FOR MORE THAN 20 YEARS

DRUG FORMULARY REVIEW™

Utilization, Criteria and Outcomes

AHC Media LLC

IN THIS ISSUE

Statement of Financial Disclosure:
Barry A. Browne, PharmD (Pharmacist Editor), John Hope (Editor), Lee Landenberger (Editorial Group Head), and Paula Cousins (Managing Editor), and Erica Oelfke (Author, insert) report no relationships with companies related to this field of study.

JANUARY 2007
VOL. 23, NO. 1 • (pages 1-8)

Analyzing reasons for ICU adverse drug events: Look beyond cost and frequency of use

The frequency, severity, and preventability of adverse drug events (ADEs) in intensive care units (ICUs) are not associated with a drug's cost or frequency of use, according to researchers writing in the *American Journal of Health System Pharmacy*. Researchers from the University of Pittsburgh said critical care pharmacists should set drug monitoring priorities not only by cost alone, but also based on frequency of use and potential for causing an ADE.

Although ADEs occur in some 30% of hospitalized patients, patients in ICUs are at greater risk of having an ADE. University of Pittsburgh assistant professor **Sandra Kane-Gill**, PharmD, and her colleagues said the increased ADE risk for critically ill patients is related to the higher number of medications administered, acute changes in organ function that affect drug pharmacokinetics, and increased length of hospital stay. For example, the incidence of ADEs in a medical ICU was reported to be 19 events per 1,000 patient days, higher than the 10 events per 1,000 patient days reported for general care units.

In the past, the researchers said, ADE prevention efforts by institutions, professional organizations, and the government has been limited because of the labor and expense involved with ADE surveillance. But the recent public interest in patient safety is shifting the paradigm toward ADE prevention.

The researchers said the presence of pharmacists in ICUs and general medicine units has been shown to reduce the rate of preventable ADEs by 66%. Other techniques that can work include computer-based monitoring of drug interactions, therapeutic duplication, and dosage checks.

Critical care pharmacists have many patient care responsibilities, the researchers said, and thus have a limited amount of time available to perform each function. Budgeting in most hospitals encourages departments to focus on cost reduction rather than cost avoidance when changing processes or improving quality.

Kane-Gill tells *Drug Formulary Review* there has been a lack of data on ICU adverse events and broader monitoring would be appropriate. She says most facilities don't track ICU-specific data because of a lack of time and resources, but says any specific monitoring increases could help properly allocate drug monitoring priorities.

Monitoring costs not sufficient

"Since ICU drug costs contribute to at least 38.4% of a hospital's total drug costs and have increased at a rate twice that of non-ICUs, many cost-containment efforts encourage pharmacists to monitor the appropriate use of costly ICU medications," the researchers wrote. "However, this strategy may not be the most effective approach, since direct costs are not the only costs associated with drug use. The use of treatment algorithms and guidelines may aid pharmacists in cost-containment efforts but does not address the prevention of ADEs. Further, patients who have an ADE incur an additional cost of $3,000 to $7,000, clearly justifying efforts to increase the prevention and detection of ADEs. Identification of the drugs most commonly associated with ADEs may improve patient safety and contain costs."

Kane-Gill's study sought to compare the rates, preventability, and severity of ADEs associated with: 1) high- and low-cost drugs used in the ICU; 2) high- and low-use drugs in the ICU; and 3) high-cost versus high-use drugs in the ICU.

The researchers defined an adverse drug event as an injury resulting from drug treatment. Preventable ADEs were defined as medication errors in which a patient received a drug resulting in harm. All others were classified as nonpreventable ADEs.

High-cost medications were defined as those accounting for the top 50% of cumulative ICU medication costs for the study period. All remaining medications were considered low-cost. Cost was determined by multiplying units of medication charged to a patient by the pharmacy acquisition cost.

Because of the large number of medications in the pharmacy database and the small number of units associated with many of the drugs, usage was narrowed to those medications most frequently used in an ICU before frequency of use could be quantified. Initial selection of appropriate drugs came from a literature review on ICU drug use. Then, critical care pharmacists practicing in ICUs from 37 different institutions were asked to list the top 10 most frequently used medications in the ICU. High-use medications were defined as the top 50% of all medications used during the study period.

The researchers reported a 32% difference in the number of medications associated with ADEs between the high-cost and high-use groups. Although the difference was not statistically significant, they said, it illustrates that monitoring high-cost and high-use drugs is equally important in the ICU setting.

Three drugs both high-cost and high-use

Only three drugs (lorazepam, mucophenolate, and propofol) were considered both high-cost and high-use, demonstrating a minimal overlap between the categories based on reports generated from an intensive ADE program. Heparin, the medication associated with the most ADEs,

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. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. 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, #381-000-07-054-H01, will be available **January 1, 2007-December 31, 2008.**

AHC Media LLC has designated up to 6 contact hours (0.6 CEUs) annually for this program. Participants will receive statements of credit within 6 weeks after receipt of the post-test and evaluation form, provided a passing grade of at least 70% is achieved. Health system pharmacists and pharmacy benefits managers are the target audience of this activity; however, anyone involved in prescribing, dispensing, patient counseling, formulary selection, or reimbursement processes might benefit from participation.

