PEARLS FROM THE PRACTITIONER

Capsule Commentaries: Selected Oral Antifungal Drug-Drug Interactions with Itraconazole and Terbinafine

James Q Del Rosso, DO[a,b,c]

[a]Adjunct Clinical Professor (Dermatology), Touro University Nevada, Henderson, NV
[b]Research Director, JDR Dermatology Research Las Vegas, NV
[c]Dermatology and Cutaneous Surgery, Thomas Dermatology, Las Vegas, NV

ABSTRACT

This article provides a review of selected drug-drug interactions with itraconazole and terbinafine that are clinically relevant with potential for toxicity. These include itraconazole and certain statin agents, itraconazole and digoxin, and terbinafine and some antidepressants, with commentary suggestions on management.

INTRODUCTION

Terbinafine and itraconazole are oral antifungal agents utilized in dermatology to treat a variety of superficial mycotic infections. Itraconazole is associated with a long list of potential drug-drug interactions, and terbinafine with a shorter list; importantly, both may induce clinically significant interactions when administered concurrently with certain drugs.[1,2] A complete review of drug-drug interactions is beyond the scope of this review, which serves as a capsule summary of three selected drug-drug interactions with itraconazole or terbinafine, with commentary suggestions on management.

ITRACONAZOLE

Statins. Three commonly used "statins"(simvastatin, atorvastatin, lovastatin) used to treat hyperlipidemia are metabolized by hepatic cytochrome P450 (CYP) 3A4.[3] Potent inhibitors of CYP 3A4, such as itraconazole, ketoconazole, posaconazole, and erythromycin can induce muscle cramping, and in some cases rhabdomyolysis, by decreasing the metabolic clearance of these "statin" agents which causes higher serum levels; multiple cases of myopathy related to such interactions have been reported.[1-4]

Commentary: If antifungal therapy is needed in a patient using a statin metabolized by CYP3A4, potential options are (1) topical antifungal therapy if appropriate for the infection being treated (2) use of a non-CYP3A4-inhibiting antifungal agent such as terbinafine or (3) temporary discontinuation of the statin therapy with the approval of the prescribing clinician.[1]

Digoxin. Itraconazole has been shown to reduce the tubular renal excretion of digoxin, reported to be related to inhibition of p-glycoprotein; digoxin toxicity associated with this interaction has been reported.[5-8] One study demonstrated that itraconazole produced a 56% increase in serum digoxin levels as compared to placebo.[5]

Commentary:
As digoxin exhibits a narrow therapeutic-safety index, an alternative approach to antifungal therapy is suggested to avoid this interaction.

TERBINAFINE

Antidepressants. Terbinafine is an inhibitor of hepatic CYP 2D6, which has been shown to markedly increase serum levels of tricyclic antidepressants (eg nortriptyline, amitriptyline, imipramine) metabolized by CYP 2D6; toxicity has been reported with these interactions, presenting as ataxia, fatigue, dizziness/vertigo, appetite loss, and difficulty swallowing.[8-10] Some selective serotonin reuptake inhibitors (eg paroxetine, fluoxetine) are metabolized by CYP 2D6; terbinafine has been shown to increase peak serum levels through inhibition of paroxetine metabolism.[11]

Commentary:
When oral antifungal therapy is needed in a patient on an antidepressant that is metabolized by CYP 2D6, an alternative approach to antifungal therapy that is also expected to be effective and devoid of drug-drug interactions appears to be a prudent approach.

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Corresponding Author:
James Q. Del Rosso, DO
JDR Dermatology Research
9080 West Post Road
Suite 100
Las Vegas, Nevada 89148
702-331-4123
jqdelrosso@yahoo.com

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