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Experts push the systems approach to reduce hospital medication errors

Bringing pharmacists and patients together critical to success

A general consensus has emerged among national pharmacy organizations and academic researchers on the merits of a systems-based analysis of medication error correction and prevention. Now, selling the approach to hospital administrators, pharmacy directors, and the rank and file is at hand.

Richard Cook, MD, director of the National Patient Safety Foundation's cognitive technologies laboratory at the University of Chicago, has researched and written extensively on patient safety, complex system failures, and human performance. He acknowledges that the "systems approach" seems to contradict a lot of commonly held assumptions and that it sometimes meets with a great deal of resistance, largely because it seems easier to blame the individual than to change long-held procedures.

"We're all Stalinists," Cook says, "because we want to blame individuals instead of fixing the system. Stalinists thought their system was perfect but that people kept trying to sabotage it. We see modern health care in the same way: as a perfect world except for the people messing it up. In reality, it is the opposite. The world is full of hazards, and people actually work to make it safer."

According to proponents of the systems approach, one of the main reasons accidents are often blamed on human error is "hindsight bias." Because investigators already know an accident happened, they tend to think practitioners should have seen it coming.

One of the classic examples of a systems failure is in cases of drug-drug reactions. Studies have shown that by the time a patient receives a medication, coordination and review of that patient's medical history have not made it from records to pharmacy to nursing, if the history was adequately compiled to begin with. Any resulting adverse reaction often leads to finger-pointing. In many cases, simply linking departmental computers would have been a workable systems solution because it

would allow any medication concerns in a patient's medical history to be highlighted along the way.

In terms of automation, observational studies have found that 24-hour dispensers or storage cabinets often are checked less frequently as technology has advanced. In the past, caregivers could check each other's work. More recently, it's been shown that automated dispensers are checked more frequently at the front end, when bulk drugs are loaded, but less frequently at the back end, when medications are placed in patient envelopes.

Failures beget complexity

Cook says organizations tend to react to failure by "blaming and training." There's a call for sanctions and new regulations, rules, and technology. Those interventions can make the system even more complex and introduce new forms of failure. The whole cycle then repeats itself. The point is not to add another layer of protocol, but to see where the existing system failed, he explains.

"When we actually look at the details, we find out that failure occurs differently than the way we thought," says Cook. "So the solutions may be different, too. Many of the things we often propose to do have side effects, like computer order-entry systems, bar coding, things like that. They can improve system performance, but they come with their own problems as well."

Due to advances in automation, systems analyses have been championed largely by pharmacy. One of the first major documents to shed light on the pros and cons of automation and medication errors as part of the systems analysis was the White Paper on Automation in Pharmacy, which was detailed in the February 1999 issue of *Drug Utilization Review.* The document was commissioned by a coalition of seven national pharmacy organizations.

"In the pharmacy world, there is already a movement to simplify the systems — to have smaller formularies, for example," Cook says. "There's an awareness of the problems caused by drugs with sound-alike names. We know the visual identification of drugs is made more difficult when you switch suppliers, but we switch suppliers all the time. [The process of systems analysis] is an ongoing activity. What effect each possible change will have on safety is the subject of hot debate."

The Institute for Safe Medication Practices (ISMP) in Warminster, PA, is actively engaged in the process. The agency often is asked to perform systems analyses of the medication process for health care organizations. ISMP has identified 10 common weaknesses in medication systems and categories that include patient information; drug information; communication of drug information; labeling, packaging, and drug nomenclature; drug storage, stocking, and standardization; drug device acquisition, use, and monitoring; environmental stressors; competence and staff education; patient education; quality processes; and risk management.

ISMP president **Michael Cohen** says when his agency goes into a hospital to do a systems analysis, every facet is covered.

"We spend three days at the hospital. We speak to everyone: nurses, doctors, and pharmacists. We go into the operating rooms, we go through the computer system, we look at all the records to see how well they are communicating drug orders. We'll ask the nurses how they communicate drug information to patients. Our reports are quite detailed, and they're up to 30 to 40 pages long. We focus on the system, not the staff. We don't single anyone out. It is a completely objective review, which is very helpful."

How is information shared?

Cohen says it is crucial to make sure everyone involved in patient care has access to complete patient and drug information.

"When you look at an error, you have to ask whether you had all the information you needed. Was it because you didn't know the patient had kidney disease, for example, and therefore got the wrong drug? Even something like not having the correct patient bed number can matter."

According to the National Consumers League, lack of information about drugs is one of the main reasons almost 50% of American patients do not comply with their medication regimes. ISMP found that pharmacy staff are not routinely involved in direct patient education. It recommends the implementation of automatic educational consultations by pharmacists when patients are receiving certain classes of medications or being discharged on more than five medications.

Similarly, ISMP found that pharmacists often are unavailable for face-to-face communication on patient care units, meaning they are not present when medication is prescribed and administered — the stages when errors occur most often. ISMP therefore recommends moving the pharmacist into patient care areas.

Recent studies have demonstrated the benefits of such communication, including one published in the *Journal of the American Medical Association* over the summer (1999; 282:267-270) and covered in *DUR* last month. Researchers led by Lucian Leape, MD, of the Harvard School of Public Health, found that when pharmacists went on rounds in the intensive care unit, medication errors were reduced substantially. **(See *DUR*, November 1999, p. 168, for details.)**

"Communication by direct contact is a much more reliable system than entering information into a computer."

Cook points out that many system fixes are a matter of providing for quality face-to-face communication. "We tend to use the computer as a communications device or fancy telex, which is why studies like Leape's are so interesting. Communication by direct contact is a much more reliable system than entering information into a computer and expecting people who receive the information to understand what you are doing and why you are doing it, with no context. That is why Leape's research is so attractive. There's a real important lesson in that kind of study: People make safety, not technology."

ISMP's findings support that lesson. The organization reports that policies for handling conflicts over medication use often are ineffective or absent. Moreover, it found that flawed communication contributes to some 10% of the serious errors that occur during drug administration. It recommends that institutions develop a process that clearly specifies the steps practitioners should take to resolve drug therapy conflicts.

Other recommendations involve the dispensing of medications. ISMP warns that removing drugs from labeled containers and putting them in cups for administration greatly increases the chance the medication will be given to the wrong patient. The agency recommends using original containers throughout the entire process, right up to administration.