Editor: **John Hope**.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@ahcmedia.com).
Managing Editor: **Paula Cousins**, (816) 237-1833, (paula.cousins@ahcmedia.com).
Senior Production Editor: **Nancy McCreary**.

Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

was categorized as high-use but low-cost. If medication monitoring had a strictly monetary focus then Heparin would be missed, the researchers said. Although morphine was associated with the second highest number of ADEs, it was not ranked as either a high-use or high-cost drug.

"The large number of ADEs occurring in low-cost and low-use groups and the severity of these ADEs demonstrate that the mechanism to prioritize medication monitoring in the ICU extends beyond cost and use," the researchers said. "Monitoring priorities of critical care pharmacists should include the frequency of ADEs and the potential for incurring injury from a medication."

Although the severity and preventability of ADEs did not vary significantly between high-cost and high-use groups, the high frequency of ADEs indicates opportunity for improvement in ADE prevention, the report said. The most preventable ADEs involved antihypertensives. Anticoagulants were commonly associated with life-threatening events and a prolonged length of stay, further justifying pharmacist monitoring of the use of this class of medications.

Of the 17 high-cost medications, 53% were associated with ADEs. The low-cost group had significantly fewer medications associated with ADEs (9.01%). But the researchers said it should be remembered that 88 low-cost medications were associated with 241 ADEs. And similar percentages of the ADEs were severe and preventable in the high-cost and low-cost groups, although a larger sample size is needed to verify the results.

The researchers said that while it seems logical that high-use medications would be associated with more ADEs because of the frequent exposure, this did not hold true in the study. A similar percentage of medications in the high-use and low-use groups were associated with ADEs (80% vs. 69% respectively). Some 35% of them were severe and 9% were preventable in both groups. High-use medications were not associated with more ADEs than were low-use medications, and this may reflect reduced reliance on ADE reporting or clinicians' familiarity in handling high-use medications.

Monitoring useful

"Monitoring the frequency, preventability, and severity of events using surveillance data is useful for guiding institutional patient safety directives," the researchers said. "For those institutions that do not have an intensive ADE surveillance program, 13 medications (see chart) can be used as a guide for focusing clinicians' monitoring priorities. The results of this study can be used to develop patient safety prevention initiatives for anticoagulants, antibiotics, and sedatives, which could include the implementation of heparin nomograms and sedation protocols."

Download the research report at:www.ajhp.org/cgi/content/full/63/19/1876. ■

Medications Associated with More Than Five ADEs[a]

Medication	No. ADEs[b]
Heparin	27
Morphine	19
Fentanyl	12
Piperacillin	10
Phenytoin	9
Tacrolimus	8
Vancomycin	8
Propofol	7
Haloperidol	7
Levofloxacin	7
Quinupristin-dalfopristin	6
Famotidine	6
Warfarin	6

[a]ADEs = adverse drug events.

[b]Data were collected from October 1997 through June 2001. ADEs included all levels of severity as indicated by a modified version of the National Cancer Institute Toxicity Criteria.[20]

Appropriate antibiotics needed for VAP management

Clinicians who manage ventilator-associated pneumonia (VAP) patients should promote appropriate use of antibiotics to optimize patients' outcomes and prevent antibiotic resistance. That's the finding of researchers from St. Louis University Hospital, Washington University School of Medicine, and Barnes-Jewish Hospital's pharmacy department who published their findings in *Pharmacotherapy*. They said a strategy of de-escalation incorporates their philosophy with administration of broad-spectrum empiric antimicrobial therapy based on patient risk factors, serial assessment of clinical markers to monitor the response to empiric therapy, implementation of locally

developed and clinician-accepted protocols to minimize the number of antibiotics when cultures are positive and/or when clinical improvement occurs, as well as shortening therapy to 7-8 days in patients with uncomplicated VAP and an appropriate clinical response to treatment.

Optimizing antimicrobial therapy

According to the researchers, VAP is the most common infection complication in patients receiving mechanical ventilation and accounts for exorbitant resource use in ICUs. Antimicrobial management of VAP incorporates an initial broad-spectrum empiric regimen to ensure appropriate coverage with de-escalation of therapy after 48-72 hours based on culture results and sensitivities.

VAP occurs at a rate of 5-16 cases per 1,000 ventilator days, and accounts for some 80% of all hospital-acquired pneumonias requiring intensive care. Mortality rates are 25-50% and as high as 76% in patients who develop bacteremia or who are infected with high-risk pathogens such as *Pseudomonas aeruginosa* or *Acinetobacter* species.

Antimicrobial management of VAP is balanced between providing appropriate initial broad-spectrum treatment in a timely manner and avoiding unnecessary use if antimicrobials by narrowing their spectrum or by discontinuing anti-infective treatment after 48-72 hours based on culture results and susceptibilities.

