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### Drug Interaction Profile of Posaconazole

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#### ABSTRACT

Adverse drug events resulting from drug-drug interactions may lead to emergency department visits, hospitalizations, prolonged length of stays, increased medical care costs, and death. Despite the efforts of research, clinical studies, and active reporting to identify and explain these drug interaction pathways, clinicians are often unaware of such drug-drug interactions. Therefore, it is imperative for pharmacists to identify these potential drug-drug interactions and notify the clinicians as well as the patients so that appropriate safety measures and monitoring methods are implemented. Specifically, immunocompromised patients often receive multiple drug regimens which are associated with toxicities and are highly susceptible to drug-drug interactions. Because of the increased use of azole antifungals in the prophylaxis or treatment of invasive fungal infections among these patients, a close monitoring of drug-drug interactions is warranted. Posaconazole (PCZ), an extended spectrum azole antifungal, has been indicated for use in the prophylaxis of invasive fungal infections in immunocompromised patients. The intent of this article is to increase the awareness of the potential drug-drug interactions with PCZ by reviewing the available drug interaction studies of PCZ and other therapeutic agents, specifically Mylanta, cimetidine, phenytoin, midazolam, cyclosporine, tacrolimus, rifabutin, and glipizide. Excluding Mylanta and glipizide, significant interactions had been observed when PCZ was co-administered with these agents. Therefore, avoidance of PCZ with these and other agents which share the same metabolic pathways is recommended. Otherwise, frequent monitoring of drug levels and for adverse drug events as well as dose adjustments may be warranted.

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#### INTRODUCTION

Adverse drug events have been an inherent component of medication use. It was not until after the "To Err Is Human: Building a Safer Health System" report that they became the focus of patient care in all health care environments.<sup>1</sup> One possible contributing factor is the concomitant use of medications that have the potential for clinically significant interactions.<sup>2-5</sup> These adverse drug events resulting from drug-drug interactions may lead to emergency department visits, hospitalizations, prolonged length of stays, and increased medical care costs as well as death in both inpatient and outpatient settings.<sup>3-9</sup> The root cause of this problem is probably multifactorial. Despite the efforts of research, clinical studies and active reporting to identify and explain these drug interaction pathways, clinicians are often unaware of such drug-drug interactions.<sup>10-14</sup> In order to improve patient safety and quality of care in the health system, the Joint Commission has established a number of standards and safety goals for health care practice to improve the safety of using medications and effectiveness of communication among caregivers.<sup>15</sup> Regardless of which health care practice environment, it is imperative for pharmacists to identify these potential drug-drug interactions and notify the clinicians as well as the patients so that appropriate safety measures and monitoring methods are implemented.

Immunocompromised patients (i.e., cancer, HIV/AIDS, and solid organ transplantation) often receive multiple and prolonged drug therapies not only for the treatment of their underlying diseases but also for the treatment and prophylaxis of complications from their immunocompromised states. These complex drug regimens are associated with toxicities and are highly susceptible to drug-drug interactions that further complicate their drug regimens. Because of the increased use of azole antifungal agents in the prophylaxis or treatment of invasive fungal infections among immunocompromised patients, a close monitoring of drug-drug interactions is warranted.<sup>16-19</sup>

Posaconazole (PCZ) is an extended spectrum azole antifungal agent with a chemical structure similar to itraconazole. It has received FDA approval for use in the prophylaxis of invasive fungal infections in particular aspergillosis and candidiasis in high risk immunocompromised patients who are 13 years or older.<sup>20</sup> By disrupting fungal cell wall synthesis, PCZ has fungicidal activity against *Cryptococcus neoformans*, *Aspergillus (fumigatus, flavus, and terreus)*, *Blastomyces dermatitidis*, *Trichosporon* and specific *Candida* species (*krusei, parapsilosis, lusitanae* and *inconspicua*).<sup>20, 21</sup> It also has shown fungistatic activity against most other *Candida* species, *Scedosporium*, *Coccidioides*, *Zygomycetes* and specific *Fusarium* strains (*oxysporum* and *moniliforme*).<sup>20, 21</sup>