A critical eye on automation

Another issue is the use of automated dispensing technology. ISMP says the lack of safety procedures and inadequate check systems can result in storage errors. The organization also says medications should not be available routinely for administration to patients without appropriate order screening by pharmacists.

Cohen agrees with Cook's statement that technology meant to improve safety sometimes can have the opposite effect.

"Over the last year, we had 20 reports related to IV infusion pumps used to administer critical care drugs. The manufacturers have put in a little computer where you enter the patient's weight, the dose ordered by the doctor and the concentration of the drug, and the rate is calculated for you. This was designed to reduce errors, but using it actually can increase them, because you have to make three separate entries. The technology made the system more complex instead of simplifying it."

There's another consideration most practitioners will be able to relate to, particularly staff who transcribe orders: environmental stressors. When transcribing is done in an area with a high frequency of noise, interruptions, and constant activity, ISMP says the process is vulnerable to slip-ups. It cites a study that found those distractions are responsible for three quarters of transcription or computer-order entry errors.

The health care system is already complex, and it is becoming even more so. Cook says the health care system is constantly changing at all levels: organizational, technical, managerial, social, and political. Those levels affect each other, so improving safety depends on understanding those interactions. People are adapting to the changes all the time, so the system is in a constant state of flux. To improve safety, health care providers, including pharmacists, must try to anticipate the impact of those changes and act on them.

SOURCES

- **Richard Cook**, MD, Director, Cognitive Technologies Laboratory, National Patient Safety Foundation, University of Chicago. Telephone: (773) 702-1234. Web: www.npsf.org
- **Michael Cohen**, MS, FASHP, President, Institute for Safe Medication Practices, Warminster, PA. Telephone: (215) 947-7797. Web: www.ismp.org.

"Pharmacy is moving toward a knowledge-based role and away from the traditional role of dispensing medications. This is part of the shifting professional base. Safety is created by what you do in your work everyday, not by the technology or policies. Safety emerges from the technical work that you do," Cook says.

[Editor's note: To receive a reprint of the White Paper on Automation in Pharmacy, contact lead author Ken Barker, PhD, Department of Pharmacy Care Services, Auburn (AL) University. Telephone: (334) 844-5152.] ■

Gender-specific health care new but growing

Pharmacy a leader on informational front lines

"Women are not just small men." That may seem obvious, but **Marianne J. Legato**, MD, FACP, founder and director of the Partnership for Women's Health at Columbia University in New York City, says that's how the health care industry has viewed women for years. Legato says medical researchers and health care providers must begin to consider the fact that differences exist between the sexes in virtually every system of the body, and use that information to tailor health care to specific needs.

Legato led a panel discussion on gender-specific medicine at the October conference of the Academy of Managed Care Pharmacy held in Atlanta. "The goal should be to use the differences between men and women to improve our current models of health and illness and to enable us to develop more effective remedies to prevent and treat illness," she says.

Gender-specific medicine is still in its infancy, but some of the first and best information has come from pharmacy. "Pharmacy gives us good information on how women metabolize drugs," Legato explains. "Medicine is behind in learning about the differences between women and men."

Phase I clinical trials long have been conducted primarily on the male population. Dosages and therapies were designed for the male body and prescribed for women without any consideration of gender and the effects it might have.

The U.S. Food and Drug Administration mandated the inclusion of women in drug trials in 1993, and the National Institutes of Health published its *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* in 1994.

"We have to address these difficult ethical and liability issues."

Women still are underrepresented in clinical trials, however, and Legato says researchers have not yet come to terms with the thorny ethical issue of conception and pregnancy during a drug study.

"I think we have to reconsider the way we study drugs in both men and women. We have to address these difficult ethical and liability issues. And until we can come up with some better alternatives such as computer modeling or using tissue parts instead of the whole patient, we aren't going to make much progress."

Legato praises some drug companies for getting on board, whether their interests are ultimately financial or altruistic. Her work at Columbia, for example, much of which has focused on cancer research, is funded largely by Procter & Gamble.

"Companies are interested because gender differences will affect the way they develop drugs, since they must now include women," she says, adding that there are commercial opportunities for pharmaceutical companies to adapt existing products to address gender differences and to develop gender-specific products.

Ruth Merkatz, PhD, RN, CDE, says Pfizer is taking advantage of those opportunities. It did extensive research on how the selective serotonin reuptake inhibitor Zoloft affected men and women when used to treat post-traumatic stress disorder. She is the director of the Women's Health team at Pfizer Inc. and is on the scientific editorial board of *The Journal of Gender-Specific Medicine* (*JGSP*), where Legato is the editor-in-chief.

"In this case, some studies showed it worked much better in women than in men for this condition, although it has been recommended for use in both genders. The discussion really focused on whether we are really looking at a different mechanism of the disease in women and men. So for me, it was exciting to see this work really making a difference."

Merkatz says the 1990s have been revolutionary in terms of broadening the way drugs are tested and understanding the physiological differences between men and women and how to treat diseases in both genders. Advocates of gender-specific medicine say more changes and research are needed.

Inside the pharmacokinetics

Mary J. Berg, PharmD, is a professor at the College of Pharmacy at the University of Iowa in Iowa City. She's also on the scientific editorial board of *JGSP,* which includes a regular feature on drugs and gender. Berg writes in the September 1998 issue that pharmacokinetics and pharmacodynamics should be studied together to form the basis of solid gender-specific pharmacology, instead of considered separately, as they traditionally have been.[1]

"This is because a medication may have a shorter half-life but greater sensitivity in one of the sexes that requires no difference in dosage between men and women. With methylprednisolone, for example, the pharmacokinetic parameters of clearance and half-life are faster in women, thereby causing lower levels of the drug in women as compared with men.

"However, the pharmacodynamic measurement of cortisol suppression requires smaller levels of methylprednisolone in women, making females far more sensitive to the effects of this drug. Therefore, despite the gender differences between pharmacokinetics and pharmacodynamics, men and women should receive the same dose of methylprednisolone normalized for weight," she writes.

Janice Schwartz, MD, is professor of medicine and chief of clinical pharmacology and geriatric medicine at Northwestern University Medical School. She's also a contributor to *JGSP.* In the September / October 1999 issue, Schwartz writes, "We are increasingly recognizing that the physiologic differences between men and women result in altered responses to drugs in women compared with men. This is an exciting and rapidly evolving area."[2] She summarizes some of the emerging data on gender-related differences in response to pain medication, specifically opioids, nonsteroidal anti-inflammatories, selective cyclooxygenase-2 (COX-2) inhibitors, and other agents. Her focus is on the clinical consequences of those data.

