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Statement of Financial Disclosure:
Barry A. Browne, PharmD (Pharmacist Editor), John Hope (Editor), Lee Landenberger (Associate Publisher), Paula Cousins (Managing Editor), and Michele Bryant (Author, insert) report no relationships with companies related to this field of study.

FEBRUARY 2008
VOL. 24, NO. 2 • (pages 9-16)

Study finds daptomycin outperforms vancomycin

Better overall resource use and more rapid resolution

Research conducted at the Detroit Medical Center found that Cubist Pharmaceuticals' daptomycin for injection (Cubicin®) outperformed vancomycin in resolving the signs and symptoms of complicated skin and skin structure infections.

Lead researcher **Michael Rybak**, PharmD, MPH, professor of pharmacy, adjunct professor of medicine, and director of the anti-infective research laboratory at Wayne State University, tells *Drug Formulary Review* in a news briefing on his group's research that while daptomycin is significantly more expensive than vancomycin, total treatment costs were comparable between the two drugs because daptomycin works faster than vancomycin.

"Patients receiving daptomycin achieved more rapid resolution of symptoms and clinical cure and had a decreased duration of inpatient therapy compared with those receiving vancomycin," Rybak says of his results, which were published in the December 2007 issue of *Pharmacotherapy*.

Hospitals have to be concerned about skin and skin structure infections, given that Centers for Disease Control and Prevention data for 2004 showed that such infections were the primary diagnosis in some 562,000 hospital discharges, with an average length of stay of 4.7 days. Bacterial skin diseases cover a wide spectrum of clinical conditions, ranging from local superficial infections to life-threatening aggressive infections. In any event, prompt treatment with an appropriate antibiotic is a key to limiting subsequent complications.

Skin and skin structure infections are most commonly caused by gram-positive organisms, including *Staphylococcus aureus* and *Streptococcus* species. "The increasing prevalence of methicillin-resistant *S. aureus* [MRSA] in the hospital and community complicates treating skin and skin structure infections," Rybak says. "An important concern is that MRSA is associated with a significant increase in cost of care."

For Rybak's study, eligible patients included adults between ages 18

and 85 who were admitted to the hospital with complicated skin and skin structure infections. Patients in the study's treatment arm were required to meet institutional criteria for receiving vancomycin, including established risk factors for MRSA. Matched controls (4:1 match) were selected from all patients with complicated skin and skin structure infections treated with vancomycin identified at a concurrent period of time in which data were available in medical records for all necessary clinical evaluations.

Treatment population

Of the 56 patients who were enrolled to receive daptomycin in the treatment arm, three were ultimately found to be not evaluable. So the research evaluated 53 patients who received daptomycin and 212 patients treated with vancomycin. "There were no significant differences noted in age, sex, severity of illness, comorbidities, or type of infection between the two groups," Rybak says. However, a significantly higher proportion of patients who received vancomycin was admitted to a surgical service and had a history of antibiotic use or hospitalization.

While all patients in both groups achieved clinical success by the end of therapy, a significantly higher proportion of patients who were treated with daptomycin achieved clinical success by days 3 and 5. Thus, according to Rybak, 90% of daptomycin patients showed clinical success at day 3 and 98% at day 5, compared with 75% of vancomycin patients at day 3 and 81% at day 5. And a significantly greater proportion of patients receiving daptomycin achieved clinical cure at the end of inpatient antimicrobial therapy (77% of daptomycin patients vs. 42% of vancomycin patients).

While the cost of antistaphylococcal therapy was greater by itself in patients treated with daptomycin than in those treated with vancomycin, because the cost to hospitals of branded daptomycin is much higher than the cost of generic vancomycin, the total cost of hospitalization still was reduced in the daptomycin group.

Overall resource use better with daptomycin

"Although no benefit in end-of-therapy mortality was seen," Rybak says, "overall resource utilization was reduced approximately $2,500 in patients treated with daptomycin, likely because of the shorter duration of intravenous antibacterial agents required for treatment. Despite the higher costs of daptomycin when comparing intravenous antistaphylococcal therapy alone, the cost between groups was similar when other inpatient antimicrobial agents were included in the analysis."

One explanation was the high cost of oral agents, often linezolid (Pfizer's Zyvox®), in patients who were initially treated with vancomycin and then transitioned to linezolid. "When considering total cost of hospitalization, treatment with daptomycin appears to be a cost-effective alternative," Rybak says. "One important limitation of this analysis was our inability to control for a higher prevalence of *S. aureus* and MRSA in patients receiving vancomycin, and it has been reported that patients with MRSA tend to have a longer length of stay than patients with

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcmedia.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $499. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $83 each. (GST registration number R128870672.)

