Possible Drug Interactions in Oral Treatment of Onychomycosis

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A variety of medications may interact with oral antifungal agents used to treat onychomycosis. This article summarizes some possible consequences of concurrent administration of various therapeutic agents with the oral antifungals fluconazole, griseofulvin, itraconazole, ketoconazole, and terbinafine.

Oral antifungal medications used to treat onychomycosis are generally safe, with very low rates of serious adverse events. However, when an oral antifungal medication is given concurrently with another therapeutic agent, an adverse drug interaction may occur. Some possible consequences of concurrent use of various therapeutic agents with oral antifungal agents prescribed for the treatment of onychomycosis are summarized in this article. The oral antifungals discussed are fluconazole (Diflucan®),† griseofulvin (Fulvicin®, Grifulvin®, Gris-PEG®), itraconazole (Sporanox®), ketoconazole (Nizoral®), and terbinafine (Lamisil®).

The pharmacologic mechanisms underlying drug interactions are pharmacokinetic and/or pharmacodynamic.[1-3] Pharmacokinetic drug interactions affect the concentration, or the patient's blood levels, of a medication. The factors that determine the blood level of a drug at any given time include its absorption, distribution, metabolism, and elimination. Pharmacodynamic drug interactions affect a patient through competition for similar receptors or physiologic systems, resulting in either additive, synergistic, or antagonistic activity. For example, because many of the oral antifungals are metabolized by the liver and excreted renally, concurrent medications that may impair hepatic or renal function should be monitored closely.

The major types of drug interactions involving the oral antifungal agents used to treat onychomycosis are the result of pharmacokinetic factors that either limit gastrointestinal absorption or affect drug metabolism through their effect on the cytochrome P-450 catabolic enzymes.[1-6] For example, griseofulvin, itraconazole, and ketoconazole are best given with a meal because their respective gastrointestinal absorptions are increased by the presence of food.[7-9] Furthermore, the absorptions of itraconazole and ketoconazole increase in an acidic gastric pH.

The cytochrome P-450 enzymes catalyze the intramolecular biotransformation of substrate drugs into more easily handled compounds that can be further processed for clearance and removal.[1, 2, 10] Griseofulvin is a cytochrome P-450 enzyme inducer. Therefore, the metabolic clearance of certain concurrent substrate drugs may be accelerated by the presence of griseofulvin, leading to possible therapeutic failure. The imidazole antifungal agents represented by fluconazole, itraconazole, and ketoconazole are, to various degrees, human cytochrome P-450 3A inhibitors; fluconazole is also a cytochrome P-450 2C9 inhibitor. Therefore, depending on the pharmacokinetic factors of the particular imidazole as well as its blood concentration, the metabolism of cytochrome P-450 3A substrate drugs may be impaired, resulting in potentially toxic concentrations of the drugs. In addition, the imidazoles are themselves cytochrome P-450 3A substrates and may suffer metabolic acceleration by inducers, resulting in decreased imidazole levels and possible loss of antifungal effectiveness.

Table 1 lists various medications whose concurrent use with oral antifungal drugs may lead to adverse interactions. The reader should refer to the manufacturer's specific product literature for additional data or the most current prescribing recommendations. The imidazole antifungals have greater potential for clinically significant drug interactions than the other oral antifungal agents. Therefore, it is prudent to use caution with this class of drugs.

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†As of this writing, fluconazole has not yet been approved by the US Food and Drug Administration for the treatment of onychomycosis.