PCZ is orally bioavailable and its gastrointestinal absorption is enhanced when co-administered with food or a nutritional supplement regardless of gastric pH.<sup>22-26</sup> In phase I clinical trials, the mean maximum plasma concentration ( $C_{max}$ ) values (ng/mL) were 555 and 2607 after a single oral 400 mg dose and a multiple oral dose regimen (400 mg twice daily for 8 days) of PCZ suspension, respectively.<sup>27, 28</sup> PCZ has a large apparent volume of distribution (V/F), suggesting extensive tissue penetration and is highly protein bound (> 98.5%).<sup>27, 29</sup> The mean systemic exposure value of PCZ suspension for the single dose phase was 18425 ng • h/mL whereas the multiple dosing phase was 26740 ng • h/mL.<sup>27, 28</sup> The major elimination route of PCZ is fecal (77%) with a mean apparent systemic clearance (CL/F) of 421 mL/min and a half-life ( $t_{1/2}$ ) of 24 hours (h) in a single 400 mg dose study.<sup>27</sup> The  $t_{1/2}$  is longer (~35 h) in multiple dosing studies.<sup>28</sup> PCZ is hepatically metabolized into multiple inactive glucuronides by phase II UDP-glucuronosyltransferase.<sup>27</sup> Having a pregnancy category C status, PCZ may be harmful to the fetus during pregnancy and its safety is uncertain in lactation.<sup>20</sup> Therefore, avoidance of PCZ during pregnancy and lactation is recommended. Otherwise, PCZ is considered safe and well tolerated. The most commonly reported side effects (>10%) in small, single and/or multiple dosing phase I studies of PCZ, included headache, fatigue, nausea, and dry mouth.<sup>22-29</sup> PCZ is available in the United States as an oral suspension (40 mg/mL). Its dosing regimen ranges from 200 mg daily to three times daily depending on the disease state.<sup>20, 30-33</sup> No dosing adjustment of PCZ is needed in renal failure or dialysis patients.<sup>29</sup> The clinical data of PCZ use in hepatic impairment, bariatric, and pediatric populations are still limited. Routine monitoring of electrolytes and liver function tests is recommended during PCZ therapy.<sup>20</sup>

The purpose of this article is to increase the awareness of the potential drug-drug interactions with PCZ when used in prophylaxis or treatment of invasive fungal infections among immunocompromised patients. Our goals are to promote the safe use of medications by improving communication among health care providers and to prevent adverse drug events. This article describes the available clinical drug-drug interaction studies with PCZ and other therapeutic agents specifically Mylanta, cimetidine, phenytoin, midazolam, cyclosporine, tacrolimus, rifabutin and glipizide.<sup>26, 34-37, 39, 40</sup> A brief summary of these studies is displayed in Table 1.

## DRUG REVIEW

### Mylanta (antacid)

The over-the-counter Mylanta is known for its use in heartburn and/or dyspepsia. Courtney et al. conducted a randomized, open label, four way crossover pharmacokinetic study in healthy volunteers (n=12) to evaluate the effect of altering gastric pH on the relative systemic absorption of PCZ.<sup>26</sup> Maximum strength Mylanta, containing aluminum hydroxide and magnesium hydroxide, was used. The Mylanta dose was 20 mL, which provided a total of 102 mEq of acid neutralizing capacity to increase the gastric pH above 3.5. After a 10-hour overnight fast, all subjects were randomized to receive a single 200 mg PCZ tablet and 200 mL of regular water under four different conditions (either alone, immediately after a standardized high fat meal, Mylanta alone, or Mylanta and a standardized high fat meal).<sup>26</sup> A 7-day washout period was used between each study phase. A series of blood samples were collected according to the study protocol, and plasma PCZ concentrations were measured by standardized high performance liquid chromatographic (HPLC) methods. The analyses of the data were discussed in detail in the original research article.<sup>26</sup>

The baseline characteristics of these subjects were non-obese males with a mean age of 34 years. The races were both blacks and whites in a 2 to 1 ratio.<sup>26</sup> The pharmacokinetic results of this study demonstrated that Mylanta did not significantly alter the relative systemic absorption of PCZ under all treatment conditions. In the presence of food and Mylanta, the pharmacokinetic parameters [i.e.,  $C_{max}$ , time to reach  $C_{max}$  ( $T_{max}$ ), area under the concentration time curve (AUC),  $t_{1/2}$ , CL/F and V/F] were similar

to those in the presence of food only.<sup>26</sup> The relative oral bioavailability value of PCZ was estimated to be 88% [90% confidence interval (CI): 71%-110%]. Similar effects were observed in the fasting state with or without Mylanta and the corresponding relative bioavailability of PCZ was 115% [90% CI: 92-143].<sup>26</sup> In each group there was intersubject variability of PCZ's systemic absorption that ranged from 29% to 45%. This phenomenon concurred with previous studies and remains to be elucidated.<sup>22-25,27-29</sup> The relative bioavailability of PCZ values were significantly enhanced in the presence of food with or without acid (308%,  $p=0.001$  and 400%,  $p=0.001$ , respectively).<sup>26</sup> The rates of absorption remained relatively constant among all study phases. Only one subject experienced a mild headache. The V/F and CL/F values of PCZ were three fold higher in the fasting state than in the nonfasting state. The authors explained that these observations were a result of decreased PCZ absorption under fasting conditions because the elimination rate constants did not change among all four treatment phases.