The researchers said their de-escalation strategy attempts to unify those principles into a single approach that optimizes patient outcomes while minimizing the emergence of antibiotic-resistant pathogens. Optimizing antimicrobial therapy for VAP, they said, requires applying rigorous diagnostic strategies, prescribing appropriate initial empiric therapy based on local pathogens and susceptibility rates, maximizing antimicrobial pharmacokinetic and/or pharmacodynamic profiles, using protocols to change from broad- to narrow-spectrum therapy, and administering a short course of treatment.

First step is diagnosis

Definitive diagnosis is the first step in optimizing VAP treatment. The diagnosis of VAP is generally based on findings of new or worsening infiltrates on chest X-rays, systemic signs of infection (including fever and leukocytosis), and bacteriologic evidence of pulmonary parenchymal infection obtained with bronchoscopic or nonbronchoscopic techniques. Bronchoscopic sampling of the lower airways using a protected specimen brush or bronchoalveolar lavage is the most accurate method of establishing a microbiologic diagnosis of VAP short of direct tissue examination.

After microbiologic specimens are obtained, the next principle of antibiotic de-escalation is expedient administration of an appropriate empiric regimen to patients with suspected VAP. Antimicrobial treatment is defined as appropriate when a documented microbiologic infection (positive culture result) is treated with an agent that demonstrates in vitro activity against the organism at the time the pathogen is identified on culture. Failure to treat with an appropriate initial antimicrobial regimen may increase morbidity and mortality rates. The study reports on other research that prospectively evaluated empiric use of antibiotics in 430 cases of ICU-acquired pneumonia. In the 34% of patients who did not receive appropriate antimicrobial therapy, rates of shock and attributable mortality were significantly higher than those of patients giving appropriate empiric coverage.

Initial antibiotics are generally selected in the absence of identified pathogens. To safeguard against inappropriate empiric regimens and their associated increased risk of mortality, clinicians must be aware of the microorganisms likely to cause VAP in their patients, which vary depending on the onset of infection.

After an initial broad-spectrum antimicrobial regimen is started, the next component of adequate therapy is prescribing the proper dose and interval to achieve sufficient intrapulmonary drug concentrations for a clinical and microbiologic response. To do so, the researchers said, clinicians must understand the pharmacokinetics and pharmacodynamics of antimicrobials and the minimum inhibitory concentrations (MIC) that the Clinical and Laboratory Standards Institute assigns for each bacterial pathogen.Pharmacokinetic parameters such as absorption, dilution, metabolism, and elimination for a given dosage regimen establish the pharmacokinetic profile. And antimicrobial pharmacodynamics relates the concentration of the drug at the site of action with regard to the antibiotic's therapeutic and toxicological effects. The relationship between the pharmacokinetic and pharmacodynamic variables, the pharmacokinetic-pharmacodynamic profile, determines the drug's microbiologic and clinical efficacy.

Steps in Determining Correct Dose

The researchers said prescribing the correct dose and interval of antimicrobial for VAP is a multistep process involving: 1) consideration of the antimicrobial MIC breakpoint for targeted organisms or the microbe-specific MIC for each antimicrobial tested for an isolated organism; 2) the pharmacokinetic-pharmacodynamic parameter associated with clinical benefit and the dose likely to achieve the desired pharmacokinetic-pharmacodynamic endpoint in critically ill patients; 3) the patient's renal and hepatic function; and 4) the characteristics of antimicrobial distribution into the lung and/or the established lung serum concentration ratios, as determined using antibiotic concentrations in lung-tissue samples, epithelial-lining fluid, alveolar macrophages, and intrapulmonary micro dialysis techniques.

Evaluate patient response daily

To ensure that patients are appropriately treated for VAP, the researchers said, their clinical response to therapy should be continuously assessed. Patients' response to the empiric regimen should be evaluated daily using clinical aids such as the clinical pulmonary infection score. Lack of clinical improvement after 48-72 hours of antibiotic therapy is an indication for an intensified search for the etiology of VAP. The researchers said the search might include bronchoscopy if not previously performed, a search for alternative diagnoses or sites of infection, and possible adjustments to the antimicrobial agents used or optimization of pharmacokinetic-pharmacodynamic endpoints.

Using the de-escalation strategy, the initial and appropriate broad-spectrum regimen should be adjusted based on the patient's clinical and microbiologic response. Modifications include decreasing the number and spectrum of antibiotics and shortening the duration of therapy if signs of clinical improvement are observed or if a causative organism is identified.

Shorter treatment durations OK

Treatment durations shorter than the traditional 14- to 21-day regimens appear to have acceptable clinical outcomes, according to the study, with decreased antimicrobial resistance. The optimal duration of antibiotic therapy for uncomplicated, bronchoscopically diagnosed VAP was addressed in a trial comparing eight- and 15-day courses of treatment. The prospectively defined endpoint was death from any cause at 28 days after the onset of VAP. Patients in the eight-day group had a mortality rate of 18.8% compared with 17.2% in the 15-day group, an absolute difference of 1.6%, indicating noninferiority.

