Cephalosporin antibiotics are commonly prescribed by dermatologists for treating bacterial skin and soft tissue infections.

However, when a patient who is allergic to penicillin needs treatment with a cephalosporin, there’s often concern regarding the risk of allergic reaction.

The incidence of cross-reactivity is 8% to 18%. Yet, more recent evidence suggests that the risk of cross-reactivity is lower than what has been previously reported.

What Causes the Risk of Cross-Reactivity?

The risk of allergic reaction between penicillins and individual cephalosporins correlates to the presence or absence of similar side chains in the drugs’ chemical structures.

Due to these structural entities, the risk of cross-reactivity in penicillin-allergic patients is extremely negligible or non-existent with some cephalosporin agents.

A thorough review of available data indicate that the frequently cited 8% to 18% risk of cross-reactivity to cephalosporins among penicillin-allergic patients is not accurate, is misleading to clinicians, and requires revision.

As penicillins and cephalosporins are both beta-lactam structural derivatives, it has been assumed that allergic cross-reactivity is likely due to the structural similarity of the beta-lactam nucleus.

In fact, experimental and clinical studies suggest that risk of cross-reactivity between penicillin and individual cephalosporins correlates to structural similarity of the 7-position side chain; potential for cross-reactivity within the cephalosporin group itself correlates with structural similarity of the 3-position side chain.¹

The risk of cross-reactivity between penicillin and individual cephalosporins correlates with structural similarity of the 7-position side chain.

Assessing the Risk of Allergic Reactions

Several studies have evaluated use of cephalosporin antibiotics in patients with a history of, or skin test positivity for, penicillin allergy.

A summary of data from 25 such studies indicates the following:

1. First-generation cephalosporins — such as cephalexin (Keflex) and cefadroxil (Duricef) — exhibit an increased risk...
of allergic reaction in penicillin-allergic patients.

2. This risk is not observed with second- or third-generation cephalosporins such as cefdinir (Omnicef), cefpodoxime (Cedax) and cefuroxime (Ceftin).

Observing Structural Differences

These differences are explained by side chain structural characteristics. Based on 7-position side chain similarity to penicillin or amoxicillin, the attributable increased risk of allergic reactions in patients with penicillin allergy for first-generation cephalosporins is 0.4% and for specific latter generation agents, such as cefdinir (Omnicef), cefuroxime (Ceftin) and cefpodoxime (Cedax), is “nearly nil”. The risk of anaphylaxis associated with cephalosporin use has been cited to range from 0.1% to 0.0001%, with no cases of fatal anaphylaxis reported in children.

Guideline Changes Underway

Use of oral cephalosporin antibiotics is common in dermatologic practice, including scenarios related to surgical and cosmetic procedures. Some cephalosporins, due to their spectrum of antibiotic activity and favorable safety profiles, are commonly prescribed for treatment of postoperative infection or for prophylaxis in selected cases.

Based on the above information, changes in guidelines for cephalosporin use in penicillin-allergic patients have already occurred. The American Academy of Pediatrics (AAP) has endorsed the use of cefdinir (Omnicef) and two other oral cephalosporins — cefuroxime (Ceftin) and cefpodoxime (Cedax) — in penicillin-allergic patients with bacterial sinusitis, excluding reactions associated with severe morbidity and mortality such as toxic epidermal necrolysis, anaphylaxis, Stevens-Johnson syndrome and multiorgan drug hypersensitivity syndrome. Similar AAP guidelines are in place for treatment of acute otitis media.

References


Table 1: 7-Position Side Chain Structure of Penicillins and Selected Cephalosporins*

<table>
<thead>
<tr>
<th>Structural Similarity</th>
<th>Structurally Dissimilar to Penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Reactivity More Likely</td>
<td>Cross-Reactivity Unlikely</td>
</tr>
<tr>
<td>Related Penicillin G</td>
<td>Related Amoxicillin</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>(Italics indicate availability as oral formulation)</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Reference 1.
Shoe Allergies

Background. Contact dermatitis from shoes is a common and often easily managed disorder.

Methods. Four patients who presented at a university hospital with foot dermatitis from shoe allergens were evaluated. Each received a European Standard Series patch test.