AHC Media LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program, #381-000-08-094-H01-P, will be available **January 1, 2008-December 31, 2008.**

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methicillin-susceptible *S. aureus*."

Rybak says that while he would not say to hospitals that daptomycin should be considered the primary drug to be used in such cases, he believes hospitals should always consider it as an option.

Asked about the issue of antibiotic resistance, Rybak tells *Drug Formulary Review* it "can be a particular concern when one agent such as vancomycin has been relied upon for a long time. Vancomycin has been clinically available for close to 50 years and susceptibility to it has been significantly changing in the last 10-20 years. There have been some reports of resistance to daptomycin, and other alternative agents to vancomycin, but so far these cases have been infrequent. Resistance to daptomycin could increase in the future, but we now have several drugs for treating MRSA and don't have to rely on just one. This should ease the burden in relying only on vancomycin as our primary treatment for MRSA."

Rybak says physicians need to look at each patient individually in determining which drug to use, including each drug's safety profile, implications for possible drug interactions, and overall compatibility with each patient. "We need to use serious drugs to treat serious infections especially with a pathogen as problematic as MRSA," he concludes. ■

[Editor's note: Contact Dr. Rybak at m.rybak@wayne.edu.]

Medication management help HMO diabetes patients

Pharmacist recommendations shared with physicians

When pharmacists run diabetes management programs for HMO patients, the patients have better health outcomes than patients who are only monitored for long-term blood sugar control. That's the takeaway from a nine-month study that evaluated the effect of such pharmacist-run diabetes management programs.

Principal investigator **Lourdes Planas**, PhD, an assistant professor at the University of Oklahoma, College of Pharmacy, tells *Drug Formulary Review* the findings "help support the increasing role of proactive pharmacists. Pharmacists are proactively teaching patients to control their diabetes when they provide medication therapy management. They are teaching them about healthy eating habits and self-monitoring of blood sugar levels so they can be empowered to take care of their diabetes."

The study was funded by a grant from the ASHP Foundation. Planas presented it during the 2007 American Society of Health-system Pharmacists' midyear clinical meeting in December.

The research came about, Planas tells *Drug Formulary Review*, because her co-investigator, **Kimberly Crosby**, PharmD, wanted to find a way to document and evaluate medication therapy management with an eye to developing ways to formalize the practice so more health system patients could benefit from it. With the grant funding they received, they worked to set up a true experimental design through the Community Care HMO and pharmacists at the May Drug Stores.

Sixty-five participants enrolled in the study, with 38 in the intervention group receiving monthly medication therapy management services and 27 in the control group that received A1c monitoring every three months. All the patients entered the study with a hemoglobin A1c greater than 7.0%.

Changes in A1c levels and percentage of patients at goal A1c (less than 7%) were compared between the intervention and control groups after nine months of study participation. The incidence of drug therapy problems among intervention group participants also was reported.

Results from the 43 patients who completed the study included:

- Change in A1c was significantly greater in the intervention group than in the control group: mean A1c level of 7.65 in the intervention group at baseline and 6.95 at nine months, compared with control group levels of 7.74 at baseline and 7.98 at nine months.
- Change in percent of patients at goal A1c (less than 7.0%) was significantly greater in the intervention group than in the control group: 33% of participants in the intervention group were at goal at baseline and 58% at nine months, while the control group reported 16% were at goal at baseline and 11% at nine months.

Various services included

Medication therapy management services included diabetes education (the nature of the illness, how to manage it, how to use a glucose monitor, and dietary considerations); drug therapy

assessment, checking patients' blood glucose monitors, and foot care. Recommendations were forwarded to the patients' doctors.

Planas says that while the intervention group had monthly visits with the pharmacists, they probably didn't need to be seen that often. "Based on patient severity, they wouldn't need to be seen every month," she says. "We found it was difficult for people to make and keep appointments each month."

Both Community Care and the May drugstore chain were pleased with the study results, Planas says, and there is hope the HMO will carve out some payment for such services.

Of interest to other health plans considering implementing such a program, while preliminary cost-savings analyses were not statistically significant, the raw data show cost-savings as a result of the program. In the intervention group, Planas tells *DFR*, costs decreased $2,180 over the nine-month period, while in the control group costs increased $3,664. Costs for prescription drugs increased in both groups; for the intervention group they went up $241 and for the control group $369.

[Editor's note: For more information contact Dr. Planas at (405) 271-6878, ext. 47294.] ■

FDA urged to promote hospital RFID

Future lies in unit-dose packaging

InfoLogix CEO **David Guilan** says FDA should be involved in encouraging hospitals to adopt barcode and radio frequency identification (RFID) solutions to help prevent medication mix-ups such as occurred with actor **Dennis Quaid**'s children at Cedars-Sinai in Los Angeles. Quaid's twin newborns received 1,000 times the usual dose of heparin.