She found that with opioids, pain relief with fewer side effects than morphine-like medications may be achieved with kappa-opioids in women but not men, and that quantitative differences in responses to NSAIDs may occur in men and women. COX-2 inhibitors are effective in both genders, but women are more likely to have sulfa allergies, which are a contraindication to these drugs. Schwartz concludes that no gender-related differences have been found in response to topical lidocaine. "These differences suggest the importance of developing gender-specific strategies for pain relief, and highlight the need for further investigation of gender-related pain treatment strategies."

Direct to consumer

Another concern is simply getting the information out. "We're trying," says Legato. "We have a series of pamphlets available for patients, and we're involved in educational campaigns. I talk to women all over the country. They love the information. I think it is sometimes a reflex for physicians to tell a woman, 'I've never heard of that, so you must be hysterical or something.' I think women are now more confident about pushing for answers and better information."

Merkatz agrees. "The era of women just going to a doctor and being told what to do is over. In terms of the drugs they take, I think they should know the name; they should know why they are taking it and what the side effects are. My real

SOURCES

- **Marianne J. Legato**, MD, FACP, Founder and Director, The Partnership for Women's Health at Columbia University, New York, NY. Telephone: (212) 305-9514.
- **Ruth Merkatz**, PhD, RN, CDE, Director, Women's Health Team, Pfizer Inc., New York City. Telephone: (212) 733-2721.
- **The Partnership for Women's Health**. Web: partnership.hs.columbia.edu.
- ***The Journal of Gender-Specific Medicine***. Web: www.mmhc.com/jgsm/index.shtml.

goal is for them to ask the doctor or pharmacist if the drug has been tested in women as well as men, and whether there are differences in the way the drug will affect them in comparison [to men]."

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Managed Care Spotlight: A Case Study

Pharmacist counseling of at-risk Medicare patients

Merging MCO, PBM efforts retains members

Surveys of Medicare beneficiaries indicate they want drug benefits. Officials at Diversified Pharmaceutical Services in Bloomington, MN, say 75% of Medicare beneficiaries choose to enroll in managed care plans just to get that coverage. They say out-of-pocket drug costs are a key determinant of health care consumer satisfaction and that the exhaustion of the drug benefit doubles the member disenrollment rate.

From the provider's perspective, the pharmacy benefit can be a double-edged sword.

"If you give patients medication, it will keep them out of the hospital," says **Patricia Flannery**, BSN, is senior director of Health Systems for United HealthCare. "So you are hoping for a cost offset in the future. However, we want to retain patients, and they disenroll when they hit the limit, no matter what that limit is. So we have to find a way to manage the benefit and retain the patient."

Many managed care organizations are struggling with the pharmacy benefit and with their Medicare strategies. Some want to drop the benefit, while some are trying to manage it better and keep costs down. But the reality is that the pharmacy benefit is often the first thing to be cut.

After consulting with its medical directors, pharmacy managers, sales directors, members, and physicians, United HealthCare decided it would try to approach pharmacy as a service provided by processes that can be improved. That's different than thinking of pharmacy as the place where subscribers pick up drugs. Working with its prescription drug benefit manager, Diversified Pharmaceutical Services, the firm set out to develop a program that would integrate with overall care coordination, decrease medication costs, and increase patient satisfaction. That program was called "Rx for Healthy Living."

To make it work, the agency had to be specific about what population would benefit the most and how to reach it. United HealthCare serves some 440,000 Medicare beneficiaries. Research indicated Medicare members taking five or more different prescription drugs were most likely to miss prescription refills, take incorrect dosages, or mix incompatible medications. Those members, identified through pharmacy data, became the focus of the program.

The company sent those patients surveys designed to assess how they were taking their medications and whether they were experiencing any difficulties with them. About half of them responded.

"A clinical pharmacist would review each survey profile and make recommendations. The profile gave them access to more information than they could get from claims. It gave them prescription information, along with information on over-the-counter drug usage, vitamins, and herbals, since we find more and more cases of herbals interacting with prescription medications. They also were able to get detailed information on how these patients were taking their medications, whether they miss doses, and whether they understand why they are taking their medications," says **Raymond Brown**, PharmD, MS, director of specialty clinical services at Diversified Pharmaceutical Services.

Responding to patient needs

Members then were offered intervention on three levels, depending on the severity of their situation. These measures could be taken individually or in combination, according to the needs of the patient:

1) Members receive a follow-up letter from a pharmacist, with tips and recommendations on taking their medications.

2) Members receive a phone call from the pharmacist to discuss their medication issues.

3) Physicians are sent information on the

patient's drug use, including notice that incompatible medications are being mixed.

Of the members who chose to participate, 45% required a consultation, and 15% had serious clinical issues.

"The average consultation resulted in four recommendations," says **F. Everett Neville**, PharmD, director of senior clinical programs. "Two were cost-related, like switching to generics. Cost was the primary concern of members, since most do not have unlimited benefits and many say they don't take their medications because they can't afford them." The other major recommendations concerned evaluations of whether multi-drug regimens could be decreased or whether drugs were being adequately used.

Specific cases

The cases included a patient who was on the diuretic furosemide at a daily dose of 40 mg but was not taking potassium. The patient had a prescription for potassium, but hadn't filled it because he didn't know what it was for.

Another could not afford her medication, so the pharmacist recommended generic alternatives to her physician. The physician agreed to most of the recommendations, and the patient was able to afford the drugs. Overall, 90% of the patients said they felt the program was helpful, and 96% said they wanted it to be continued. United HealthCare has continued the program, even as it analyzes the quantitative data, including the return on investment for readmission rates.

Officials say Rx for Healthy Living may be expanded to include patients referred by nurse care coordinators, along with those identified through the pharmacy data.

"It is a matter of being able to get an open dialogue going between patients and clinicians," says Brown. "To do this, you have to make it as easy as possible for the patient. It is just basic good use of pharmacy skills to open that dialogue."