Table 1. Drugs Listed by Generic Name, with Brand Name Example(s), That May Interact with Oral Antifungal Agents

Concurrent Therapeutic Agent	Oral Antifungal(s)	Consequences of Interaction and Suggestions for Management
Alcohol	Griseofulvin, ketoconazole	Disulfiram-like reactions may occur. Avoid.[9, 11]
Alprazolam (Xanax®)	Itraconazole,[a] ketoconazole	Prolonged sedation may occur. Avoid.[12, 13]
Amphotericin B (Fungizone®)	Ketoconazole	Antifungal antagonism reported. Monitor antifungal therapeutic effects.[14]
Antacids (Maalox®)	Itraconazole, ketoconazole	Decreased itraconazole or ketoconazole absorption may occur. Avoid or wait at least 2 hours between dosing.[8, 9]
Aspirin	Griseofulvin	Impaired aspirin absorption may occur.[15]
Astemizole (Hismanal®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Serious cardiac arrhythmias (torsades de pointes) may occur. Avoid.[8, 9, 13]
Caffeine	Terbinafine	Increased caffeine levels occur with intravenous caffeine administration. Limit caffeine intake.[16]
Carbamazepine (Tegretol®)	Itraconazole[a]	Decreased imidazole levels may occur. Monitor antifungal efficacy.[5, 8]
Chlorpropamide	Fluconazole,[a] itraconazole,[a] ketoconazole	Hypoglycemia may occur. Avoid or monitor blood glucose levels.[8, 9, 13]
Cimetidine (Tagamet®)	Fluconazole, itraconazole, ketoconazole	Decreased imidazole absorption may occur.[8, 9, 13]
Cimetidine (Tagamet®)	Terbinafine	Increased terbinafine levels may occur.[16]
Cisapride (Propulsid®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Serious cardiac arrhythmias (torsades de pointes) may occur. Avoid.[8, 9, 13]
Corticotropin	Fluconazole,[a] ketoconazole	Discrepant results with corticotropin-stimulated cortisol testing may occur. Avoid.[13, 17]
Cyclosporine (Neoral®, Sandimmune®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Increased cyclosporine blood levels may occur. Monitor cyclosporine levels.[8, 9, 13]
Cyclosporine (Neoral®, Sandimmune®)	Terbinafine	Decreased cyclosporine levels may occur. Monitor cyclosporine levels.[16]
Diazepam (Valium®)	Itraconazole[a]	Prolonged sedation may occur. Monitor.[8]
Didanosine (Videx®)	Itraconazole, ketoconazole	Decreased itraconazole or ketoconazole absorption may occur. Avoid or wait at least 2 hours between dosing and give with a cola beverage.[8, 9]
Digoxin (Lanoxin®)	Itraconazole,[a] ketoconazole	Increased digoxin levels may occur. Monitor digoxin levels.[8, 9]
Felodipine (Plendil®)	Itraconazole[a]	Peripheral edema may occur.[8]
Glipizide (Glucotrol®)	Fluconazole,[a] itraconazole,[a] ketoconazole	Hypoglycemia may occur. Avoid or monitor blood glucose levels.[8, 9, 13]
Glyburide (Diaßeta®, Micronase®)	Fluconazole,[a] itraconazole,[a] ketoconazole	Hypoglycemia may occur. Avoid or monitor blood glucose levels.[8, 9, 13]
Hydrochlorothiazide (HydroDIURIL®)	Fluconazole[a]	Increased fluconazole blood levels may occur.[13]
Indinavir (Crixivan®)	Itraconazole,[a] ketoconazole	Increased indinavir levels may occur. Monitor.[18]
Isoniazid (Nydrazid®, Rifamate®)	Itraconazole,[a] ketoconazole	Decreased imidazole levels may occur. Avoid.[8, 9]
Loratadine (Claritin®)	Ketoconazole	Increased loratadine levels may occur, but there is no evidence of cardiac arrhythmias.[9, 19]
Lovastatin (Mevacor®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Rhabdomyolysis may occur. Avoid.[8, 13, 20]