Results. Patch tests revealed allergic responses to potassium dichromate (used as a preservative in rubber shoes), nickel sulfate, and thiurams (from rubber shoes). Patients were advised to avoid footwear made of known allergens and treated with topical corticosteroids. At follow-up, two patients were completely free of symptoms, and a third was improved.

Conclusion. Differential diagnosis of shoe allergy includes mechanical irritant dermatitis, juvenile plantar dermatosis, atopic eczema, dyshidrosis, and psoriasis. The most common allergens are rubber, polyvinyl chloride (adhesives), potassium dichromate (used in some leather shoes), nickel (shoes with metal clasps). When properly identified, foot dermatitis from shoes can be treated and managed with good results.

Narrow-Band UVB

Background. Phototherapy using ultraviolet light has been known to be effective in clearing psoriasis since the 1970s. Refinements in phototherapy found that ultraviolet B light at 311 nm wavelengths was beneficial (narrow-band UVB), but broad-band UVB and psoralen plus ultraviolet A radiation (PUVA) were also effective. This article reviews current literature on narrow-band UVB and contrasts it with other phototherapeutic options.

Methods. Comprehensive Medline search.

Summary of the Literature. For psoriasis, NB-UVB is superior to BB-UVB, but both are less effective than PUVA.

NB-UVB was found to be effective in treating atopic dermatitis both as a monotherapy and as second agent (following oral cyclosporine) for severe cases.

In one study, PUVA was as effective as NB-UVB but patients preferred NB-UVB.

Few studies exist on phototherapeutic options for seborrhoeic dermatitis but one study yielded positive results (40% median decrease in clinical scores in 2 weeks).

Extremely promising results for NB-UVB exist for treatment of vitiligo, even in pediatric applications.

Literature reports that mycosis fungoides can be treated effectively with NB-UVB, particularly when treatment is sought early. Maintenance therapy is required.

Side effects exist for all types of phototherapy, including NB-UVB.

No safety data on long-term NB-UVB were available, and initial evidence is contradictory regarding the potential risk of patients treated with NB-UVB for the development of squamous cell cancer.

PUVA increases the risk of squamous cell carcinoma.

In a study comparing NB-UVB and BB-UVB for treating psoriasis, NB-UVB was found to be more effective.

Almost all presentations involved the classic LP pattern: volar aspects of the wrists, arms, trunk, and ankles. No nail involvement was reported. Most cases were treated with topical or systemic corticosteroids, etretinate or PUVA.

Vaccination for hepatitis B is now required for schoolchildren in Italy and France, which accounts for the relatively high number of pediatric cases of LP eruptions post-hepB-vaccination (33% of the cases reported involved pediatric patients).

Conclusion. Since LP is relatively rare in children, the pediatric cases, the literature, and this particular case strongly suggest that the hepatitis B vaccine could be the cause of LP in such cases. Furthermore, there may be a genetic susceptibility to vaccine-induced LP in people who are from Mediterranean populations.
Drug Actions, Reactions, and Interactions

Treating Superficial Mycoses with Oral anti-fungal Agents, Part 2

By James Q. Del Rosso, D.O., F.A.O.C.D.

Considering the widespread prevalence of superficial mycotic infections and associated oral anti-fungal use, it is rational to periodically revisit the subject of potential drug interactions and oral antifungal agents.

The following provides an overview of potential drug interactions related to the selection of specific oral antifungal agents.

Emphasis will be placed on supportive data, clinical significance and management suggestions for the clinician when selecting oral antifungal therapy for onychomycosis and other superficial mycotic infections.

Case #1

**History:** A 52-year-old Caucasian female presented with unilateral right plantar tinea pedis and onychomycosis of multiple toenails, including both large toenails. Independently performed potassium hydroxide preparations from the right large toenail and affected plantar surface demonstrated multiple long branched hyphae. Fungal culture from the right large toenail identified *Trichophyton rubrum* as the causative pathogen.

Baseline liver function testing and complete blood cell count were unremarkable. Intermittent pruritus of the right sole is noted. The patient also reported a sense of “pressure” and discomfort of her toenails when wearing certain shoes.

**Medication History.** Current daily systemic medications used by the patient included digoxin and quinidine for atrial fibrillation and sertraline for clinical depression. The patient also mentioned that her internist might start her on warfarin in the near future due to atrial fibrillation.