The program required the use of three staff pharmacists who exclusively communicated with plan members, and one staffer to make calls and set up consultations. They used a computer program to track the data. The company initially sought to hire pharmacists with experience in counseling and consulting, but it now offers a training course and peer review sessions to existing staff. ■

SOURCES

- **Patricia Flannery**, BSN., Senior Director, Health Systems, United HealthCare, Edina, MN. Telephone: (612) 936-1300.
- **Raymond E. Brown**, PharmD, MS, Director, Specialty Clinical Services, and **F. Everett Neville**, PharmD, BS, director of Senior Clinical Programs, Diversified Pharmaceutical Services, Bloomington, MN. Telephone: (612) 820-7000.

Groups collaborate to update AMI guidelines

For the first time since 1996, the American Heart Association and the American College of Cardiology have worked together to update management guidelines for acute myocardial infarction (AMI).

The new guidelines include increased support for the use of beta-blockers in patients with left ventricular failure and suggest that beta-blockers be considered for patients in whom MI has occurred without ST segment elevation.

Also in the absence of ST segment elevation in patients with acute MI, the guidelines recommend that either subQ low molecular weight heparin or IV unfractionated heparin should be administered. Also in cases of AMI without ST segment elevation, the guidelines recommend treatment with glycoprotein Iib/IIIa receptor antagonists for patients with high-risk or refractory ischemia.

Among other items, the guidelines also recommend lowering initial dosing of heparin with its unfractionated form is used with alteplase. Bypass or angioplasty is recommended for patients younger than 75 who are in cardiogenic shock.

For female patients, the guidelines recommend that any hormone replacement therapy should not follow MI, but in cases where estrogen and progestin therapies began prior to MI, those therapies can continue.

[Editor's note: For additional information and access to the complete guidelines, contact the American Heart Association. Telephone: (214) 373-6300. Web: www.americanheart.org.] ■

Knoll pays millions in settlement to pharmacies

Price fixing, info suppression led to payment

Knoll Pharmaceuticals has agreed to pay two community pharmacy organizations $27.5 million in a recently adjudicated settlement after the drug company was found to have suppressed information that generic levothyroxine was bioequivalent to Knoll's Synthroid.

The National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) will use the funds, which are being paid in the form of a grant in annual payments of $5.5 million from 1999 to 2003, to fund the Institute for the Advancement of Community Pharmacy, which was established by the two organizations to administer the funds.

Both organizations represented a New Jersey drug store chain, RxD Pharmacies, the plaintiff in a suit against Knoll. In another part of the settlement, 37 state health plans will divide $41.8 million from Knoll, which will go to state health plans that purchased Synthroid.

Plans for the settlement funds

The pharmacy organizations say they plan to use their part of the settlement to enhance accreditation efforts for pharmacists for disease management; establish community pharmacy residencies; improve pharmacy training and public education; and establish scholarships within pharmacy schools.

The two organizations also have recently published a white paper on the expansion of nondispensing roles for community pharmacists, "Implementing Effective Change in Meeting the Demands of Community Pharmacy Practice in the United States."

In addition to the Knoll settlement, NACDS and NCPA will receive $18.5 million from another recently finalized settlement of a price fixing ruling against 20 drug companies that has been in the works for three years. In 1996, a federal judge ruled the drug companies fixed the prices of dozens of drugs sold to retail pharmacies.

The settlement will pour $723 million into the nation's community pharmacies, paid directly in proportion to each pharmacy's drug purchases between October 1989 and February 1995. ■

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Editor: **Greg Fulton**, (770) 980-1870, (gfulton@mindspring.com).
Drug Criteria & Outcomes™ Editor: **Barry A. Browne**, PharmD.
Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).
Executive Editor: **Park Morgan**, (404) 262-5460, (park.morgan@medec.com).
Managing Editor: **David Flegel**, (404) 262-5537, (david.flegel@medec.com).
Production Editor: **Terri McIntosh**.

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Questions or comments?
Call **Greg Fulton** at (770) 980-1870.

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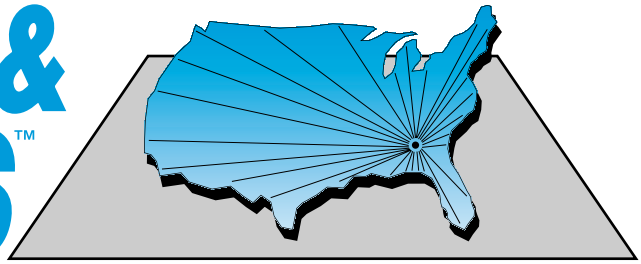

Assessing piperacillin/tazobactam (Zosyn)

By **Stephen Parker**, RPh
Jon Herrington, PharmD
Paul Holder, Pharm D
Scott & White Memorial Hospital
Department of Pharmacy Services
Temple, Texas

Introduction

Piperacillin / tazobactam (Zosyn) is an injectable antibacterial combination product consisting of the semi-synthetic antibiotic piperacillin and the beta-lactamase inhibitor, tazobactam sodium. This agent has a wide spectrum of in vitro antimicrobial activity against most aerobic and anaerobic gram-negative and gram-positive bacteria.

Piperacillin / tazobactam has FDA approval for the treatment of appendicitis and peritonitis, uncomplicated and complicated skin structure infections, postpartum endometriosis or pelvic inflammatory disease, community acquired pneumonia (moderate severity), and nosocomial pneumonia (moderate to severe). An assessment by the medication use evaluation subcommittee of the pharmacy and therapeutics committee of Scott & White Hospital was conducted to review indications for use of piperacillin / tazobactam, dosing, adverse effects, and outcomes.

Methods

Data were collected over a four-month period by patient care pharmacists. Orders for the drug written by all services throughout the hospital were reviewed. Evaluation included appropriateness of use, dose (with potential dose reduction based on determination of renal function), adverse events, and clinical outcomes. The patient care pharmacists also evaluated whether physicians narrowed the spectrum of antibiotic therapy by changing to piperacillin in cases where *Pseudomonas aeruginosa* was cultured.

Summary of data

A total of 84 charts of adult patients were reviewed throughout the hospital. The data collected are summarized in the accompanying table **(see p. 2)**.

Results

Of the 84 total patients, data on appropriateness of dosing with respect to renal function were available on only 53 patients. Twenty-nine of those 53 patients (55%) had piperacillin / tazobactam dosing regimens appropriately adjusted for renal dysfunction. Dosing regimens were not adjusted for renal dysfunction in 24 of the 53 patients (45%).