Overall, the recurrence of pulmonary infection, the number of mechanical ventilator-free days, and the length of stay in the ICU did not differ between the groups. In the eight-day group, the number of antibiotic-free days by day 28 increased, and the isolation of resistant pathogens when recurrence was diagnosed decreased. Also in the eight-day group, relapse rates tended to increase when the etiologic organism was *P. aeruginosa* or an *Acinetobacter* species, without compromising survival. ■

Pharmacist-managed clinics succeed

Pharmacist-managed diabetes care clinics achieve high screening rates and attain treatment goals more often than national averages, according to two separate studies published in the *American Journal of Health-System Pharmacy*. Researchers also found that most patients and providers are satisfied with the services provided by a pharmacist-managed lipid clinic. The clinics help improve patients' LDL cholesterol, total cholesterol, and triglyceride levels.

An estimated 20.8 million Americans-7% of the U.S. population-have diabetes mellitus, and the number of Americans living with diabetes is projected to more than double by 2060 or even sooner.

Researchers from the University of California at San Diego and elsewhere said patients can benefit from an individualized approach to comprehensive diabetes care. Comprehensive care involves a multidisciplinary approach with evaluation and education from specialty practitioners, such as endocrinologists, pharmacists, exercise physiologists, diabetes educators, nurses, dietitians, podiatrists, and ophthalmologists. The researchers said a cornerstone of diabetes treatment is drug therapy, often with complex regimens, including multiple oral and injectable agents. A collaborative agreement between physicians and pharmacists is an innovative strategy to treat patients with diabetes that takes advantage of pharmacists' expertise in disease management and drug

monitoring. Improved patient outcomes and reduced costs to health care systems are potential benefits of implementing an innovative ambulatory clinic model for diabetes treatment.

The research was conducted at the Naval Medical Center San Diego, a 500-bed comprehensive teaching hospital that treats more than 5,000 patients with diabetes. In mid-1999, ambulatory care pharmacist specialists were specifically hired to expand the current pharmacist-managed ambulatory care services in anticoagulation and lipid clinics and to create new clinics, including two pharmacist-managed diabetes care clinics.

In early 2000, the ambulatory care pharmacist team at the medical center developed two diabetes care clinics for patients in the endocrinology and primary care clinics. Working collaboratively with a board-certified endocrinologist and primary care physicians, clinical practice guidelines and treatment algorithms were created based on national standards of care for diabetes and related comorbidities, including hypertension and hyperlipidemia. The primary care diabetes care clinic was managed by two pharmacists, while the endocrinology diabetes care clinic was managed by one pharmacist who also was a certified diabetes educator.

Effectiveness analyzed at end of year one

One year after the clinics opened, a continuous-improvement report analyzed effectiveness. Data from patients with Type 2 diabetes who were enrolled in the pharmacist-managed diabetes care clinics and had two or more clinic encounters with a clinical pharmacist were analyzed. Primary outcome measures were changes from baseline (clinic enrollment) in diabetes-related markers: glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, body mass index, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and blood pressure.

Even though other ambulatory care programs were operating at the medical center, collaborative work in a disease requiring such comprehensive management as diabetes was unfamiliar there, the researchers said. Because initial pharmacist-managed diabetes care clinic development met with some resistance from physicians, particularly the primary care clinic, a physician-mandated level of care specifying the extent of care a pharmacist could provide was conceived and implemented. Referring physicians could select from among three levels of diabetes care. Each level indicated the care each physician was comfortable with the pharmacist providing and did not reflect the severity of patients' diabetes and comorbid conditions.

Depending on the scope of the referral, clinical pharmacists provided patients with one of these care levels: diabetes self-care education and counseling (Level 1); Level 1 care plus diabetes treatment and monitoring, including evaluation, laboratory monitoring, and modification of pharmacotherapy (Level 2); and Level 2 care plus education, treatment, and monitoring of co-morbid conditions including hypertension and hyperlipidemia (Level 3).

The pharmacists performed limited physical assessments for Level 2 and 3 patients, including blood pressure measurements and foot examinations. The primary care clinic enrolled patients in all three levels, while the endocrinology clinic enrolled only Level 3 patients. In the primary care clinic a physician could choose to move a patient from one level to another at any time. As their comfort level increased with the pharmacist-provided care, the researchers said, physicians advanced the majority of their patients to Level 3 care.

Individualized programs

Patients who were not meeting their metabolic goals or who needed in-depth disease education and counseling were referred to the clinics from the internal medicine and primary care clinics. After a 90-minute initial visit, patients met with a clinic pharmacist every 4-12 weeks for 45-60 minutes of individualized diabetes education, monitoring, and pharmacotherapy assessment and treatment. The frequency of visits and telephone follow-up was determined by each patient's specific needs. Physicians were located in the same clinic space, so patients were evaluated if the pharmacist identified acute symptoms requiring physician evaluation or diagnosis. Individualized treatment plans were created with patient input to emphasize the patient's role in the process and to empower individuals to take control of their diabetes.