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Table 1—*Continued*

Concurrent Therapeutic Agent	Oral Antifungal(s)	Consequences of Interaction and Suggestions for Management
Methylprednisolone	Itraconazole,[a] ketoconazole	Increased methylprednisolone levels may occur.[9]
Midazolam (Versed®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Prolonged sedation may occur. Avoid.[8, 9, 13]
Nevirapine (Viramune®)	Itraconazole,[a] ketoconazole	Theoretically, decreased imidazole levels may occur. Monitor therapeutic antifungal effects.[21]
Nifedipine (Adalat®, Procardia®)	Itraconazole[a]	Peripheral edema may occur.[8]
Oral contraceptives	Griseofulvin	Oral contraceptive-pill failure may occur. Avoid concurrent administration or use additional approved method of contraception (barrier, spermicide).[7]
Phenobarbital	Griseofulvin, itraconazole[a]	Decreased oral antifungal agent levels may occur. Monitor antifungal efficacy.[8, 22]
Phenytoin (Dilantin®)	Fluconazole,[a] itraconazole,[a] ketoconazole	Changes in phenytoin levels[8, 9, 13] or decreased imidazole efficacy may occur.[5] Monitor clinical status and phenytoin levels.
Quinidine (Quinidex®)	Itraconazole[a]	Tinnitus and/or hearing loss reported.[8]
Ranitidine (Zantac®)	Itraconazole,[a] ketoconazole	Decreased itraconazole or ketoconazole absorption may occur. Avoid or wait at least 2 hours between dosing and give with a cola beverage.[8, 9]
Rifabutin (Mycobutin®)	Itraconazole[a]	Decreased oral antifungal levels may occur. Avoid or monitor antifungal efficacy.[8]
Rifampin (Rifadin®, Rifamate®)	Fluconazole,[a] itraconazole, ketoconazole, terbinafine	Decreased oral antifungal levels may occur. Avoid or monitor antifungal efficacy.[8, 9, 13, 16]
Ritonavir (Norvir®)	Itraconazole,[a] ketoconazole	Theoretically, increased imidazole levels may occur.[23]
Simvastatin (Zocor®)	Itraconazole[a]	Rhabdomyolysis may occur. Avoid.[8]
Sucralfate (Carafate®)	Itraconazole, ketoconazole	Decreased itraconazole or ketoconazole absorption may occur. Avoid or wait at least 2 hours between dosing and give with a cola beverage.[8, 9]
Tacrolimus (Prograf®)	Itraconazole,[a] ketoconazole	Increased tacrolimus levels or nephrotoxicity may occur. Monitor renal function and tacrolimus levels.[8, 9, 24, 25]
Terfenadine (Seldane®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Serious cardiac arrhythmias (torsades de pointes) may occur. Avoid.[8, 9, 13]
Terfenadine (Seldane®)	Terbinafine	Small increase in terbinafine levels reported.[16]
Theophylline (Primatene®, Theo-Dur®)	Fluconazole[a]	Increased theophylline levels may occur. Monitor theophylline levels.[13]
Tolbutamide	Fluconazole,[a] itraconazole,[a] ketoconazole	Hypoglycemia may occur. Avoid or monitor blood glucose levels.[8, 9, 13]
Triazolam (Halcion®)	Fluconazole,[a, b] itraconazole,[a] ketoconazole	Prolonged sedation may occur. Avoid.[8, 9, 13]
Vincristine (Oncovin®)	Itraconazole[a]	Neurotoxicity may occur.[8]
Warfarin (Coumadin®)	Fluconazole,[a] itraconazole,[a] ketoconazole	Increased anticoagulation may occur. Monitor prothrombin activity.[8, 9, 13]
Warfarin (Coumadin®)	Griseofulvin	Decreased anticoagulation may occur. Monitor prothrombin activity.[7]
Zidovudine (Retrovir®)	Fluconazole[a]	Increased zidovudine levels may occur. Monitor zidovudine levels.[13]

[a] Applies to continuous daily dosing schedules. It is not known if the interaction will occur with intermittent dosing schedules. Further interaction studies are needed with imidazole intermittent dosing schedules.

[b] May occur only if high doses of fluconazole (≥ 400 mg/day) are used on a continuous daily dosing schedule.

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