Aminoglycosides were utilized in conjunction with piperacillin / tazobactam in 18 of the 84 evaluable patients. In six of those 18 patients receiving both piperacillin / tazobactam and an aminoglycoside, administration was separated by less than two hours.

This regimen is of concern because beta-lactam antibiotics and aminoglycosides have the potential to inactivate each other when both are administered within a two-hour period.

Piperacillin / tazobactam was utilized in two

Correction

In the August 1999 *Drug Utilization Review*, the medication use evaluation appearing in the newsletter's *Drug Criteria & Outcomes* section, "Enteral feeding tubes complicate drug therapy" by Christina Beckwith, PharmD, and Richard Barton, MD, University of Utah Hospital, was inadvertently published without proper pursuit or acknowledgement of its original publisher, Lippincott's *Hospital Pharmacy. DUR* regrets the error. ■

Piperacillin/Tazobactam Assessment

Summary of Data

Indication	Number of Patients	Average length of therapy with Zosyn (days)	Improvement clinical status	Febrile after 72 hours of antibiotic
Community-acquired pneumonia	19	5.5	14	7
Aspiration pneumonia	12	7.8	10	3
Uncomplicated UTI	10	6.1	10	0
Nosocomial pneumonia	7	6.3	6	0
Intra-abdominal	6	6.3	4	1
Diabetic foot injection	4	5	4	0
Gynecologic	4	7.6	3	1
Skin and soft tissue	4	6.7	1	2
Cholecystitis	3	5	1	2
Bacteremia	5	8	3	2
Lung abcess	2	15	1	1
Pyelonephritis	1	5	1	0
Other	6	12	4	2

Source: Scott & White Memorial Hospital, Department of Pharmacy Services, Temple, TX.

patients for surgical prophylaxis. From the available data, it is not possible to determine whether that use was appropriate.

P. aeruginosa was isolated from cultures in eight patients. The division of infectious diseases / department of pharmacy's antibiotic streamlining team (AST) recommended narrowing antibiotic therapy to piperacillin in six of the eight cases; however, therapy was narrowed in only one of those patients. Secondary infection involving organisms requiring beta-lactam coverage was present in the two cases where recommendations to narrow coverage were not made by the AST.

Conclusions

In 34 of the 84 (40%) cases reviewed, a more narrow-spectrum, less-expensive agent could have been ordered. While piperacillin / tazobactam is FDA-approved for community-acquired pneumonia (CAP), the wide spectrum of this agent is not necessary in most cases of CAP.

Piperacillin / taxobactam should be reserved for patients with documented pseudomonal infections when co-infection with anaerobes or other potentially resistant gram-negative organisms is suspected.

While piperacillin / tazobactam is appropriate empirically when *Pseudomonas* is suspected,

coverage should be narrowed once culture results are obtained. This is important to help prevent the development and spread of resistant organisms.

Data from this MUE suggest that ceftriaxone in combination with oral doxycycline could have been utilized in the 19 patients with CAP. Cefazolin or another narrow-spectrum antimicrobial agent could have been utilized in the 11 patients with uncomplicated urinary tract infection.

In the four patients with cellulitis, both cefazolin and nafcillin are active against the common infecting organisms (streptococci and / or staphylococci), and either would be preferred over piperacillin / tazobactam due to each agent's spectrum of activity.

[Editor's note: For more information, contact the authors at Scott & White Hospital, 2401 S. 31st St., Temple, TX 76508. Telephone: (254) 724-2111.] ■

COX-2 inhibitors: A review of prostaglandin pathway

By **Christine Petraglia**, RPh
Nancy Jordan, PharmD, BCPS
Neal Kelly, MD
Holyoke (MA) Hospital
Department of Pharmacy

Introduction

The first of the COX-2 (cyclooxygenase) inhibitors arrived this year with a flurry of media promotion. Touted as super-aspirin, prescriptions for celecoxib (Celebrex), topped 2.5 million in its first three months on the market.

The second COX-2 inhibitor, rofecoxib (Vioxx), with an in vitro selectivity 1,000 times that of celecoxib, was approved this spring. To understand the excitement generated by this new class of nonsteroidal anti-inflammatory drugs (NSAIDs) a review of prostaglandin pathway is warranted.

Prostaglandins are synthesized from arachidonic acid catalyzed by the enzyme cyclooxygenase. It had been believed that only one form of cyclooxygenase existed until Simmons and coworkers discovered an isoenzyme. COX-1 is present in most cells and tissues catalyzing the production of prostaglandins necessary for normal homeostatic functions (e.g. PGE_2 for gastrointestinal mucosa protection; thromboxane for platelet function and regulation of blood flow; and PGI_2 for platelet function, kidney function, regulation of blood flow, and gastrointestinal protection).

On the other hand, COX-2 is not present in most resting tissues with the exception of the brain, reproductive organs, and kidneys but is rapidly induced at sites of inflammation and is responsible for the production of prostaglandins involved in the inflammatory response.

Inhibition of COX-2 should not affect the everyday prostaglandins that are involved in homeostasis. Therapeutic doses of celecoxib and rofecoxib appear to inhibit only COX-2. The potential advantage of these products is lack of GI bleeding and lack of inhibition of platelet aggregation as compared to salicylates or traditional NSAIDs.

Pharmacology and administration

Celecoxib is approved for use in osteoarthritis (OA) and rheumatoid arthritis (RA). For OA, the approved dose is 200 mg daily or 100 mg BID. Doses of 100 mg to 200 mg BID are recommended for RA. The capsules may be administered without regard to timing of meals. The medication appears to be as effective as older NSAIDs for these conditions but may be less effective for acute pain and hence is not approved for that condition.

Rofecoxib has indications that include OA, acute pain in adults (such as dental pain and post-orthopedic surgical pain), and primary dysmenorrhea. Rofecoxib does not have an indication for RA. For OA, 12.5 mg and 25 mg once daily without regard to meals was shown to decrease joint stiffness upon morning awakening. Fifty mg once daily was effective for reducing moderate to severe pain and for dysmenorrhea (for a maximum of five days). The product is available in 12.5 and 25 mg tablets and as an oral suspension.

The most frequent adverse reactions associated with celecoxib were dyspepsia (8.8%) and diarrhea (2%); whereas, the most prevalent ones with rofecoxib were upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), headache (4.7%), heartburn (4.2%), epigastric discomfort (3.8%), and dyspepsia (3.5%).