Guilan tells *Drug Formulary Review* that widespread adoption of the new technology will come through standardization and that FDA is needed to help pull that together. "We're very used to seeing and using UPC codes in grocery stores now," Guilan says. "But we're not seeing that yet in medical care."

According to Guilan, part of the problem is that drug companies ship their products in bulk and they then have to be repackaged into unit doses to be dispensed. The bulk bottle might be bar-coded, but each individual pill isn't, creating an opportunity for mistakes when pills are repackaged.

"The future lies in shipping products using blister-pack technology so that hospitals will not have to repack medications," he says. "And using RFID technology, a lot more information can be put on each package, right down to the temperature where the drugs are stored."

He says changes definitely are coming and that the Quaid case may push the issue over the top, although the technology still needs to mature a bit.

"We know there are 200,000 mistakes a year that are related to a patient's death," he says. "And yet only 20% of the hospitals are using bar-coding."

Guilan notes that RFID is a bit expensive today, but says it used to be thought that bar-coding was too expensive to pursue. Ultimately, he says, the question is, "How do you put a price on life?"

He notes that it probably costs hospitals as much to repackage drugs they receive in bulk as it would to change the technology. And he says he believes hospitals would be willing to pay more for drugs that would be delivered from the manufacturer in unit-dose packages.

"I expect we'll see this initiative in place in the next 24 months," Guilan tells *Drug Formulary Review*.

InfoLogix provides technology and RFID-based intelligence solutions to enable the mobile enterprise. The company says it uses the industry's most advanced technologies to increase the efficiency, accuracy, and transparency of complex business and clinical processes for the health care industry and the commercial marketplace.

[Editor's note: More information is available on-line at: www.infologixsys.com.] ■

Permanent CPT codes approved for MTM services

Codes enhance professional services for patients

The Pharmacist Services Technical Advisory Coalition (PSTAC) has obtained approval for permanent CPT codes for billing pharmacists' medication therapy management (MTM) services.

Pharmacist leaders say having the codes will expand pharmacists' ability to provide professional services to their patients.

CPT (Current Procedure Terminology) codes are approved by the American Medical Association as the nomenclature used by the health care industry to report professional services, laboratory tests, and medical procedures in health care claims. The new pharmacist codes, making permanent temporary codes that had been assigned, have new numbers and took effect January 1.

The new codes are:

• **Medication Therapy Management Service(s) (MTMS)**: describe face-to-face patient assessment and intervention as appropriate, by a pharmacist, upon request. MTMS is provided to optimize the response to medications or to manage treatment-related medication interactions or complications.

MTMS includes the following documented elements: review of the pertinent patient history, medication profile (prescription and nonprescription), and recommendations for improving health outcomes and treatment compliance. These codes are not to be used to describe the provision of product-specific information at the point of dispensing or any other routine dispensing-related activities.

99605: Medication therapy management service(s) provided by a pharmacist, individual, face-to-face with patient, with assessment and intervention if provided; initial 15 minutes, new patient.

99606: Initial 15 minutes, established patient.

99607: Each additional 15 minutes (list separately in addition to code for primary service).

PSTAC is a coalition of seven national pharmacy organizations including the American College of Clinical Pharmacy, the Academy of Managed Care Pharmacy, the American Pharmacists Association, the American Society of Consultant Pharmacists, the American Society of Health-system Pharmacists, the National Association of Chain Drug Stores, and the National Community Pharmacists Association.

The coalition has been successful at integrating pharmacists and their professional services into the traditional medical services billing model. PSTAC provides the national leadership necessary to secure pharmacy's position in the national electronic data interchange environment related to health encounter/claims processing and payment of pharmacist professional services. ■

Size matters—but not for clinical services

Though larger hospitals reported better efficiency

Further proof of the importance of clinical services to hospital pharmacist care comes in research from the University of Illinois that found that clinical services remain essentially the same no matter how big a hospital is, even when there are differences based on hospital size on a number of workload and productivity measures.

The research has implications for staff recruiting and retention because the results offer an understanding of the quality of care provided in smaller hospitals. While there has been a common assumption among pharmacists that larger hospitals are a more attractive place to work because they provide a greater variety of clinical pharmacy services, this research shows that smaller hospitals dedicate a proportionately equal amount of time and provide the same types of clinical services as do larger hospitals.

One goal of the study was to come up with comparative statistics pharmacy administrators could use to look at their hospital's efficiency when compared to other facilities of similar size. Another goal was to provide data policymakers could use in better determining staffing and resource needs.