Comprehensive patient education focused on diabetes and long-term complications, identification and self-treatment of hypoglycemia, self-monitoring of blood glucose and pattern management, the importance of preventive care, proper foot and skin care, and nutrition and physical activity guidelines. Pharmacists referred clinic patients to other health care providers when indicated. And once patients met all of their metabolic targets, they were referred back to their primary care physicians for ongoing management.

Pharmacists improved clinical outcomes

One-year outcome data from the clinics demonstrated that pharmacist involvement in caring for patients with Type 2 diabetes mellitus significantly improved clinical outcomes, the researchers said. For that time period, the overall mean reduction in HbA_{1c} was 1.3%. The outcomes remained consistent or improved three years after the clinics opened. Estimated cost avoidance to the medical center was $17,157 per year. When extrapolated to the entire medical center diabetes population, the cost avoidance analysis indicated a potential annual saving of $616,000 to $735,000.

Other diabetes-related markers, including blood pressure and lipid values, also improved in clinic patients. Although improved glycemic control due to increased oral diabetes medication or insulin use may result in weight gain, patients managed in the clinics maintained their body mass index without significant weight gain at the end of year one.

Analysis of a pharmacist-managed lipid clinic was conducted at the Louis Stokes Cleveland Veteran Affairs Medical Center. Most patients and providers were satisfied with the services provided by the pharmacist-managed lipid clinic and the clinic helped improve patients' LDL cholesterol, total cholesterol, and triglyceride levels.

Gap between recommendations and practice

The Lipid Treatment Assessment Project, a large-scale trial to evaluate the achievement of LDL cholesterol goals, found that only 38% of patients achieved their individual National Cholesterol Education Program-specified LDL cholesterol goals. And only 18% of patients at highest risk (those with cardiovascular disease) achieved their goals.

A pharmacist-managed lipid clinic is one strategy to increase patients' attainment of LDL cholesterol goals. Several studies have found improved lipid management, including attaining LDL cholesterol goals, with pharmacist-managed clinics compared with control groups managed by primary care physicians. The success of the pharmacist-managed clinics was attributed to increasing patient education and providing more intensive lipid monitoring. Little research attention has been focused on patient and provider satisfaction with the pharmacist-managed lipid clinics and how satisfaction relates to objective measures of clinical care.

The Stokes Cleveland VA Center established a pharmacist-managed lipid clinic in October 2003. The clinic is primarily telephone-based, with face-to-face sessions occurring only when requested by patients. Patients with complicated dyslipidemia are referred to the clinic by their health care provider. Three types of consultations may be requested—nonformulary drug requests, drug therapy recommendations, and lipid therapy management. The clinic is staffed by one clinical pharmacy specialist who conducts telephone interviews with the patients and is responsible for the prescribing and monitoring of lipid-lowering drugs. The pharmacist also provides information on diet and exercise modification to all clinic patients.

The primary objective of the study was to assess patient and provider satisfaction with the newly-established pharmacist-managed lipid clinic. Secondary objectives were to determine the percent change in lipid levels and the percentage of patients achieving their LDL cholesterol goals.

Ninety percent of patients satisfied

Some 96 patients (91.4%) were strongly or somewhat satisfied with the care received from the clinic. And 88 patients (83.8%) reported that they found the materials provided by the pharmacist about cholesterol, diet, and exercise helpful, while 93 patients (88.6%) said the pharmacist adequately addressed their questions and concerns. Although 91 patients (86.7%) felt they had a better understanding of their lipid-lowering medications after completing the consultation, only 23 providers (46.9%) felt that patients had a better understanding of these medications. One-fifth of patients said they would prefer face-to-face appointments.

Overall, providers reported a high level of satisfaction, as 87.8% of providers responded that they

COMING IN FUTURE MONTHS

- Pharmacists' role in emergency departments
- Finding ways to include clinical services in productivity monitoring
- Pharmacists' role in hospitals and health systems continues to change
- Improving intrathecal baclofen therapy
- Managing anticoagulation treatment

were strongly or somewhat satisfied with the care provided by the pharmacist. And 98% of providers found the progress notes written by the pharmacist to be helpful, and 81.6% of providers reported the monitoring of cholesterol-lowering agents to be appropriate. However, 18 physicians (36.7%) did not believe the lipid clinic helped reduce the amount of time the provider spends with patients with hyperlipidemia.

A total of 87 patients (82.9%) felt that their cholesterol levels had improved. Based on the observation that 91.8% of providers stated that they would refer additional patients to the clinic, continued growth of the pharmacist-managed clinic seems promising.

To further assess clinic effectiveness, objective data were collected from patient charts. Significant improvements in total cholesterol, LDL cholesterol levels, and triglyceride levels were observed from baseline to discharge or to the most recent lipid panel, the researchers reported.