**Table 1. Drug Interactions Studies of Posaconazole (PCZ) and Selected Agents<sup>a</sup>**

| <b>Drug/Dose</b>                   | <b>PCZ Tab</b> | <b>PCZ Susp</b> | <b>Duration of Therapy</b> | <b>Effects on PCZ</b>  | <b>Effects on Agent</b>   |
|------------------------------------|----------------|-----------------|----------------------------|--|---|
|                                    | <b>Dose</b>    | <b>Dose</b>     |                            |  |   |
| Cimetidine 400 mg q12h             | 200 mg qd      | ND              | 10 days                    | $C_{max} \downarrow 40\%$<br>$AUC \downarrow 40\%$   | ND  |
| Cyclosporine bid <sup>b</sup>      | 200 mg qd      | ND              | 10 days                    | NS   | $C_0 \uparrow$  |
| Glipizide 10 mg <sup>c</sup>       | ND             | 400 mg BID      | 10 days                    | NS   | NS  |
| Midazolam 0.05 mg/kg S.D.          | 200 mg qd      | ND              | 10 days                    | NS   | $AUC \uparrow 83\%$   |
| Mylanta 20 mL S.D.                 | 200 mg S.D.    | ND              | One time                   | NS   | ND  |
| Phenytoin 200 mg qd                | 200 mg qd      | ND              | 10 days                    | $C_{max} \downarrow 41\%$<br>$AUC \downarrow 50\%$<br>$CL/F \uparrow 90\%$                               | $C_{max} \uparrow 16\%$<br>$AUC \uparrow 16\%$  |
| Rifabutin 300 mg qd                | 200 mg qd      | ND              | 10 days                    | $C_{max} \downarrow 43\%$<br>$AUC \downarrow 49\%$<br>$CL/F \uparrow 100\%$<br>$t_{1/2} \downarrow 42\%$ | $C_{max} \uparrow 31\%$<br>$AUC \uparrow 72\%$<br>$CL/F \uparrow 42\%$                      |
| Tacrolimus 0.05 mg/kg <sup>d</sup> | ND             | 400 mg BID      | 7 days                     | NS   | $C_{max} \uparrow 121\%$<br>$AUC \uparrow 358\%$<br>$t_{1/2} \uparrow$<br>$CL/F \downarrow$ |

<sup>a</sup>All interactions refer to alterations of PCZ pharmacokinetics unless otherwise stated.

<sup>b</sup>Dosing is individualized based on target trough concentrations

<sup>c</sup>Specific agent was administered on days 1 and 11

<sup>d</sup>Specific agent was administered on days 1 and 14

Tab = Tablet; Susp = Suspension; S.D. = Single dose

$C_{max}$  = Maximum plasma concentrations; AUC = area under the plasma concentration versus time curve;

CL/F = Apparent systemic clearance;  $C_0$  = whole blood trough concentration;  $t_{1/2}$  = half-life

kg = kilograms; mg = milligrams; mL = milliliters; q12h = every 12 hours; qd = daily; bid = Twice daily

ND = No data available; NS = No significant interaction

Adapted from references 26, 34-37, 39, and 40; see text for specific discussions and citations

The authors concluded that PCZ oral absorption was independent of gastric pH and was enhanced in the presence of food.<sup>26</sup> However, the major concern with this study was the single dose of Mylanta may not be sufficient to sustain a gastric pH above 3.5 for longer than 1 hour since the mean  $T_{max}$  of PCZ was greater than 7 hours.<sup>26</sup> The authors did not postulate an explanation of their observations in terms of gastric pH on PCZ absorption. Additionally, the effects on PCZ bioavailability from the presence of a more potent acid suppressant, either a histamine-2 receptor antagonist (H2RA) or a proton pump inhibitor, or from gastrointestinal disorders (i.e., achlorhydria and spontaneous or drug induced hyperchlorhydria) remain to be determined. At the present time, concomitant use of an antacid and PCZ appears to be safe and does not affect the systemic exposure of PCZ.

**Cimetidine (histamine-2 receptor antagonist)**

Cimetidine, one of the oldest H<sub>2</sub>RA, is known for its use in heartburn, dyspepsia, and/or upper gastrointestinal bleeding by raising the gastric pH. Cimetidine is also accepted as a CYP3A4 inhibitor. Courtney et al. conducted a randomized, open label, two-way crossover, multiple dose drug interaction study in which healthy subjects (n=12) were randomly assigned to 10 days of either PCZ 200 mg tablet PO daily (phase 1) or same dose of PCZ and cimetidine 400 mg PO every 12 hours (phase 2).<sup>34</sup> The two phases were separated by a 7-day washout period. A series of blood samples were collected according to the study protocol. Blood samples measuring plasma concentrations of PCZ and cimetidine were performed by the standardized HPLC techniques. The mean C<sub>max</sub> and AUC values of PCZ both decreased by 40% in phase 2 as compared to phase 1.<sup>34</sup> The relative systemic exposure of PCZ in the presence of cimetidine was estimated to be 61% (90% CI: 54%-69%).<sup>34</sup> The mean T<sub>max</sub> and t<sub>1/2</sub> values were 7 h and 35 h in both treatment phases. No adverse effect was reported.