The clinician considered oral antifungal treatment. What potentially significant drug interactions may be identified prior to initiation of therapy?

**Drug Interaction Case Summary.** This case illustrates potentially significant drug interactions between digoxin, quinidine and certain antidepressant agents. Consideration is also given to potential interactions with warfarin should this medication be started based on the patient history.

**Digoxin.** Concurrent administration of itraconazole with digoxin may cause a significant increase in digoxin serum levels. Documented cases of digoxin toxicity have been reported in association with the co-administration of itraconazole.

The literature also reports rare cases of increased serum levels of digoxin related to concurrent use of ketoconazole.

The development of digoxin toxicity after concurrent use of itraconazole may be related to inhibition of P-glycoprotein, a membrane transport protein found in intestinal mucosa and renal tubules. It has been suggested that inhibition of P-glycoprotein by itraconazole impairs the renal pump mechanism responsible for tubular secretion of digoxin into the urine.

**Terbinafine, fluconazole and griseofulvin can be safely administered to patients utilizing digoxin.**

**Quinidine.** Concurrent administration of itraconazole is contraindicated in patients taking quinidine. Itraconazole increases plasma concentrations of quinidine with cases of toxicity reported. The clinical onset of the interaction often manifests as tinnitus, and serious cardiovascular reactions may occur.

Transient increase in quinidine plasma levels has also been reported with concurrent use of ketoconazole.

Interaction with quinidine has not been reported with terbinafine and is not anticipated based on current understanding of metabolic pathways.

Interaction between griseofulvin or fluconazole with quinidine also does not appear to occur.

**Antidepressants.** The hepatic metabolism of the antidepressant agents, including tricyclic derivatives and selective serotonin re-uptake inhibitors (SSRIs), is dependent on the specific agent prescribed.

Older antidepressants, such as imipramine, nortriptyline and amitriptyline are metabolized by CYP 2D6.

Of the SSRIs, fluoxetine (Prozac) is metabolized by CYP 2D6 and paroxetine (Paxil) is metabolized by CYP 2D6 and CYP 3A4; both are potent inhibitors of CYP 2D6. Many SSRIs share their metabolism among multiple CYP enzymatic pathways. For example, sertraline (Zoloft) is metabolized by CYP 3A4, CYP 2D6 and CYP 2C19. Shared enzymatic metabolism allows for potential shunting of the antidepressant drug to a different “available metabolic enzyme” should one of the enzymes responsible for the metabolism of the antidepressant be inhibited by another co-ingested drug.

Of the available SSRIs, sertraline and escitalopram (Lexapro) share their metabolism among three metabolic enzymes (CYP 3A4, CYP 2D6, CYP 2C19) and are reported to have a low potential for drug interactions. Terbinafine is an inhibitor of CYP 2D6. Examples of drugs that are metabolized by CYP 2D6 include older anti-
High-Profile Drug Interactions in Dermatology

Within dermatology, the clinical significance of drug interactions has been made evident by the withdrawal from the marketplace of the “non-sedating” antihistamines, terfenadine and astemizole, due to the increased propensity for prolongation of the QTc interval with subsequent ventricular arrhythmia when these agents were co-administered with erythromycin, ketoconazole or itraconazole. This “hallmark interaction” is directly related to inhibition of the cytochrome (CYP) 3A4 metabolic pathway by several macrolide antibiotics and azole anti-fungal agents.

Due to the predominant role of CYP 3A4 in the metabolism of approximately half of drugs currently available on the market, the potential for widespread impact related to CYP 3A4 inhibition, as well as other less predominant CYP metabolic isoenzymes, has received significant notoriety. Several warnings and contraindications have emerged related to drug interactions including recommendations to avoid co-administration of some macrolide antibiotics or azole anti-fungal agents with HMG-CoA reductase inhibitors (cholesterol-lowering agents), some benzodiazepines and some cardiac drugs, including digoxin and quinidine.

Due to variations in metabolic pathways, significant differences in the potential for interactions have been established when comparing griseofulvin, terbinafine (Lamisil), ketoconazole (Nizoral) and the triazoles, itraconazole (Sporanox) and fluconazole (Diflucan). Overall, as compared to the oralazole anti-fungal agents, terbinafine is associated with the most favorable safety profile with regard to clinically significant drug interactions.