Lead researcher **Glen Schumock**, PharmD, MBA, FCCP, director of the University of Illinois at Chicago's Center for Pharmacoeconomic Research, says little is known about how hospitals, which the American Hospital Association says range from six beds to more than 2,000 beds, differ with respect to pharmacy efficiency or scope of services by hospital size. The data were collected from a 50-item web-based survey sent to pharmacy directors at Consorta, Inc., member hospitals, a group purchasing organization that at the time comprised 60% of the nonprofit Catholic hospitals in the United States. Responses were received from 110 (45.5%) of the 242 surveyed organizations.

Schumock divided the respondents this way: Hospitals with fewer than 100 staffed beds were placed in the small hospital group, those with 100-300 staffed beds were considered medium hospitals, and those with more than 300 beds were placed in the large hospital category. The analysis covered 31 small hospitals, 48 medium

hospitals, and 31 large hospitals.

Respondents were asked to give the number of budgeted full-time equivalents (FTEs) for various positions within the pharmacy. Just about every hospital showed a budgeted position for a pharmacy director. Positions of clinical coordinator were related to hospital size. The number of FTEs considered clinical pharmacists was significantly smaller in small hospitals than in medium and large hospitals. But the difference between medium and large hospitals was not statistically significant. Schumock says this trend was not observed for the number of staff pharmacists, which was significantly different for all three groups, as were the numbers of FTEs in the positions of pharmacy buyer, technician, and secretary or administrative assistant.

Productive and paid hours weekly

Respondents were asked to report the total number of productive and paid hours per week for the entire pharmacy department. The three groups differed significantly for both values. Compared with small hospitals, medium hospitals had approximately four times more productive hours and large hospitals had approximately nine times more productive hours. For paid hours, medium hospitals had approximately four times more than small hospitals, and large hospitals had approximately eight times more than small hospitals.

Total staff time was also categorized by type of activity (drug dispensing, clinical, managerial, and other). There were significant differences in the allocation of staff time for drug-dispensing activities between small hospitals and medium and large hospitals (but not between medium and large).

Interestingly, the three groups did not differ significantly in the percentage of time allotted for clinical activities.

However, time spent on managerial activities was significantly different, with small hospitals spending the most time on managerial activities in contrast to medium and large hospitals. The remainder of staff time dedicated to all other activities was similar among the groups and included billing, secretarial and administrative assistant, and quality assurance activities among others.

Pharmacy dispensing workload was measured by the sum of the total doses administered, processed, billed, or dispensed per year. There was a significant difference among the three groups for number of doses.

Inpatient working hours

Schumock asked respondents about the total weekly hours of operation of the inpatient pharmacy and reports those hours of operation differed significantly among all three groups. The larger the hospital, he says, the more time the pharmacy is in operation.

Participants were given a list of common clinical pharmacy services and were asked to indicate which services their facility provided and to identify any other clinical services not listed.

There were no significant differences among the three groups in terms of the percentage of hospitals providing a specific service except for drug therapy monitoring, IV to PO switch programs, in-service education, and rounds with physicians

Pharmacy workload and productivity were assessed for each group of hospitals by a series of calculated ratios. Small and large hospitals differed significantly with respect to number of FTEs per 1,000 patient days and FTEs per 100 occupied beds. Small hospitals also differed significantly from medium and large hospitals with respect to number of FTEs per 1,000 adjusted patient days and FTEs per 1,000 pharmacy adjusted patient days

All three groups were significantly different in terms of the number of FTEs per 1,000 case-mix index (CMI)-adjusted patient days, while there were no significant differences among the groups in the ratios of FTEs per 1,000 doses dispensed per year, FTEs per 1,000 admissions, and productive hours per paid hours.

Calculated ratios for each size group

Pharmacy and hospital cost efficiencies were assessed for each hospital size group through a series of calculated ratios. There were no significant differences among the groups for any of the calculated ratios; however, there were noticeable trends within the ratios for each hospital size.

Generally, costs and hospital size are inversely related. Schumock says this was most evident for pharmacy personnel expenditures per occupied bed and per admission, pharmaceutical expenditures per admission, total pharmacy expenditures per admission, and total hospital expenditures per admission.

A direct relationship between costs and hospital size was observed for pharmaceutical expenditures per occupied bed and total hospital expenditures

per occupied bed. Total pharmacy expenditures per occupied bed decreased between small and medium hospitals ($30,080.23 and $28,056.68, respectively) and increased between medium and large hospitals ($30,726.83).

Schumock says he expected that many of the variables the researchers asked about would differ based on hospital size. But they found it interesting and potentially significant, he says, that small hospitals appeared to dedicate a proportionately equal amount of effort to clinical activities as do medium and large hospitals, with the overall percentage of staff time being the same for all three groups.