The incidence of endoscopically proven gastroduodenal ulcers over a twelve-week period was 7% (placebo 4%) with celecoxib and 5.9% (placebo 5%) with rofecoxib. That compared with

A COX-2 Overview

Brand Name	Celebrex	Celexa	Cerebyx
Generic name	celecoxib	citalopram hydrobromide	fosphenytoin sodium
Strength and form	100 mg, 200 mg capsules	20 mg, 40 mg tablets	50 mg PE*/ml - 2ml and 10 ml vials
Pronunciation	sell´-uh-brecks	sell-eks´-uh	ser´-uh-bicks
Manufacturer	Searle	Forest Labs	Parke-Davis
Indication	Osteoarthritis and adult RA	major depression	seizure prevention and treatment
Dosage and Administration	OA: 200 mg daily or 100 mg bid RA: 100-200 mg bid (oral)	20-40 mg daily (oral)	status epilepticus: 15-20 mg/PE/kg maintenance dose: 4-6 mg PE/kg/day (intravenous)

*PE = phenytoin equivalent

Source: Holyoke (MA) Hospital Department of Pharmacy.

10% to 35% for other NSAIDs such as diclofenac, ibuprofen, and naproxen.

The renal effects of COX-2 inhibitors are similar to those of older NSAIDs, and subsequently, the drugs should be used with caution in those prone to renal dysfunction and avoided in those with advanced kidney disease. The incidence of liver function test evaluations was similar to that of placebo, but both products emphasize warning patients to be on the lookout for signs/symptoms of hepatotoxicity. COX-2 inhibitors do not inhibit platelet aggregation. Anemia may be seen in patients on this medication, and hemoglobin and hematocrit should be followed if patients exhibit any signs or symptoms of blood loss. Fluid retention and edema have been reported with both drugs.

Expected drug interactions include diminished antihypertensive effect with ACE inhibitors and diminished natriuretic effect with furosemide. Lithium levels are increased by 17%, necessitating close monitoring of levels with the addition or deletion of celecoxib therapy, and a similar response can be expected with rofecoxib.

Celecoxib is metabolized via the CYP2C9 isoenzyme in the liver and is an inhibitor of CYP2D6 isoenzyme. Fluconazole, through its inhibition of the CYP isoenzyme, increases celecoxib levels by 200%. Lovastatin, another 2C9 inhibitor commonly used in the elderly for hyperlipidemias, may be expected to have a similar effect, although no studies or reports establishing an interaction are known to date.

Similarly, since celecoxib inhibits the CYP2D6 isoenzyme, caution should be used with drugs such as tricyclic antidepressants, phenothiazines, metoprolol, propranolol, risperidone, venlafaxine, haloperidol, paroxetine and sertraline.

CYP450 plays a minor role in rofecoxib metabolism, but use of a nonspecific drug inducer such as rifampin resulted in a 50% decrease in rofecoxib levels. Other potentially significant drug interactions with rofecoxib include methotrexate (increased methotrexate levels) and warfarin (increased INR). The U.S. Food and Drug Administration recently mandated changes to celecoxib labeling indicating the post-marketing surveillance has shown that bleeding events particularly

in the elderly associated with increased INRs occurred during concomitant celecoxib and warfarin therapy. Both drugs are contraindicated in patients with aspirin allergies.

Summary

Will COX-2 inhibitors be everything they promise to be? Even with the in vitro specificity, serious bleeding events have occurred. Since serious GI damage can occur anytime during therapy and often occurs without symptoms, monitoring for those events and proper patient selection cannot be overlooked. The constitutive presence of COX-2 in the kidney probably negates the potential of decreasing the renally associated side effects of NSAIDs. Initially, it was thought it might be advantageous to use COX-2 inhibitors in patients on warfarin to decrease the risk of bleeding because they do not increase bleeding time, but both medications have shown to increase the INR, and clinically significant bleeding has occurred in elderly patients.

Acetaminophen is currently the drug of choice for osteoarthritis, recommended by groups such as the American Geriatric Association because of the risks associated with NSAIDs. Switching all patients to COX-2 inhibitors at this time would not seem warranted until post-marketing surveillance confirms that the incidence of GI bleeding is truly decreased.

Converting patients at risk for GI bleeding to COX-2 inhibitors does not negate the need for continual monitoring and patient education regarding the signs and symptoms of serious GI effects. Using the lowest dose for the shortest amount of time will aid in reducing the chance of developing GI problems. Cost, as always, is a consideration, and these drugs have been priced competitively to compete with other newly marketed NSAIDs. Older NSAIDs and generic versions still remain less expensive.

Error alert for celecoxib

Fifty-four instances of medication errors resulting from name confusion with Celebrex were reported to the FDA within the first few months of marketing. This spring, co-marketers Searle and Pfizer sent out a fax to all pharmacists notifying them of confusion with look-alike / sound-alike drugs.

Celebrex; Celexa (citalopram), a new SSRI for depression; and Cerebyx (fosphenytoin) were the focus of the memo and are summarized in the table. **(See p. 4.)**

Ready for a pop quiz?

Now that prevention of medication errors is on your mind, test your skills. Look at the list of orders below and see if you can identify any potential problems. Answers immediately follow:

Orders

1. Verbal order for alteplase 15 mg bolus, 0.75 mg/kg over 30 minutes and 0.5 mg/kg over 60 minutes for a 48-year-old, 78 kg male.
2. Glyburide ½ tablet of a 12.5 mg tablet daily.
3. Catapres TTS 0.1 mg to skin qd.
4. Motrin 800 mg tid with food. Patient is on Clinoril.
5. Trovan 500 mg IV qd.
6. Demerol 50 mg with 25 mg Vistaril IV q3h p.r.n. severe pain.
7. Kefzol 1 g IV q6h. 89-year-old patient with creatinine of 2.4.