The author concluded that a multiple daily PCZ regimen was safe and well tolerated. PCZ absorption is independent of gastric pH as previously demonstrated with Mylanta. However, the co-administration of PCZ with cimetidine should be avoided because of the decrease in the relative bioavailability of PCZ at a gastric pH of 3 or greater.<sup>20</sup> This discrepancy between the effect of gastric pH on PCZ's systemic exposure suggests the presence of other mechanisms, i.e., competition between PCZ and cimetidine for the same transport protein. The involvement of the CYP450 system and/or other mechanisms on PCZ's systemic exposure requires further investigation. If a H<sub>2</sub>RA is needed, an alternative such as famotidine with minimal or no cytochrome P450 (CYP450) enzyme system involvement may be used.

**Phenytoin (antiepileptic)**

Phenytoin is a first generation antiepileptic agent which has a narrow therapeutic index and is metabolized primarily through the hepatic CYP450 3A4 (CYP3A4) isoenzyme system. The work of Courtney et al. involved a randomized, open label, parallel, multiple dose study in which healthy subjects (n=36) were randomly assigned to three 10 day treatment arms: PCZ 200 mg tablet PO daily (group 1), phenytoin 200 mg PO daily (group 2), and the same doses of PCZ and phenytoin (group 3).<sup>35</sup> A series of blood samples were collected according to the study protocol. Blood samples measuring plasma concentrations of PCZ and phenytoin were performed using validated HPLC methods.

At steady state, the mean relative systemic bioavailability of PCZ was decreased by 50% after the co-administration of oral PCZ (200 mg tablet daily) and oral phenytoin (200 mg daily) despite no significant change in mean C<sub>max</sub> values between days 1 and 10.<sup>35</sup> This phenomenon was explained by the increased CL/F of PCZ by 90% in the presence of phenytoin, an UDP-glucuronosyltransferase inducer.<sup>35</sup> Conversely, the relative systemic exposure of phenytoin was increased by 16% when co-administered with PCZ.<sup>35</sup> The authors suggested that when patients are receiving PCZ, avoidance of phenytoin is warranted. The magnitudes of the changes in bioavailability of PCZ and phenytoin are still uncertain, because clinically, the dosing with these agents is different and the toxicity may appear sooner than 10 days. The baseline demographics of these subjects and adverse effects were not reported. Finally, careful monitoring of phenytoin levels is warranted when both drugs are used together.

**Midazolam (sedative)**

Because of its extremely short t<sub>1/2</sub>, midazolam continuous infusion is used primarily in the intensive care unit or surgical procedures as a sedative. The effects of PCZ on the activity of several drug metabolizing CYP450 enzymes were investigated.<sup>36</sup> This study used non-obese adult subjects (n=13, age range 18 to 45) who were randomly assigned to receive oral PCZ (200 mg tablet daily) or no drug for 10 days.<sup>36</sup> After a 14 day washout period, subjects crossed over to the alternate study group. A standardized CYP450 cocktail with corresponding surrogate substrates consisted of caffeine (CYP1A2), tolbutamide (CYP2C8/9), dextromethorphan (CYP2D6 and total CYP3A4) and chlorzoxazone (CYP2E1). This cocktail was given to both study groups 2 hours after the administration of PCZ under fasting conditions on day 9. In addition, midazolam (0.05 mg/kg in 100 mL of 0.9% saline), a benzodiazepine which undergoes hepatic CYP3A4 metabolism, was given in place of the CYP450 cocktail on day 10 as a 30 min infusion.<sup>36</sup> A series of blood and urine samples were performed according to the study protocol. Plasma and urine concentrations of PCZ, other CYP450 markers and their metabolites were analyzed by standardized laboratory techniques.