Further, they say, the scope of clinical activities provided in small hospitals was not greatly different from that provided by medium or large hospitals, with just a few services being provided more often in larger hospitals.

Larger facilities more efficient

The data do show, however, that as the size of the hospital increases, pharmacy departments become more efficient. In terms of productivity, larger hospitals had fewer FTEs per 1,000 adjusted patient days, fewer FTEs per 1,000 pharmacy adjusted patient days, and fewer FTEs per 1,000 CMI-adjusted patient days. Larger hospitals also had lower values for FTEs per 1,000 patient days and FTEs per 100 occupied beds.

These findings are not particularly surprising, according to Schumock and his colleagues, and are supported by data from the 2005 ASHP national survey of pharmacy practice in hospital settings.

In terms of costs, pharmacy and hospital expenditures per occupied bed and per admission generally decrease as hospital size increases.

One would expect that there are certain economies of scale with respect to staffing and costs that occur when the volume of work and patient population increase, the researchers say. ■

NEWS BRIEFS

ASHP fighting National Drug Code problems

The American Society of Health-system Pharmacists (ASHP) says it has intensified its fight against what it sees as a costly and burdensome requirement that hospital outpatient departments report National Drug Code (NDC) numbers. ASHP and Safety Net Hospitals for Pharmaceutical Access (SNHPA) said they have asked Congress to help resolve the issue. They asked the House Energy and Commerce Committee and Senate Finance Committee to secure an exemption from the Centers for Medicare and Medicaid Services' (CMS) rule that outpatient departments report the 11-digit NDC numbers on single-source drugs and 20 multiple-source drugs when submitting Medicaid claims. CMS has refused to grant the exemption. The Deficit Reduction Act requires states to collect NDC numbers to secure rebates on physician-administered drugs beginning Jan. 1, 2008. CMS ordered outpatient departments to comply with the rule.

In writing to the committees, ASHP and SNHPA questioned the accuracy of CMS' interpretation of the law governing Medicaid drug rebates, which currently exempts drugs administered by hospital clinics. ASHP also said it believes the requirement will be costly for outpatient pharmacy departments since many will have to upgrade technology to accurately report the NDC numbers.

Some 60% of health systems responded to an ASHP survey by indicating they did not have the information systems to report all the NDC numbers. While CMS estimated the cost to comply with the requirement at $ 0.09 per claim, ASHP's survey

COMING IN FUTURE MONTHS

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found an estimated cost of $10.80 per claim. ■

Chain store druggist says firing caused by Plan B

A Target store pharmacist who opposes abortion says the chain fired him for refusing to fill prescriptions for the Barr Pharmaceuticals Plan B emergency contraceptive. In a suit filed in Detroit federal court, **Brian Bundy** said that "as a result of his sincerely held belief that life begins at conception, [he] cannot dispense a drug that would terminate that life if used."

Bundy says he informed Target of his strong Christian beliefs before he was hired in April 2006 and was told he could refer customers wanting Plan B to another pharmacy. He was fired seven months later after Plan B became available over-the-counter to customers older than age 18. He says he did not want to dispense it with or without a prescription and the company insisted he dispense it to OTC customers.

A Target spokeswoman said the store values the diversity of its pharmacists and their religious beliefs but also has an obligation to meet the needs of its customers, especially health care needs. She said the company's policy on Plan B sales accommodates both pharmacist religious beliefs and customer needs, but would not state the policy for the Detroit News, citing the pending litigation. Legal observers say no cases involving refusal to dispense Plan B have yet been decided by a federal appeals court. ■

No increased Nexium/Prilosec heart risk

FDA says its comprehensive, scientific review of known safety data for AstraZeneca's gastroesophageal reflux disease (GERD) drugs omeprazole (Prilosec®) and esomeprazole (Nexium®) did not find an increased risk of heart problems.

FDA says it recommends that health care providers continue to prescribe and patients continue to use the products as instructed in their labeling.

FDA looked at two long-term studies that did not specify how heart problems, such as heart attacks, were defined or verified. As a result, the agency says, evaluating the information that was gathered about the safety of both drugs in the studies was challenging. The assessment of the information from the data gathered was further supported, FDA says, by an additional analysis of 14 comparative studies of omeprazole, four of which were placebo-controlled.