On average, the clinical pharmacist contacted patients and evaluated lipid levels and lipid-lowering therapy every two months. This resulted in achievement of goal LDL cholesterol by 72 patients (68.6%) after a mean of 3.2 months in the pharmacist-managed lipid clinic. The researchers said that although there appears to be a parallel between satisfaction with the care provided and clinic effectiveness, a causal relationship cannot be established with the study methodology. "If patients are more closely monitored and more satisfied with the lipid management," the researchers concluded, "they may be more likely to have a better understanding of their lipid therapy and improved medication adherence." ■

NEWS BRIEF

Special considerations for bariatric surgery patients

Patients who have undergone bariatric surgery should take steps to be sure they are absorbing their medications and nutrients, according to University of Kentucky researchers writing in the Oct. 1, 2006, *American Journal of Health-System Pharmacy*. In the study, **April Miller**, PharmD, and **Kelly Smith**, PharmD, reviewed previously published literature to assess potential problems that bariatric surgery patients may have with absorption of medication and nutrients.

The authors focused on Roux-en-Y gastric bypass, the type of bariatric surgery most often performed in the United States. They said this form of gastric bypass surgery is associated with more absorption problems than other procedures because it combines techniques that restrict the amount of food passing through the stomach and impairs the ability of the small intestines to absorb nutrients.

"Both the smaller stomach size and the decreased absorption ability of the small intestines can mean that medications may not work as intended," Smith said. "It's important for physicians and pharmacists to be aware of these patients' special needs to make the best choices about appropriate medications."

Consider alternate formulations and delivery

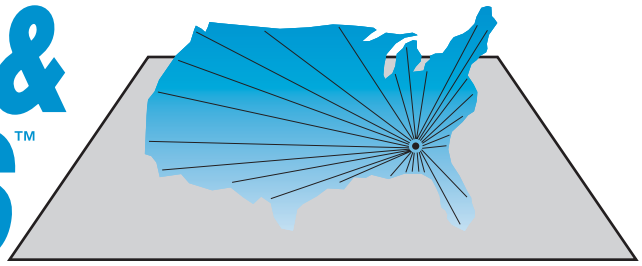
Extended-release and delayed-release medications may not work properly because of the shortened small intestine, Smith said. Some of the necessary changes could be as simple as prescribing a liquid medication, which would be more easily absorbed than a tablet or capsule, and using immediate-release formulations, she added.

The study also found that patients could benefit from medications that are administered through patches worn on the skin, injection, suppositories, or nasal spray.

Nutrition deficiencies may also be a problem, Miller said, including deficiencies of calcium and fat-soluble vitamins (A, D, E, and K). Patients also are at higher risk for developing anemia because of deficiencies in iron, vitamin B_{12}, and folate.

"After bariatric surgery, all patients should take a daily multivitamin and calcium supplementation, preferably in a powder or liquid form to enhance absorption," Miller said. "Monthly B_{12} injections and early bone density testing should also be considered." ■

DRUG CRITERIA & OUTCOMES™



Oxymorphone (Opana®) Formulary Evaluation

Part 1: Indications, Mechanism of Action, Pharmacokinetics, Contraindications, and Adverse Effects

By **Erica Oelfke**, PharmD Candidate, Auburn (AL) University

Oxymorphone hydrochloride (Opana® and Opana ER®) is a semi-synthetic opioid analgesic tablet for oral administration. It is a morphine-like agonist and a CII drug with an abuse liability similar to other opioids. Oxymorphone is available as 5 mg and 10 mg tablets for oral administration. The extended release (ER) formulation is available as 5 mg, 10 mg, 20 mg, and 40 mg tablets, also for oral administration. (See Table) Oxymorphone injection (Opana injection®) is available in 1 mg/mL in 1 mL ampules and 1.5 mg/mL in 10 mL multiple - dose vials.

Morphine immediate release (IR) and controlled release (CR)/extended release (ER) is the standard opium alkaloid for comparative purposes.

Indications

Oxymorphone is indicated for relief of moderate-to-severe acute pain where the use of an opioid is appropriate. Oxymorphone ER is indicated when continuous opioid therapy is necessary for an extended period of time. Oxymorphone injection may be useful in patients in whom IM or SC administration of large volumes of other opiate agonists is associated with discomfort or is precluded because of small muscle mass.

Morphine IR tablets/solution is indicated for relief of moderate-to-severe pain, while morphine SR tablets/capsules may be preferable in those requiring continuous opioid therapy for an extended period of time. Morphine SR is not intended for use as an as-needed analgesic. Morphine injection is indicated for relief of moderate-to-severe pain, preoperative apprehension, preoperative sedation, control of postoperative pain, supplement to anesthesia, analgesia during labor, and acute pulmonary edema.

Mechanism of Action

Oxymorphone is a semi-synthetic phenanthrene-derivative opiate agonist. The precise mechanism of action of oxymorphone is unknown, but its effects are believed to result in analgesia.

Morphine is a phenanthrene - derivative opiate agonist; morphine is the principal alkaloid of opium and considered to be the prototype of the opiate agonists.