Steady state PCZ concentrations were reached after 8 days with mean (%Coefficient of variation [CV]) C<sub>max</sub> (ng/mL), T<sub>max</sub> (h), AUC (ng • h/mL), and CL/F (mL/min) values of PCZ were 1073 (31), 6.9 (21), 19,465 (32), and 188 (34), respectively.<sup>36</sup> Based on the aforementioned information under fasting conditions, the systemic exposure of oral PCZ 200 mg tablets showed an accumulation index of 1.9. Plasma- or urine ratios of CYP450 markers and their metabolites were examined to assess the effects of PCZ on the CYP450 isoenzymes. Plasma ratios of 1,7-dimethylxanthine to caffeine and 6-hydroxychlorzoxazone to chlorzoxazone were examined in order to assess CYP1A2 and CYP2E1 activities, respectively. Urinary ratios of combined 4-

hydroxytolbutamide + carboxytolbutamide and tolbutamide, dextromethorphan and dextrorphan and dextromethorphan and 3-methoxymorphinan were measured in order to assess the effects of CYP2C8/9, CYP2D6 and total (intestinal and hepatic) CYP3A4, respectively. Furthermore, hepatic CYP3A4 activity was measured when midazolam was given with PCZ. Overall, PCZ did not affect the CYP450 isoenzymes 1A2, 2C8/9, 2D6, 2E1 and total CYP3A4 with the exception of hepatic CYP3A4. The inhibitory effect of PCZ on hepatic CYP3A4 is demonstrated by a significant increased mean AUC (%CV) (ng • h/mL) of midazolam in the presence of PCZ as compared to in the absence of PCZ [93.4 (29) vs. 51.4 (29), respectively,  $p < 0.01$ ].<sup>36</sup> This results in a relative 1.83 (90% CI: 1.57 to 2.14) fold increase in midazolam exposure.<sup>37</sup> The authors concluded that unlike other azole antifungal agents (i.e., itraconazole and ketoconazole), PCZ has limited potential drug interactions because of its sole inhibition of hepatic CYP3A4.

Interestingly, this study demonstrated that PCZ is a potent CYP3A4 inhibitor by reducing the CL/F of midazolam. In clinical practice, the pharmacological effect of midazolam can be assessed based on a sedation protocol. Dosing of midazolam can be done by adjusting the rate of infusion. The reason why PCZ had no effect on the total CYP3A4 activity remained to be elucidated because intestinal interactions among the CYP450 markers could not be excluded. Complete voiding of the urinary bladder to measure each CYP450 marker and its metabolites was questionable. Overall, the ideal approach is to avoid co-administration of PCZ with other CYP3A4 substrates which include an extensive list of drugs, including but not limited to calcium channel blockers, calcineurin inhibitors, ergot alkaloids, HIV-1 protease inhibitors, HMG-CoA reductase inhibitors and vinca alkaloids.<sup>2</sup>

### **Cyclosporine and tacrolimus (calcineurin inhibitors)**

Cyclosporine (CSA) and tacrolimus (FK506) belong to a class of immunosuppressants called calcineurin inhibitors which play a major role as maintenance therapy in the prevention of acute allogeneic graft rejection in solid organ transplantation. Both CSA and FK506 are CYP3A4 and P-glycoprotein (P-gp) substrates.<sup>16</sup> Previous studies reported that PCZ undergoes extensive hepatic metabolism yielding glucuronide metabolites.<sup>27</sup> PCZ is also a hepatic CYP3A4 enzyme inhibitor as discussed previously.<sup>36</sup> Sansone-Parsons et al. examined the effects of oral PCZ on the systemic exposures of CSA and FK506 in two separate, open label, and single center, drug interaction studies.<sup>37</sup> The CSA-PCZ study was conducted in heart transplant recipients ( $n=4$ ) who had normal cardiac function and resided in United States, whereas the FK506-PCZ study was performed in healthy volunteers ( $n=36$ ) who lived in England. Subjects were excluded from both studies if they were tested positive for hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV) antibodies. A series of blood samples were collected according to the study protocol. All study drug concentrations were analyzed by liquid chromatography and mass spectrometry techniques.

In the CSA-PCZ study, patients were excluded if they were smokers, strict vegetarians, or blood donors within the past 3 months. Other exclusions included a history of mental illness, receiving treatment for mood disorders, and medications that can interact with CSA as specified in the article.<sup>37</sup> Heart transplant recipients receiving a stable CSA regimen for 6 weeks or longer were administered oral PCZ 200 mg tablet daily for 10 days.<sup>37</sup> PCZ was administered in the evening on day 1 and after a high fat content breakfast from day 2 to 10. The investigators adjusted the CSA dose for each subject depending on corresponding trough concentration ( $C_0$ ).