Although those studies were not specifically conducted to assess the risk of heart problems, and patient follow-up was incomplete, they did not suggest an increased risk of heart problems with using omeprazole and esomeprazole. ■

DRUG CRITERIA & OUTCOMES™

Antifungal agents: A bad reputation for drug interactions

By **Michele Bryant**, PharmD Candidate, Samford University

Advances in drug therapy over the last few decades have revolutionized the management of many common disease states. With these advances, the incidence of polypharmacy, or the concomitant use of multiple medications in a patient, has become a more common occurrence. Unfortunately, this can lead to drug interactions that cause a decrease in the effectiveness of medications or result in adverse drug reactions.

Antifungal agents have been notoriously associated with many drug interactions, but it is difficult to determine which drugs cause clinically significant drug interactions. To help make this process less complicated, the individual classes of antifungal agents can be evaluated based on mechanisms and types of interactions.

Most drug interactions can be characterized as either pharmacodynamic or pharmacokinetic interactions.[1] Pharmacodynamic interactions involve additive or antagonistic pharmacologic effects and are usually rapid in onset, although some will present more slowly.[2] Pharmacokinetic interactions involve interactions that interfere with four main processes: absorption, distribution, metabolism, and elimination.[1] These types of interactions are usually less predictable than pharmacodynamic interactions due to the variability of individual patients.[2] The most serious pharmacokinetic interactions with systemic antifungal agents occur by the inhibition and induction of cytochrome P450 (CYP) enzymes, the major enzymes in the liver that metabolize active substances not endogenously produced.[1]

Azole Antifungal Agents

Typically, the most well known drug interactions with antifungal agents occur with the "azole" antifungal agents. These agents act by inhibiting ergosterol synthesis in the fungal cell membrane by interacting with 14-alpha demethylase, a cytochrome P450 enzyme that is necessary for the conversion of lanosterol to ergosterol, an essential component of the membrane.[3] Azole antifungals cause clinically significant drug interactions because they inhibit the elimination of various drugs by competition for the CYP3A4 enzyme, a major enzyme in human cells involved in the hepatic metabolism of many drugs.[1] Through this mechanism, the clearance of the affected drugs is decreased and blood concentrations are elevated, meaning that the pharmacological effects of the affected drugs are prolonged and dose-dependent toxicity is increased.[1]

There are two groups included in the azole antifungal agents: the imidazole group, which includes ketoconazole (Nizoral®), clotrimazole (Mycelex®), and miconazole (Monistat®), and the triazole group, which includes itraconazole (Sporanox®), voriconazole (VFEND®), posaconazole (Noxafil®), and fluconazole (Diflucan®).

Ketoconazole, itraconazole, and voriconazole are strong inhibitors of the CYP3A4 enzyme, with ketoconazole being the strongest, and these agents all show similar drug interaction profiles.[1] While blood concentrations of any drug that is heavily metabolized by the CYP3A4 enzyme could potentially be affected by the concomitant use of ketoconazole, itraconazole, or voriconazole, there are some interactions that are more clinically significant.

A life-threatening interaction with these three azoles may occur due the inhibition of the metabolism of dofetilide and quinidine, and the use of these medications concomitantly has been associated with QT prolongation and torsade de pointes.[1-3]

The use of ketoconazole, itraconazole, and

voriconazole with HMG-CoA reductase inhibitors (i.e., statins) that are metabolized through the CYP3A4 enzyme system, which includes simvastatin, lovastatin, and atorvastatin, could substantially increase the risk of developing myopathy, rhabdomyolysis, and acute renal failure.[2,3] If no alternative to a short course of treatment with a systemic azole antifungal is available, it is recommended to suspend the statin therapy during treatment with the azole antifungal.[2,3] Pravastatin is not metabolized by the CYP3A4 enzyme; therefore, it could be used with patients when longer treatment periods with these drugs are necessary.[3]

Ketoconazole, itraconazole, and voriconazole also significantly impair the clearance of oxidatively metabolized benzodiazepines, such as alprazolam, midazolam, triazolam, diazepam, and clonazepam.[2,3] Lorazepam, oxazepam, and temazepam may be the safest alternatives to use concomitantly with these medications since these drugs are not oxidatively metabolized.[2,3]

Ketoconazole, itraconazole, and voriconazole used concomitantly with fentanyl (i.e., transdermal patches) can result in respiratory depression, and other analgesics not metabolized by CYP3A4 (e.g., codeine, morphine, tramadol) should be used instead.[2]

Narrow therapeutic index drugs that may be affected by administration of azole antifungals include digoxin, phenytoin, and warfarin; therefore, close monitoring of these medications should occur during treatment with this group of drugs.[1-3]

Use of corticosteroids with ketoconazole, itraconazole, and voriconzole can lead to increased plasma concentrations of the steroids, especially methylprednisolone and budesonide, thus amplifying the immunosuppressive and adverse effects of the steroids.[2,3] Prednisolone and prednisone pharmacokinetics seem to be less susceptible to CYP3A4 inhibitory interactions with ketoconazole than methylprednisolone.[2,3]

