Iatrogenic metrorrhagia after the use of itraconazole for onychomycosis

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Abstract:
We present first case report on itraconazole, a drug very commonly used for onychomycosis, used along with simvastatin that caused metrorrhagia. The suggested probable mechanism is the inhibition of steroidogenesis, especially estrogens that resulted in low-estrogen breakthrough bleeding. This article emphasizes the importance of drug interaction check prior the initiation of onychomycosis treatment.

Keywords:
Itraconazole, low estrogen breakthrough bleeding, metrorrhagia, simvastatin

Introduction
A broad-spectrum imidazole antimycotic inhibits sterol synthesis in fungal cell membranes;¹ however, due to its poor selectivity for CYP450 3A4 and potent inhibition of CYP450 3A4, these drugs interfere with CYP450 3A4 in testis, ovary, adrenal gland, kidney, and liver.² Ketoconazole was found to inhibit cholesterol synthesis and steroidogenesis (testosterone and estrogen) through an inhibitory effect on 14 alpha-demethylase, 17,20-desmolase, 16 alpha-hydroxylase, 17 alpha-hydroxylase, 18 hydroxylase, and 11 beta-hydroxylase.³ Itraconazole belongs to imidazole/triazole group of antifungal agents. It works by inhibiting the lanosterol 14α-demethylase fungal enzyme that is a part of cytochrome P450 3A4 family. This enzyme converts lanosterol to ergosterol and is required in fungal cell wall synthesis.²³ Itraconazole binds in the circulation almost completely to plasma proteins, especially albumin and some to red blood cells. Being very lipophilic, it concentrates, after absorption, in fat, omentum, vaginal and cervical tissues, skin, and nails.² Itraconazole increases serum concentrations of simvastatin probably by inhibiting CYP P450 3A4-mediated metabolism.⁴

Case Report
A 69-year-old female patient presented with a long history of toenails alteration. She had never been treated for onychomycosis, and there was no history of trauma. She was obese (high 167 cm, weight 101 kg) with a 5-year history of diabetes mellitus Type II and a 14-year history of arterial hypertension. Her everyday medication list included enalapril (angiotensin-converting enzyme inhibitor, simvastatin, hydroxymethylglutaryl-coenzyme A reductase inhibitor, a class of lipid-lowering medications) and metformin (oral hypoglycemic agent). Dermatological examination revealed the deformation of one-half of the inner part of the nail plate of both toenails, hyperkeratosis under the deformed nail plates and slight erythema around the nails. A potassium hydroxide (KOH) preparation under direct microscopy revealed numerous spores and pseudohyphae. In addition, Candida albicans was isolated by cultivation on the ATG-agar medium. Liver enzyme tests (aminotransferases, gamma-glutamyl transferase, and alkaline phosphatase)
were within normal values, no other medical concerns reported. Therefore, itraconazole 100 mg twice daily by oral administration was started for 1-week pulse therapy per month for the following 3 months. At monthly control, the patient informed about unexpected vaginal bleeding of 3-day duration 6 days after initiation of antimycotic therapy. A detailed gynecological examination reported no abnormal findings. The treatment with itraconazole was continued based on the favorable clinical evolution and good drug tolerability by the patient. Next month, the patient reported another vaginal bleeding of 2-day duration 5 days after itraconazole intake. Again, no abnormalities were found on gynecological examination. The suspected culprit drug itraconazole was discontinued. During the next 3 months, after itraconazole cessation, the patient denied metrorrhagia and any other gynecological problem.

**Discussion**

We assume that drug interaction between itraconazole and simvastatin raises the concentrations and toxicity of both drugs, itraconazole and simvastatin, the second being also a potent CYP450 3A4 inhibitor resulting in the inhibition of estrogen synthesis in fat tissue and ovaries. Low estrogen and estradiol result in abnormal progesterone and estrogen ratio. Consequently, this abnormal hormonal ratio leads to low-estrogen breakthrough uterine bleeding. As the patient reported metrorrhagia 2 times few days after the introduction of itraconazole, the Naranjo adverse drug reaction (Naranjo ADR) probability scale score was calculated (Naranjo ADR score of six meaning probable ADR) leading to the conclusion that itraconazole was determined as the probable culprit. Metrorrhagia (low estrogen breakthrough bleeding) due to concomitant use of itraconazole and simvastatin was diagnosed. As dermatologists, we prescribe antifungal agents very often so we must be aware of possible side effects and explore possible drug interactions, and the patient must be informed. Concomitant use of itraconazole as a potent inhibitor of CYP450 3A4 with simvastatin should be avoided, or the dosage of the drug should be reduced.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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