylase.^{1,2,3} The combination of these agents likely led to a profound reduction in cortisol levels, resulting in adrenal crisis.^{1,2,3}

This case highlights the importance of considering drug-drug interactions and their potential to exacerbate underlying endocrine conditions.^{1,2,3} In patients with EAS, who are already at risk for adrenal insufficiency, the addition of medications like fluconazole, particularly when combined with steroidogenesis inhibitors such as osilodrostat, warrants

careful monitoring of adrenal function.^{1,2,3}

The patient's management required immediate intervention with intravenous hydrocortisone to stabilize their condition, underscoring the critical need for prompt recognition and treatment of adrenal crisis. Following stabilization, the patient underwent bilateral adrenalectomy as planned, which is a definitive treatment for refractory hypercortisolism in EAS, particularly when the source of ectopic ACTH is elusive or inaccessible. This surgical approach effectively eliminates the primary source of cortisol production, necessitating lifelong glucocorticoid and mineralocorticoid replacement therapy.

This specific case serves as a crucial reminder for healthcare professionals managing patients with EAS, especially those on multiple medications. The interplay between osilodrostat, a potent inhibitor of 11 β -hydroxylase, and fluconazole, a broad-spectrum antifungal with significant CYP3A4 inhibitory properties, created a synergistic effect leading to severe hypocortisolism. CYP3A4 is a key enzyme in the metabolism of various endogenous steroids, including cortisol precursors, and numerous exogenous drugs. Fluconazole's inhibition of CYP3A4 can reduce the clearance of drugs metabolized by this pathway, potentially increasing their systemic exposure and pharmacological effect. While osilodrostat primarily acts on 11 β -hydroxylase, its metabolism may also involve CYP enzymes, and fluconazole could theoretically impact its pharmacokinetics, further intensifying its cortisol-lowering effect. More importantly, fluconazole's direct or indirect effects on steroidogenesis, beyond CYP3A4 inhibition, could also contribute to reduced cortisol synthesis.

Clinical Implications and Monitoring Strategies

The profound reduction in cortisol levels observed in this case highlights the delicate balance required when managing hypercortisolism in EAS. Patients with EAS often present with significant comorbidities and are frequently on polypharmacy, increasing the risk of drug-drug interactions. For patients receiving steroidogenesis inhibitors like osilodrostat, vigilant monitoring of adrenal function is paramount. This includes regular assessment of serum cortisol levels, particularly during periods of drug initiation, dose adjustment, or the introduction of new medications. The addition of drugs known to inhibit CYP enzymes, such as fluconazole, ketoconazole, or ritonavir, should prompt an even higher level of caution and more frequent monitoring of cortisol and ACTH levels. Clinicians should also educate patients about the symptoms of adrenal insufficiency, empowering them to seek immediate medical attention if these symptoms arise.

Furthermore, this case underscores the importance of a comprehensive medication review for all patients with EAS, especially before initiating new treatments. Pharmacists and physicians should collaborate to identify potential drug-drug interactions that could impact steroidogenesis or steroid metabolism. In situations where co-administration of a CYP inhibitor and a steroidogenesis inhibitor is unavoidable, a proactive strategy for dose adjustment of the steroidogenesis inhibitor may be necessary to mitigate the risk of overt adrenal insufficiency. Consideration should also be given to alternative antifungal agents with a lower propensity for CYP inhibition if clinically appropriate.

Future research could focus on developing more precise guidelines for managing drug interactions in patients with EAS, particularly concerning steroidogenesis inhibitors. Pharmacogenomic studies might also help identify patients at higher risk of adverse drug reactions due to variations in CYP enzyme activity. Ultimately, this case report serves as a valuable learning tool, reinforcing the need for meticulous clinical judgment and a multidisciplinary approach in the complex management of ectopic ACTH syndrome.

CLINICAL IMPLICATIONS

This case report serves as a stark reminder of the potential for drug-drug interactions to precipitate serious adverse events, particularly in complex endocrine conditions like ectopic ACTH syndrome. The combination of fluconazole and osilodrostat leading to adrenal crisis is a specific warning for clinicians managing patients with hypercortisolism and concomitant fungal infections. It underscores the necessity of a thorough medication review, not just for direct interactions, but for cumulative pharmacological effects on metabolic pathways.

For prescribing clinicians, this means heightened vigilance is required when initiating fluconazole in patients already on steroidogenesis inhibitors, especially those with compromised adrenal reserve. Routine monitoring of cortisol levels and electrolyte balance should be considered, even if the patient appears stable. The industry, particularly manufacturers of antifungal agents and adrenal-targeting therapies, should emphasize these potential interactions in their prescribing information, providing clearer guidance on co-administration risks and monitoring protocols.

Patients, often navigating multiple specialists and complex medication regimens, rely on their healthcare providers to foresee and mitigate such risks. This case illustrates that even seemingly routine antifungal prescriptions can have profound consequences in specific patient populations. It reinforces the need for integrated care and clear communication among specialists to prevent iatrogenic complications, ensuring patient safety remains paramount.

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