The heart transplant recipients in the CSA-PCZ study were all Caucasian males with a mean age of 54 years. The authors stated that steady state plasma PCZ concentrations increased CSA  $C_0$  levels which led to CSA dosage reductions (ranging from 14% to 29%) in three out of the four patients.<sup>37</sup> Adverse effects that were considered drug related in this study included diarrhea, nonherpetic cold sores, dysuria, flank pain, hematuria, urinary tract infection, pain, rash, and gastritis.<sup>37</sup> Although there are a few critical issues on the design and results of this study, co-administration of PCZ and CSA requires frequent monitoring of CSA  $C_0$  concentrations to ensure transplant therapeutic ranges are maintained.<sup>38</sup> The authors suggested that three fourths of the original dosage reduction of CSA should be done when initiating PCZ therapy. However, caution should be employed with this approach because the recommendation was based on data from three subjects, CSA  $C_0$  concentrations and their changes were not reported, acute graft rejection rate was not evaluated, and the therapeutic dose of PCZ is higher than the one used in this study.

In the other study, Sansone-Parsons et al. examined the effects of PCZ on FK506. Healthy adult subjects received a single PO dose of FK506, 0.05 mg/kg on days 1 and 14 after a 10 hour fast. PCZ was administered as a 400 mg PO suspension twice daily from days 7 to 14 after a high fat breakfast.<sup>37</sup> This allowed for a 5-day washout period of FK506.

The baseline characteristics of these subjects included non-obese, 50% male, 92% Caucasians with a mean age of 26 years. The results of this study demonstrated that PCZ significantly increased the systemic exposure of FK506. The means (%CV)  $C_{max}$  (ng/mL) and AUC (ng • h/mL) values of FK506 in the absence and presence of PCZ were 24.2 (31) vs. 51.7 (18) and 207 (52) vs. 875 (27), respectively.<sup>37</sup> The mean (%CV)  $t_{1/2}$ , and CL/F values of FK506 in the presence of PCZ were 35.9 (10) h and 4.31

(30) liter/h, respectively.<sup>37</sup> The corresponding values of FK506 when given alone were 29 (15) h and 21.4 (56) liter/h, respectively.<sup>37</sup> The median (range)  $T_{max}$  (hours) values were the same in both study phases [1.5 (1-3)]. The two most common adverse effects reported during co-administration of FK506 and PCZ were mild to moderate paresthesia (56%) and headache (39%).<sup>37</sup> Overall, the authors suggested that one third of the original dosage reduction of FK506 should be done when initiating PCZ therapy. Again, caution should be taken with this suggestion based upon similar reasons as mentioned earlier in the CSA study.

In the above studies, the pharmacokinetic properties of PCZ were similar to those previously reported when co-administered with CSA or FK506. However, a wide range of intersubject variability of plasma PCZ concentrations (74%-141% and 30% in CSA-PCZ and FK506-PCZ study, respectively) was reported.<sup>37</sup> This variation in pharmacokinetic profile of PCZ remains to be elucidated. Conversely, the changes in the  $C_0$  of CSA and AUC of FK506 were postulated by the inhibition of CYP3A4 metabolism and of P-gp transport mediated by PCZ. Until further information is generated on the interaction pathways, avoidance of these combinations is necessary. Otherwise, close monitoring of CSA or FK506 concentrations is warranted when these drugs are co-administered with PCZ.

### Rifabutin (rifamycin derivative)

Rifabutin, a rifamycin derivative, has a role in the prevention and treatment of mycobacterium related tuberculosis or opportunistic infection in immunocompromised individuals. Krishna et al. conducted a nonrandomized, open label, parallel, multiple dose pharmacokinetic study in healthy volunteers (n=24) to evaluate the interaction between PCZ and rifabutin at steady state.<sup>39</sup> Subjects were randomly assigned to receive either PCZ alone for 10 days (group 1) or rifabutin co-administered with PCZ for 10 days (group 2). Subjects received daily doses of PCZ (tablet, 200 mg) and rifabutin (capsule, 300 mg). In group 2, steady state levels of rifabutin were established 7 days (days -7 to 1) prior to the administration of PCZ (from days 1-10). Blood samples were collected according to the study protocol. Plasma PCZ and rifabutin concentrations were measured by standardized HPLC techniques.

Study subjects included Caucasians males with a mean age (range) of 27 (20 to 40) years and with a mean weight of 73 kg.<sup>39</sup> Four subjects in group 2 did not complete the study because of adverse reactions (i.e., leukopenia in 3 subjects and dizziness, headache and fever in the other). The mean (%CV)  $C_{max}$  (ng/mL), AUC (ng • h/mL) and median (range)  $T_{max}$  (h) of PCZ were 766 (37), 12629 (43) and 5 (5-15), respectively.<sup>39</sup> The pharmacokinetic parameters of PCZ were significantly altered by rifabutin (group 2). The mean (%CV) of  $C_{max}$  (ng/mL), AUC (ng • h/mL), and median (range)  $T_{max}$  (h) were 428 (29), 6389 (38) and 7 (3-10), respectively.<sup>39</sup> Co-administration of rifabutin resulted in a 43% and 49% reduction in  $C_{max}$  and AUC of PCZ, respectively. This reduction in PCZ systemic exposure was associated with a 2-fold increase in PCZ clearance (CL/F, 307 vs. 594 mL/min) and a 42% decrease in PCZ  $t_{1/2}$  (27.4 vs. 15.9 hours).<sup>39</sup> In group 2, the two consecutive mean rifabutin  $C_0$ s (ng/mL) on day -1 and day 1 of PCZ co-administration were comparable (64.1 vs. 72.1).<sup>39</sup>