Oxymorphone modulates pain and exhibits significant specificity at the opioid μ receptor, with less binding to the κ receptor. Oxymorphone differs from morphine in a ketone-group, which makes the molecule more lipid-soluble, conferring greater potency and a more rapid onset of action than morphine. The moderate lipid solubility of oxymorphone facilitates rapid penetration into neurovascular membranes of the brain and spinal cord.

Opioids selective for the μ receptors should display analgesia, decrease respiratory function, slow gastrointestinal function, increase sedation, and inhibit the release of acetylcholine and dopamine. Opioids selective for the κ receptors should display more analgesia, reduce GI motility, increase psychotomimesis, increase sedation, and increase diuresis. It is important to note that drugs that are relatively selective at standard doses may interact with other receptor subtypes when given at higher doses, leading to changes in their pharmacological profile. Morphine, oxycodone, and other related opiates are principally strong μ

Table: Dosage/Availability/Administration

Drug	Equianalgesic Doses		Approximate Equianalgesic 24-hour Dose (assumes around-the-clock dosing)		Ususal Starting Dose (Adults > 50 kg (doses NOT equinanalgesic)	
	Parenteral	Oral	Parenteral	Oral/Other	Parenteral	Oral/Other
Morphine	10 mg	30 mg	3-5 mg q 4 h	10 mg q 4 h	2.5-5 mg q 4 h	5-10 mg q 4 h
Oxymorphone	1 mg	10 mg	0.3-0.5 mg q 4h	5 mg q 6 h	0.5 mg q 4 h	5-10 mg q 4-6 h
Oxymorphone ER	NA	10 mg	NA	10 mg q 12 h	NA	5 mg q 12 h

agonists. Buprenorphine (Buprenex®), butorphanol (Talwin®), and nalbuphine (Nubain®) are examples of κ agonists.

Pharmacokinetics

Food may lead to excessive peaks in absorption of oxymorphone; doses should be given at least one hour prior to eating or two hours after. Oral bioavailability is ~10%; the onset of action with oral immediate release is 15-30 minutes and analgesia is maintained for 4-5 hours, depending on the route of administration. Opana injection has an onset of action of 5-10 minutes and analgesia is maintained for 3-6 hours.

Morphine administration with food may decrease the rate of absorption of ER capsules. Oral bioavailability is 20-40%. Peak analgesia occurs within 60 minutes following oral administration and 20-60 minutes after rectal administration. Peak analgesia occurs within 50-90 minutes following subcutaneous injection, 30-60 minutes after IM injection, and 20 minutes after IV injection. Analgesia is maintained for 3-6 hours with morphine.

Oxymorphone protein binding ranges from 10-12%; it is highly metabolized by the liver. Mean half-life is 3-4 hours and less than 1% of oxymorphone is excreted in the urine as the parent drug.

Morphine protein binding is 36%; it is highly metabolized by the liver. Mean half-life is 2-3 hours and up to 2-12% of morphine is eliminated unchanged in the urine.

The **Table** above summarizes information regarding dosage, availability, and administration.

Contraindications

Both oxymorphone and morphine display similar adverse effects. Due to morphine's high usage, more adverse effects are reported compared to oxymorphone.

Oxymorphone should not be administered to patients with respiratory depression, acute or severe bronchial asthma; hypercarbia; paralytic ileus; moderate-to-severe hepatic impairment; or known hypersensitivity to oxymorphone or morphine analogs such as codeine.

Morphine should not be administered to patients with respiratory depression; known or suspected paralytic ileus; pruritus; or urinary retention, which may persist for 10-20 hours after administration.

Epidural and intrathecal injection of morphine is contraindicated in patients whose concomitant drug therapy or medical condition would contraindicate administration of the drug by these routes, such as when infection is present at the injection site or the patient has uncontrolled bleeding diathesis or is receiving anticoagulants.

In patients with myocardial infarction, morphine causes a decrease in systemic vascular resistance, which may result in a transient fall in systemic arterial pressure and lead to severe hypotension; however, this usually is not a particular threat to supine patients. Morphine should be used with caution in patients with toxic psychoses. Some commercially available formulations of morphine sulfate injection contain sulfites that may cause allergic-type reactions. Morphine sulfate ER (Avinza®) contains fumaric acid. Safety of dosages exceeding 1.6 g daily has not been established; dosages contain a quantity of fumaric acid that may be associated with serious renal toxicity.

Warnings and Precautions

Oxymorphone use with alcohol and drugs of abuse is associated with additive effects; oxymorphone has an abuse liability similar to morphine and other opioid agonists.

Respiratory depression is the chief hazard. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate ther-

apeutic doses may dangerously decrease pulmonary ventilation.

Serious adverse events and deaths have occurred as a result of inadvertent overdosage of concentrated morphine sulfate oral solutions. Milligrams (mg) were mistakenly interchanged for milliliters (mL) of the concentrated preparation, resulting in 20-fold overdoses. It is important that prescriptions for morphine sulfate oral solution be written clearly and filled with the proper concentration of morphine sulfate oral solution to prevent potential medication errors.

Commercially available strengths of morphine sulfate ER capsules are not appropriate for children; the contents of the capsules should not be sprinkled onto applesauce for administration to children.