Answers

1. Verbal orders are not accepted for alteplase. Weight-based dosing is only to be used for patients less than 65 kg to avoid increases in intracranial bleeding associated with higher doses.
2. Glyburide is available as 1.25 mg, 2.5 mg, and 5 mg tablets. In addition, a micronized form, Glynase, is available in 1.5 mg, 3 mg, and 6 mg doses. Daily doses range between 1.5 mg and 20 mg per day. Had it not been for the unusual dose of 12.5 mg, the potential for a fivefold dosage error existed since the prescriber had intended the dose to be ½ of a 2.5 mg tablet.
3. These patches are changed every seven days, not daily.
4. An example of duplicate therapy. Review the medication Kardex or pharmacy printout for current patient medications. Be sure to discontinue any medications you no longer wish the patient to have.
5. Trovan (alatrofoxacin) is a new extended-spectrum fluoroquinalone with a dosage range of 100 mg to 300 mg IV daily. The prescriber may have been thinking of levofloxacin, whose usual dose is 250 mg to 500 mg daily.
6. Hydroxyzine (Visatril) should not be given via the IV route. IV use results in hemolysis. Intra-arterial or subcutaneous injection has resulted in tissue necrosis. Intra-arterial administration also has led to necrosis of an extremity resulting in amputation of digits. Hydroxyzine should only be given by deep IM administration. For an IV alternative consider promethazine or droperidol.
7. The appropriate dose for this patient based on his renal function would be 500 mg every 12 hours.

Source: Holyoke (MA) Hospital Department of Pharmacy.

When ordering any drug, it is imperative to neatly write or print and correctly spell the drug name. Include the dosage, form, strength, number, and indication for the prescription. Remember, the pharmacist at the local drug store may not know the patient's diagnosis, so including indication for use can aid in interpreting unclear orders.

[Editor's note: For more information, contact the authors at Holyoke Hospital, 575 Beech St., Holyoke, MA 01040. Telephone: (413) 534-2500.] ■

IN THE PIPELINE

The following drugs are still in clinical trials:

✔ **Metastatic colorectal cancer treatment UFT capsules (tegafur and uracil) by Bristol-Myers Squibb.** FDA's Oncologic Drug Advisory Committee has recommended approval of first oral combination therapy, UFT capsules in conjunction with leucovorin calcium tablets for treatment of colorectal cancer. Phase III trials compared regimen to IV 5-FU and IV leucovorin. Median survival times in trial of 1,200 patients were similar (12.4 months vs. 12.6 months) in respective oral and IV groups. Major side effects such as myelosuppression, stomatitis, and mucositis were decreased in oral group, while common side effects such as diarrhea and nausea were statistically similar.

✔ **Pediatric asthma treatment budesonide inhalation suspension by AstraZeneca.** FDA has accepted for review trials of nebulized corticosteroid aimed at gaining approval as first inhalant for patients under age 4. Submission follows a 12-week trial of 359 patients ages 6 months to 8 years receiving 0.25, 0.5, 1 mg or placebo once daily. Improvements in day and night asthma symptoms and decreased use of bronchodilaters were noted. Common side effects included respiratory infection, fever, sinusitis, and rhinitis.

✔ **Hepatitis A/B combination vaccine Twinrix (Hepatitis A Inactivated & Hepatitis B Recombinant Vaccine) by SmithKline Beecham.** FDA is reviewing licensing application for the vaccine, which, compared to current separate vaccine regimens, reduces total injections from five to three over six months. In randomized trial of 773 patients, similar antibody response was found between combination vaccine and Hepatitis A vaccine Havrix and Hepatitis B vaccine Engerix.

✔ I**nvestigational antibiotic Zyvox (linezolid) by Pharmacia & Upjohn.** Formulated against gram-positive bacteria for adult and pediatric use. One phase III trial of 397 patients with hospital-acquired pneumonia, IV linezolid and aztreonam showed a 66.4 clinical success rate, comparable to IV vancomycin plus aztreonam. In a community-acquired pneumonia trial, an IV to oral linezolid regimen resulted in a 90.8% success rate. Use against vancomycin-resistant *Enterococcus* resulted in 73.7 and 88.6% success rates in 200 mg and 600 mg doses respectively. ■

New FDA Approvals

These drugs and/or new indications have received final approval from the U.S. Food and Drug Administration:

✔ **Brain cancer treatment Temodar (temozolomide) by Schering Plough.** Oral capsules, granted orphan drug status in 1998, specifically approved for treatment of refractory anaplastic astrocytoma at first relapse after disease progression during treatment with procarbazine and nitrosourea. Approval follows trials in 162 patients, 54 of whom had relapsed. Of the 54, five had complete response and seven had partial response, with a median duration of 64 weeks. Dosage is five consecutive days within a 28-day cycle, beginning at 150 mg/m^2 then increasing to 200 mg/m^2. Available in 5, 20, 100, and 250 mg.

✔ **Hormone replacement transdermal patch E2111 (estradiol hormone replacement) by Cygnus, Inc.** Approved to treat moderate to severe vasomotor symptoms associated with menopause and treatment of vulvar and vaginal atrophy. Available in 0.05, 0.075 and 0.1 mg daily doses, the system is contraindicated for patients with known or suspected pregnancy, breast cancer, estrogen-dependent neoplasia, undiagnosed abnormal genital

bleeding, active thrombophlebitis, or thromboembolic disorders.

- ✔ **Pediatric formulation of the asthma treatment Accolate (zafirlukast) by Zeneca.** New approval is for 10 mg tablet, recommended twice daily, for patients 7 or older. Approval follows initial marketing in 1996 for patients 12 or older, trials of 800 subjects, and a 52-week open label safety trial. Compared to placebo, side effects included headache (4.5% vs. 4.2%) and stomach pain (2.8% vs. 2.3%).

- ✔ **New indications for HIV therapies d4T (Zerit) and ddI (Videx) by Bristol-Myers Squibb.** New approval allows for both nucleoside analogs to be used together as part of first-line combination therapy with protease inhibitors and non-nucleoside analogues. Toxicity cautions with ddI include pancreatitis and optic neuritis. In combination with d4T, risks include peripheral neuropathy and liver function abnormalities.

- ✔ **Fertility treatment Repronex (menotropins for injection) by Ferring Pharmaceuticals.** For patients undergoing ovulation induction and in vitro protocols, human menopausal gonadotropin approved for subQ and IM injections. SubQ approval allows for self-administration of combination follicle-stimulating and luteinizing hormone. In trials, subQ administration resulted in 50% pregnancy rate within single cycle for patient undergoing in vitro fertilization.

- ✔ **Fertility treatment Antagon (ganirelix acetate) by Organon Pharmaceuticals.** An antagonist of gonadotropin-releasing hormone, drug prevents premature surges in luteinizing hormones (LH) in patients undergoing ovarian hyperstimulation. In trials less than 1% of patients experienced LH surge before the administration of chorionic gonadotropins. Dosage used in trials was the recommended 250 µg daily for an average of 5.4 days. Available in prefilled syringes 250 µg/0.5mL. Administration is subQ once daily during the early to mid follicular stage.