Interestingly, the pharmacokinetics of rifabutin were altered by PCZ. The mean (%CV) of  $C_{max}$  (ng/mL) and AUC (ng • h/mL) values of rifabutin were 438 (23) and 3975 (20) respectively, on day 1 and 569 (20) and 6833 (21) respectively, on day 10.<sup>39</sup> According to these data, co-administration of PCZ with rifabutin resulted in a 31% and 72% increase in  $C_{max}$  and AUC values, respectively. This increase in rifabutin exposure was associated with a 42% decrease in total rifabutin clearance as compared to rifabutin administered alone (CL/F, 1300 vs. 758 mL/min).<sup>39</sup>

In comparison, the frequency of adverse events was mild in nature and was observed more often in group 2 than in group 1. In group 1, these possible drug related adverse events included back pain (25%), cough (17%) and dry skin (17%) whereas headache (75%), back pain (67%), leukopenia (42%), eye abnormality (42%), and abdominal pain (42%) were observed in group 2.<sup>39</sup> Leukopenia was the only abnormal laboratory finding in both study groups. The authors concluded that co-administration of PCZ and rifabutin should be avoided and should be used only if the benefits outweigh the risks. Intense monitoring for adverse events is needed if PCZ and rifabutin are used together. These observations may be explained by the enhanced systemic clearance of PCZ by rifabutin (via induction of UDP-glucuronosyltransferase) and the decline of systemic clearance of rifabutin by PCZ (via CYP3A4 inhibition).

### Glipizide

Glipizide is an oral hypoglycemic agent which undergoes renal excretion. Courtney et al. conducted an open label, crossover study to evaluate the effect of glipizide on the relative bioavailability of PCZ in healthy volunteers (n=12).<sup>40</sup> The glipizide dose was 10 mg on days 1 and 11, whereas the PCZ dose was 400 mg twice daily from day 2 to 11. The authors found that glipizide had no effect on the relative bioavailability of PCZ and vice versa. Therefore, concomitant use of PCZ and glipizide is considered safe despite a non-clinical significant decrease in blood glucose.

## CONCLUSION

Increased awareness of potential drug-drug interactions of medication use is one key factor in preventing adverse drug events and promoting safe medications use. Regardless of which health care practice environment, it is imperative for pharmacists to identify potential drug-drug interactions and notify the health care practitioners and patients so that appropriate safety measures and monitoring methods are implemented. Because of the unique spectrum of activity and pharmacological profile, PCZ will be used more frequently in the prophylaxis for invasive fungal infections in patients who are immunocompromised. PCZ is a CYP3A4 inhibitor and has been shown to interact with a number of CYP3A4 substrates or inhibitors including cimetidine, phenytoin, midazolam, cyclosporine, tacrolimus, and rifabutin. Therefore, avoidance of PCZ with these and other agents that share the same metabolic pathways is recommended. Other agents include calcium channel blockers, calcineurin inhibitors, ergot alkaloids, HIV-1 protease inhibitors, HMG-CoA reductase inhibitors, proton pump inhibitors, and vinca alkaloids. Otherwise, frequent monitoring of drug levels and for adverse drug events as well as dose adjustments may be warranted. Information regarding the exact drug-drug interaction pathways between PCZ and the aforementioned agents is still limited and require further investigation.