Itraconazole, ketoconazole, and fluconazole may increase the anti-coagulant effect of warfarin; careful monitoring of anti-coagulation parameters (ie, international normalized ratio, prothrombin time) is recommended.

Premarketing and pharmacosurveillance studies suggested no interaction of terbinafine with warfarin. Literature review indicates two interaction reports with contradictory effects. As with the use of other oral anti-fungal agents in patients taking warfarin, monitoring of anti-coagulation parameters is suggested.

Management Suggestions:
Based on the current medication history, terbinafine may be used safely in patients treated with digoxin and quinidine.

Due to shared hepatic metabolism, interaction of terbinafine with sertraline is unlikely.

Itraconazole is contraindicated in patients utilizing quinidine and may also cause significant increases in serum digoxin levels.

Fluconazole is a potential option in this case for treatment of dermatophyte onychomycosis; however, a longer duration of therapy is required.

Due to limited efficacy for onychomycosis, ketoconazole and griseofulvin are not considered to be viable therapeutic options.

Although the risk for significant interaction appears to be less than with itraconazole, ketoconazole may alter serum levels of quinidine and digoxin.

All of the five currently available oral anti-fungal agents have been reported to potentially interact with warfarin, although the degree of risk is unclear. Griseofulvin may decrease the anti-coagulant activity of warfarin.

Medication History. Current daily systemic medications used by the patient included the following: lansoprazole and intermittent use of calcium carbonate as needed for gastroesophageal reflux disease (GERD). In addition, the patient was taking loratadine for seasonal rhinitis.

The clinician considered oral anti-fungal treatment for tinea versicolor in this patient due to extensive body surface area involvement. What potentially significant drug interactions may be identified prior to initiation of therapy?

Drug Interaction Case Summary. This case illustrates potentially significant drug interactions between specific oral anti-fungal agents and medications or ingestants which reduce gastric acidity.

Proton Pump Inhibitors/H-2 Blocker Antihistamines/Antacids. Dissolution and subsequent gastrointestinal

Case #2
History. A 32-year-old Filipino male presented with multiple hypopigmented patches located diffusely on the lateral neck, chest, back, shoulders and upper arms.

The eruption had been present for 1 year and had progressively worsened. Fine scaling was noted, which was accentuated by light scratching of affected skin with a tongue blade (“positive scratch sign”).

The clinical diagnosis of tinea versicolor is supported by a potassium hydroxide preparation demonstrating multiple short hyphae with clusters of round spores (“ziti and meatballs” pattern).
absorption of itraconazole from its capsule formulation and ketoconazole from its tablet formulation require gastric acidity.

Proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole), H-2 blocker antihistamines (cimetidine, ranitidine, famotidine) and antacids (calcium carbonate, aluminum hydroxide, magnesium hydroxide) reduce gastric acidity resulting in decreased absorption of itraconazole or ketoconazole from the intestinal tract.

It has also been suggested that concurrent ingestion of a cola beverage may enhance gastric acidity and overcome the effect of the interaction.

However, there is no evidence that ingestion of a cola beverage or citrus juice along with itraconazole or ketoconazole provides enough gastric acidity to counteract the marked increase in alkalinity caused by a proton pump inhibitor.

Interestingly, grapefruit juice has been shown to decrease the absorption and bioavailability of itraconazole. Gastrointestinal absorption of terbinafine and fluconazole are not significantly impacted by gastric pH or contents.

Although it has also been noted that the absorption of griseofulvin may be enhanced by ingestion with a fatty meal, the clinical significance of this suggestion is not clear.

Management Suggestions: Of the currently available oral anti-fungal agents, ketoconazole, fluconazole and itraconazole have demonstrated efficacy for treating tinea versicolor.

Both ketoconazole (400 mg) and fluconazole (300 – 400 mg) may be used as single-dose therapy for tinea versicolor; efficacy may be enhanced by repeating single dose treatment 1 week later.

In this case, due to use by the patient of a proton pump inhibitor (lansoprazole) and antacid (calcium carbonate), the effectiveness of either ketoconazole or itraconazole is likely to be diminished.

Fluconazole absorption is not impacted by reduced gastric acidity, favoring the use of this agent for treatment of tinea versicolor in this case.

References
4. Dominguez-Cherit J, Teixeira F,


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