Adverse Effects

Adverse effects for oxymorphone and morphine are similar. With oxymorphone, the most common (> 10%) include: hypotension, fatigue, drowsiness, dizziness, nausea, vomiting, constipation, weakness, and histamine release.

With morphine, the most common (> 10%) include: palpitations, hypotension, bradycardia, drowsiness (48%, tolerance usually develops to drowsiness with regular dosing for one to two weeks), dizziness (20%), confusion, headache, pruritus (may be secondary to histamine release), nausea (28%, tolerance usually develops to nausea and vomiting with chronic use), constipation (40%, tolerance develops very slowly if at all), xerostomia (78%), urinary retention (16%; may be prolonged, up to 20 hours, following epidural or intrathecal use), and pain at the injection site.

Pregnancy/Lactation

Neither drug should be administered during pregnancy or lactation unless the benefits outweigh the risks. It is unknown whether either drug is excreted in breast milk.

Potential for Medication Error

Look-alike/Sound-alike errors: oxycodone/oxymorphone, hydrocodone/hydromorphone, morphine/meperidine, opa/opcon-A solution.

Other potential medication errors include: confusing oxymorphone with oxymorphone ER, confusing hydromorphone injection with oxymorphone injection, and confusing oral and parenteral drug ratios to morphine.

Precautions/Warnings

Combining oxymorphone with alcohol and drugs of abuse may result in additive effects. The effect of co-ingestion of alcohol with oxymorphone has not been evaluated. Patients must not consume alcoholic beverages or prescription or nonprescription medication containing alcohol while taking oxymorphoen ER. The co-ingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased urinary retention and/or severe constipation, which may lead to paralytic ileus.

Respiratory depression is an adverse drug event. Respiratory depression is a particular problem in the elderly and in debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation. Interactions with other central nervous system depressants may occur.

Oxymorphone has an abuse liability similar to morphine and other opioid agonists. Oxymorphone tablets may be abused by crushing, chewing, snorting, or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death.

New FDA Approvals

FDA recently approved these drugs:

• QLT USA's metronidiazole vaginal gel, 0.75%, the first generic version of 3M's MetroGel-Vaginal was approved for treating **bacterial vaginosis**. FDA said QLT callenged certain patents for the branded drug and is eligible fo-r 180 days of marketing exclusivity. The agency also said the approval is an important step in its efforts to increase availability of lower-cost generic drugs.

• Genentech's trastuzumab (Herceptin®) was approved for an expanded indication of treating **HER2-positive breast cancer** after surgery in

combination with other cancer drugs. FDA gave priority review to the supplemental application for the new indication. Herceptin was first approved in 1998 for treating metastatic breast cancer. The new approval expands its use to women with cancer only in the breast or lymph nodes that has been removed with surgery. FDA said trastuzumab should only be prescribed for women diagnosed with HER2-positive breast cancer.

Trastuzumab is a targeted therapy against the HER2 protein on cancer cells. When an excessive amount of HER2 protein is present, it causes cancer cells to grow more rapidly and standard chemotherapy may be less effective.

The two studies leading to the new approval were conducted by the National Cancer Institute-sponsored Cooperative Groups, a multicenter clinical trials group. Patients in both trials received standard chemotherapy after surgery for breast cancer; approximately half the patients were also given trastuzumab. Due to positive trial results, the National Cancer Institute ended the studies early. The results showed that women who received trastuzumab combined with chemotherapy had fewer relapses for up to three years after surgery. The estimated three-year disease-free rates were 87% in women receiving trastuzumab and chemotherapy and 75% for those receiving chemotherapy alone. FDA said it is too soon to know whether trastuzumab combined with chemotherapy will increase the cure rate or lower the risk of death from breast cancer.

• The first generic versions of GlaxoSmithKline's Zofran (ondanestron) injection and Zofran injection premixed were approved. Ondanestron is indicated for **preventing nausea and vomiting** associated with initial and repeat courses of emetogenic cancer chemotherapy and preventing postoperative nausea and vomiting.

Ondanetron injection packaged in single and multidose vials is manufactured by Teva Pharmaceuticals, while the premixed injection is manufactured by SICOR Pharmaceuticals. FDA said GlaxoSmithKline agreed to waive the remainder of a six-month exclusivity period to permit approval of the Teva and SICOR applications. According to trade publications, Zofran was the 20th most expensive brand name drug used in hospitals in the United States and approval of the generic equivalents will lead to significant cost savings. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

CE Questions

1. Oxymorphone is available in which of the following forms?
A. Immediate release
B. Extended release
C. Injection
D. All of the above

2. Oxymorphone and morphine are indicated for relief of:
A. mild pain.
B. moderate pain.
C. moderate-to-severe pain.
D. All of the above

3. Morphine is the principal alkaloid of opium and considered to be the prototype of the opiate agonists.
A. True
B. False

4. Due to morphine's high usage, more adverse effects are reported compared to oxymorphone.
A. True
B. False