These azole medications may also interact with the following antiretroviral agents: protease inhibitors, including darunavir plus ritonavir, indinavir, and nelfinavir; and non-nucleoside reverse transcriptase inhibitors, including delaviridine, efavirenz, and nevirapine.[3,4] These agents may still be used concomitantly; however, dosage adjustments may need to be made.[4]

The oral bioavailabilities of these three azoles require an acidic environment for solubility. Histamine-2 (H2) antagonists, proton pump inhibitors, antacids, didanosine (ddI, powder and tablet), which contain acid buffers, have been shown to reduce plasma concentrations of these agents.[3] Intraconazole may also inhibit the metabolism of vinca alkaloids resulting in increased or prolonged peripheral neuropathies and ileus.[2,3] Similar adverse effects may be seen with the other azole drugs, although this is not as well documented.

The use of voriconazole and long-acting barbiturates is a contraindication, and caution is advised when using voriconazole with short-acting barbiturates as well.[2,3]

Finally, renal toxicity may be increased with the concomitant use of cyclosporine or tacrolimus and ketoconazole, itraconazole, or voriconazole.[1,3]

Although miconazole and clotrimazole are in the same class of antifungal agents as ketoconazole, these agents have significantly fewer drug interactions than ketoconazole. However, the uses of miconazole or clotrimazole are mainly limited to topical or vaginal application, thus significant drug interactions are uncommon.

Fluconazole and posaconazole interfere with the CYP3A4 enzymes to a lesser extent than ketoconazole, itraconazole, and voriconazole. In fact, posaconazole has the least amount of drug interactions in the azole class of antifungal agents.[2,3] However, fluconazole and fentanyl used concomitantly can result in respiratory depression and terbinafine (Lamisil®) should be considered as an alternative agent.[2]

Although the life-threatening interactions (i.e., interactions with dofetilide and quinidine) with fluconazole and posaconazole are classified as the same severity level as itraconazole and voriconazole, most other interactions are usually classified as a lower severity level.[3] The same common interactions may occur with fluconazole and posaconazole as with the other azoles, but to a lesser degree.

Polyene Antifungal Agents

Polyene antifungals, which include amphotericin B (Amphocin® conventional, AmBisome® liposomal, and nystatin [Mycostatin®] lozenge), work by binding to sterols in the cell membranes of both fungal and human cells. Amphotericin B and nystatin are usually fungistatic in vivo but may have fungicidal activity at high concentrations or against extremely susceptible organisms.[3] Most pharmacodynamic interactions caused by antifungal agents are commonly caused by amphotericin B, and the most serious interactions that can occur are nephrotoxic interactions with

agents such as antineoplastic agents, aminoglycosides, cyclosporin, salicylates, vancomycin, and zidovudine.[1,3]

Amphotericin B can also induce hypokalemia that may potentiate the cardiac toxicity of cardiac glycosides (e.g., digoxin), cisapride, and dofetilide, and it may also enhance the curariform effect of neuromuscular blockers.[1,3] These phenomena are found to be true with both the conventional and lipid formulations.

Nystatin has poor absorption through the gastrointestinal tract when administered orally; therefore, it is used topically in most cases. There are no significant drug interactions with nystatin when used topically.

Echinocandin Antifungal Agents

The echinocandins are a unique group of antifungal agents, which includes caspofungin (Cancidas®), anidulafungin (Eraxis™), and micafungin (Mycamine®). This group of antifungal agents acts by inhibiting the synthesis of a major fungal cell wall component, beta (1,3)-D-glucan, which is not present in mammalian cell walls.[3] The echinocandins are administered by intravenous infusion; therefore, many drug interactions that would occur in the gastrointestinal tract are eliminated. The great advantage of this group, however, is that these agents do not inhibit any enzyme in the cytochrome P450 enzyme system; therefore, drug interactions caused by competition of these enzymes should be eliminated.[3]

Evaluating these agents individually, micafungin was shown to increase the systemic exposure of sirolimus and nifedipine, but the mechanisms of the interactions are not known.[2,3] Patients receiving micafungin and either of these agents should be monitored for signs of toxicity, and the nifedipine dosage may need to be reduced.[2,3]

Micafungin has also caused leukopenia, neutropenia, anemia, and thrombocytopenia; therefore, concomitant use with immunosuppressive agents would warrant the monitoring of patients.