- ✔ **Pregnancy prevention therapy Plan B (levonorgestrel) by Women's Capital Corp.** For use in pregnancy prevention after unprotected intercourse or suspected contraception failure, approval follows trials showing an 89% reduction in the expected rate of pregnancy. Available in packages of two tablets, 0.75 mg, dosing regimen is one tablet within 72 hours followed by one tablet 12 hours later. ■

Field narrows as on-line pharmacy giants merge

PBMs make exclusive deals with on-line suppliers

The nation's third largest pharmacy benefit manager (PBM), Express Scripts Inc., the owner of its own on-line pharmacy, yourPharmacy.com, has agreed to purchase 19% of the on-line pharmacy PlanetRx.com in exchange for a five-year deal to be the exclusive supplier to PlanetRx.com.

As part of the deal, yourPharmacy.com will disappear from the marketplace to make way for the co-owned PlanetRx.com. PlanetRx.com now will become the exclusive supplier to some 36 million Express Scripts members.

In another merger, PCS, the nation's second-largest PBM, which is owned by RiteAid, also has set up an exclusive supplier deal by way of RiteAid's purchase of 25% of the on-line pharmacy drugstore.com.

The first on-line pharmacy to emerge earlier this year, Soma.com, has since been purchased by CVS.

Regulators lagging behind

In the meantime, government and national pharmacy organizations continue to try to play oversight catch-up to the ever-growing on-line pharmacy industry.

This summer, a hearing was held by the oversight subcommittee of the House Committee on Commerce, which was attended by representatives of the U.S. Food and Drug Administration, Federal Trade Commission, Justice Department, National Association of Boards of Pharmacy, and several Internet pharmacy representatives.

The hearing was aimed at focusing on ways to regulate the industry, specifically sites that would be considered illegal based on a lack of prescription control, faulty drug claims, and sales of unapproved drugs.

No concrete action was taken at the hearing. Instead, several overall topics to pursue were agreed upon, which included pursuing proposals on the disclosure of World Wide Web site operators, a determination of whether state or federal guidelines should be adopted, and defining proper doctor-patient relationships when prescriptions are filled on-line among other topics. ■

Significant Drug-Drug Interactions with Cisapride (Propulsid)

Precipitant Drug	Object Drug	Description
Anticholinergics/Antispasmodics atropine, belladonna, benztropine, dicyclomine, homatropine, hyoscyamine, oxybutynin, procyclidine, scopolamine, trihexyphenidyl	cisapride	Concurrent use expected to compromise beneficial effects of cisapride.
Antiarrythmics, Class 1A (disopyramide, procainamide, quinidine); Class III (amiodarone, bretylium, ibutilide, sotalol)	cisapride	Known to prolong the QT interval as seen in arrhythmias. May result in torsades de pointes. Concomitant use with cisapride contraindicated.
Antidepressants (tricyclics, nefazodone, maprotiline, fluvoxamine)	cisapride	Known to prolong the QT interval. May result in torsades de pointes. Concomitant use with cisapride contraindicated.
Antipsychotics (phenothiazines, perphenazine, amitriptyline)	cisapride	Known to prolong the QT interval. May result in torsades de pointes. Concomitant use with cisapride contraindicated.
Azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole)	cisapride	Known to prolong QT interval. Concomitant use with cisapride contraindicated.
Bepridil	cisapride	Known to prolong QT interval. Concomitant use with cisapride contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin, troleandomycin)	cisapride	Known to prolong QT interval. Concomitant use with cisapride contraindicated.
Protease Inhibitors (emprenavir, indinavir, nelfinavir, ritonavir, saquinavir)	cisapride	Known to prolong QT interval. Concomitant use with cisapride contraindicated.
Grepafloxacin, sparfloxacin	cisapride	Known to prolong QT interval. Concomitant use with cisapride contraindicated.
H_2 antagonists (cimetidine)	cisapride	Increased peak plasma level and AUC of cisapride may occur; other H_2 antagonists have no effect on cisapride absorption.
Cisapride	H_2 antagonists	GI absorption of cimetidine and ranitidine is accelerated by cisapride.
Cisapride	Anticoagulants (anisindione, coumarin, wafarin)	Since coagulation times (PT/INR) may be increased, it is advisable to check them within first few days after start and D/C of cisapride therapy. Adjust anticoagulant dose as necessary.
Cisapride	cyclosporine	Cisapride has been shown to increase peak concentrations and AUC and decrease time to peak concentration of cyclosporine. Possible mechanism is increased rate of absorption of cyclosporine. Monitor cyclosporine levels and toxicities regularly.
Cisapride	tacrolimus	Both agents are metabolized by the CYP 450 3A4 system, which may result in competitive inhibition and may produce higher plasma concentrations of one or both agents. Monitor tacrolimus plasma concentrations and look for signs of tacrolimus toxicity (i.e. nephrotoxicity, hyperglycemia, hyperkalemia). Doses of tacrolimus may need to be reduced with concurrent use.
Delavirdine	cisapride	Known to prolong the QT interval. Concomitant use should be avoided.
Diltiazem	cisapride	Diltiazem is a known CYP 450 3A4 inhibitor, and cisapride is a 3A4 substrate. Concomitant administration should be avoided due to possible QT interval prolongation and arrhythmias.
Dolestron	cisapaide	Both agents can prolong the QT interval and result in arrhythmias. Concomitant use should be avoided or cardiac function should be closely monitored.
Efavirenz	cisapride	Both agents metabolized by CYP 450 3A4 system. Competition for this pathway could result in inhibition of cisparide metabolism, creating the potential for prolongation of the QT interval and arrhythmias. Concomitant use is not recommended.

Editor's note: The heartburn medication cisapride (Propulsid, Janssen Pharmaceutica) was the subject of FDA warning letters in 1996 and 1998 based on reports of serious adverse and events and up to 38 patient deaths associated with the drug. The FDA warnings included a range of drug-drug interactions to avoid and the avoidance of use of the drug with various patient cardiovascular disorders. This is a chart of drug classes warranting caution with the use of cisapride.

Source: Scott & White Memorial Hospital, Department of Pharmacy Services, Temple, TX.

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PHARMACY PRACTICE

REGULATION AND ACCREDITATION