## REFERENCES

1. Kohn LT, Corrigan JM, Donaldson MS. To Err Is Human: Building a Safer Health System. Washington, DC: Institute of Medicine and National Academy Press; 1999.
2. Lafata JE, Simpkins J, Kaatz S, et al. What do medical records tell us about potentially harmful co-prescribing? *Jt Comm J Qual Patient Saf.* 2007;33:395-400.
3. Raschetti R, Morgutti M, Menniti-Ippoloto F, et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. *Eur J Clin Pharmacol.* 1999;54:959-63.
4. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA.* 2003;289:1652-58.
5. Lafata JE, Schultz L, Simpkins J, et al. Potential drug-drug interactions in the outpatient setting. *Med Care.* 2006;44:534-41.
6. Dennehy CE, Kishi DT, Louie C. Drug-related illness in emergency department patients. *Am J Health Syst Pharm.* 1996;53:1422-6.
7. Smith KM, McAdams JW, Frenia ML, Todd MW. Drug-related problems in emergency department patients. *Am J Health Syst Pharm.* 1997;54:295-8.
8. Wu WK, Pantaleo N. Evaluation of outpatient adverse drug reactions leading to hospitalization. *Am J Health Syst Pharm.* 2003;60:253-9.
9. Gaddis GM, Holt TR, Woods M. Drug interactions in at-risk emergency department patients. *Acad Emerg Med.* 2002;9:1162-7.
10. Shaoul R, Shahory R, Tamir A, Jaffe M. Comparison between pediatricians and family practitioners in the use of the prokinetic cisapride for gastroesophageal reflux disease in children. *Pediatrics.* 2002;109:1118-23.
11. Langdorf MI, Fox JC, Marwah RS, Montague BJ, Hart MM. Physician versus computer knowledge of potential drug interactions in the emergency department. *Acad Emerg Med.* 2000;7:1321-9.
12. Weideman RA, Bernstein IH, McKinney WP. Pharmacist recognition of potential drug interactions. *Am J Health Syst Pharm.* 1999;56:1524-9.
13. Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. *JAMA.* 1996;275:1086-7.
14. Glassman PA, Simon B, Belperio P, Lanto A. Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. *Med Care.* 2002;40:1161-71.
15. <http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/>. Accessed on December 27, 2007
16. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy.* 2006;26:1730-44.
17. Buchkowsky SS, Partovi N, Ensom MH. Clinical pharmacokinetic monitoring of itraconazole is warranted in only a subset of patients. *Ther Drug Monit.* 2005;27:322-33.
18. Joerger M, Schellens JH, Beijnen JH. Therapeutic drug monitoring of non-anticancer drugs in cancer patients. *Methods Find Exp Clin Pharmacol.* 2004;26:531-45.
19. Sagir A, Schmitt M, Dilger K, Haussinger D. Inhibition of cytochrome P450 3A: relevant drug interactions in gastroenterology. *Digestion.* 2003;68:41-8.
20. Cada DJ, Levien T, Baker DE. Posaconazole oral suspension. *Hospital Pharmacy.* 2007;42:57-72.
21. Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. *Antimicrobial Agents Chemother.* 2006;50:2009-15.

22. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br J Clin Pharmacol*. 2004;57:218-22.
23. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother*. 2003;47:2788-95.
24. Ezzet F, Wexler D, Courtney R, Krishna G, Lim J, Laughlin M. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. *Clin Pharmacokinet* 2005;44:211-20.
25. Sansone-Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. *Antimicrob Agents Chemother*. 2006;50:1881-3.
26. Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. *Antimicrob Agents Chemother*. 2004;48:804-8.
27. Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R. Disposition of posaconazole following single dose oral administration in healthy subjects. *Antimicrob Agents Chemother*. 2004;48:3543-51.
28. Sansone-Parsons A, Krishna G, Simon J, et al. Effects of age, gender, and race/ethnicity on the pharmacokinetics of posaconazole in healthy volunteers. *Antimicrob Agents Chemother*. 2007;51:495-502.
29. Courtney R, Sansone A, Smith W, et al. Posaconazole pharmacokinetics, safety and tolerability in subjects with varying degrees of chronic renal disease. *J Clin Pharmacol*. 2005;45:185-92.
30. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis*. 2006;42:1179-86.
31. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356:348-59.
32. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356:335-47.
33. Ullmann AJ, Cornely OA, Hachem BR, et al. Pharmacokinetics, safety and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother*. 2006;50:658-66.
34. Courtney R, Wexler D, Statkevich P, Lim J, Batra V, Laughlin M. Effect of cimetidine on the pharmacokinetics of posaconazole in healthy volunteers. *Intersci Conf Antimicrob Agents Chemother* 2002;42:A1838 (abstr).
35. Courtney RD, Statkevich P, Laughlin M, et al. Potential for a drug interaction between posaconazole and phenytoin. *Intersci Conf Antimicrob Agents Chemother* 2001;41:A28 (abstr).
36. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized open-label, two-way crossover study. *Eur J Pharm Sci*. 2004;21:645-53.
37. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacotherapy*. 2007;27:825-34.
38. Leung S, Poulakos MN, Kernan W. Is the drug interaction actual between posaconazole and cyclosporine? *Pharmacotherapy*. 2007;28:3e.
39. Krishna G, Persons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. *Curr Med Res Opin*. 2007;23:545-52.
40. Courtney R, Sansone A, Statkevich P, Martinho M, Laughlin M. Assessment of the pharmacokinetic (PK), pharmacodynamic (PD) interaction potential between posaconazole and glipizide in healthy volunteers. *Clin Pharmacol Ther*. 2003; 73:P45.