Caspofungin use with cyclosporine could lead to elevated levels of aspartate transaminase (AST) and alanine transaminase (AST).[2,3] Drugs that may lead to reduced concentrations of caspofungin include carbamazepine, dexamethasone, efavirenz, phenytoin, fosphenytoin, nelfinavir, nevirapine, or rifampin.[3] Caspofungin use with tacrolimus may cause reduced concentrations of tacrolimus.[3]

Anidulafungin use with cyclosporine resulted in an increased concentration of anidulafungin in clinical studies.[3] Also, in clinical studies, no dosage adjustments were needed when anidulafungin was administered with tacrolimus, voriconazole, rifampin, or liposomal amphotericin B.[3]

Allylamine Antifungal Agents

The allylamine group of antifungal agents, which includes terbinafine and naftifine (Naftin®), interfere with fungal sterol biosynthesis by inhibiting the enzyme squalene monooxygenase, a key enzyme in sterol biosynthesis in fungi. The accumulation of squalene weakens the cell membrane in sensitive fungi. The inhibition of squalene monooxygenase creates a deficiency in ergosterol, a component of fungal membranes necessary for normal growth.[3] While terbinafine has a great advantage for systemic use due to its lack of inhibition of the CYP3A4 enzyme, terbinafine has been shown to inhibit the CYP2D6 enzyme. Therefore, terbinafine may inhibit the clearance of drugs that are metabolized by the CYP2D6 enzyme, such as certain beta-blockers (e.g., metoprolol, carvedilol, propranolol), certain antiarrhythmics (e.g., flecainide, propafenone, ecainide), clozapine, codeine, fluoxetine, haloperidol, tricyclic antidepressants, meperidine, and oxycodone.

The general classifications of the interactions with these medications were typically only moderate to low in severity, with the exception of the antiarrhythmic agents flecainide, propafenone, and ecainide, which are classified as more severe.[2,3] However, the concomitant use of thioridazine and terbinafine is contraindicated.

The topical use of terbinafine has been shown to be unlikely to have any significant drug interactions.[3] Naftifine is used as a topical agent for dermatological use only and is an unlikely cause of any significant drug interactions.[3]

Miscellaneous Antifungal Agents

The remaining antifungal agents, griseofulvin (Grifulvin® V) and flucytosine (Ancobon®), do not belong to a specific antifungal class. Griseofulvin acts by disrupting the mitotic spindle structure of the fungal cell, which causes an arrest of metaphase of cell division.[3] Griseofulvin can decrease the effectiveness of warfarin and oral contraceptives by enhancing the hepatic metabolism of these medications; recommendations include enhanced monitoring of prothrombin time while taking warfarin and using alternate forms of contraception while taking griseofulvin and for one month after the drug is discontinued.[1,3]

Flucytosine acts by penetrating the fungal cells, where it is deaminated to fluorouracil by the fungal enzyme cytosine deaminase. Acting as an antimetabolite, fluorouracil competes with uracil, interfering with pyrimidine metabolism and eventually disrupting both RNA and protein synthesis of the fungal cell.[3] Flucytosine can cause significant hematologic toxicity, and enhanced myelosuppression may occur with antineoplastic agents, especially cytarabine.[1,3] Other blood dyscrasia-causing medications, such as clozapine, carbamazepine, and phenothiazines, should be used cautiously with flucytosine.[3]

Conclusion

Antifungal agents have been implicated in many cases of drug interactions mainly due to the enzymatic inhibition and induction caused by certain agents in this group of medications.[1] Although relatively few agents are most problematic, practitioners should use antifungal drugs with extreme caution due to the potential for clinically significant drug interactions.

When considering an antifungal agent, the practitioner must look at each patient case individually. It is imperative to evaluate the other medications that the patient is receiving in anticipation that there may be possible issues with drug interactions.

Each patient may also vary in the metabolism patterns of drugs; therefore, the predictability of a drug interaction in different individual patients may vary.[1] Finally, when considering treatment with an antifungal agent or any other antimicrobial agent, one must consider the susceptibility of the presumed pathogen to the antifungal agent.

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5. Pharmacokinetic interactions involve interactions that interfere with which of the following processes?
   A. Absorption
   B. Distribution
   C. Metabolism
   D. Elimination
   E. All of the above

6. The most serious pharmacokinetic interactions with systemic antifungal agents occur by the inhibition and induction of cytochrome P450 (CYP) enzymes, the major enzymes in the liver that metabolize active substances not endogenously produced.
   A. True
   B. False

7. The most well known drug interactions with antifungal agents are interactions that occur with which of the following antifungal agents?
   A. The allylamine antifungal agents
   B. The azole antifungal agents
   C. The echinocandin antifungal agents
   D. The polyene antifungal agents

8. Most pharmacodynamic interactions caused by antifungal agents are caused by:
   A. amphotericin B.
   B. caspofungin.
   C. micafungin.
   D. terbinafine.