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IN THIS ISSUE

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Multidisciplinary clinic with pharmacist improves care

Can a multidisciplinary diabetes management clinic that includes a pharmacist improve care for patients with Type 2 diabetes mellitus? The answer is a resounding yes, according to **Erin Newkirk**, PharmD, of the University of Iowa Hospitals and Clinics.

Newkirk tells *Drug Formulary Review* that while the American Diabetes Association supports medical care from a multidisciplinary team that includes a pharmacist, studies with such teams are lacking. Three earlier studies evaluated a multidisciplinary team that did not include a pharmacist and were conducted outside the United States.

The purpose of this study, then, was to evaluate patient outcomes in a multidisciplinary diabetes management clinic compared to usual care, which the researchers defined as primary care provided to patients with Type 2 diabetes mellitus in the internal medicine and family medicine clinics at the University of Iowa Hospitals and Clinics. Results of the research were presented at a recent meeting of the American College of Clinical Pharmacists.

The study population included 70 patients from the diabetes clinic that was formed at the hospital in 2002 and 35 patients each from the internal medicine and family medicine clinics. The diabetes clinic has scheduled appointments with patients and is conducted by a multidisciplinary team including a physician, physical therapist, dietitian, pharmacist, and nurse.

The primary study outcome measures compared at baseline and again at six months included changes in blood glucose, blood pressure, and weight; percentage of patients reaching blood glucose and blood pressure goals; percentage of patients receiving appropriate drug therapy; and appropriate urine microalbumin testing.

Newkirk says that at baseline, patients from the internal and family medicine clinics had lower blood glucose levels and lower diastolic blood pressure, and more patients were at blood glucose goal versus patients in the diabetes clinic group.

Blood glucose decreased significantly during the study period in patients in the diabetes clinic group and also in the usual care (internal

and family medicine clinics) group. The diabetes clinic patients also had a significant decrease in diastolic blood pressure and weight.

Significant improvements

When the researchers compared change in the outcome measures from baseline to follow-up, they found that diabetes clinic patients had a larger drop in blood glucose levels and diastolic blood pressure than did those in usual care. More patients in the diabetes clinic than in usual care were prescribed aspirin at follow-up and more were screened for microalbuminuria by follow-up.

Newkirk says that patients referred to the diabetes clinic are generally those with newly-diagnosed Type 2 diabetes mellitus or those with poorly controlled Type 2 diabetes in need of counseling, education, and management. Patients are seen by each team member initially and at follow-up visits as necessary and as time permits. The clinic is held one-half day per week for both new and return patients.

Because patients see each of the team members individually at the first appointment, that appointment generally lasts the full half-day.

Team members each have their own defined responsibilities in the diabetes clinic. Thus, the registered nurse, who is a certified diabetes educator, is responsible for educating patients on their diabetes diagnosis, signs and symptoms of hypoglycemia and hyperglycemia, treating hypoglycemia, ADA recommended goals, self-monitoring of blood glucose, and administering insulin. The physician performs a thorough physical exam and gathers much of the patients' past medical history, social history, and family history.

The dietitian evaluates patients' eating habits and helps them create a healthy and balanced food intake plan for each day. Newkirk says many individuals are taught how to count carbohydrates and plan means accordingly. The physical therapist is responsible for discussing an appropriate patient-specific exercise regimen and proper foot care. And the clinical pharmacist is responsible for obtaining a correct medication list, evaluating patients' current therapy based on their home blood glucose measurements and other lab tests, recommending lab tests to evaluate for safety and efficacy of their medications, recommending changes to the medication regimen based on these findings, and counseling on newly prescribed medications while in the clinic.

Collaborative plan development

Team members work together to collaboratively develop a plan for each patient. Patients are followed for anything from a one-time educational session to ongoing follow-up after the education session. Newkirk says the diabetes clinic's goal is to eventually refer patients back to usual care as provided by their primary care provider, although they want to also comply with an American Diabetes Association recommendation for annual educational sessions.

The study is important, Newkirk says, because the number of patients diagnosed with diabetes mellitus in the United States is quickly escalating. It is estimated that between 2000 and 2050 the number of people diagnosed with diabetes mellitus will increase by 165%.

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The estimated direct medical costs and indirect expenditures associated with diabetes in 2002 were $132 billion, a figure that is expected to rise to some $192 billion by 2020. "There will be more patients to treat to optimal goals and due to the swelling medical costs associated with the increased number of patients developing diabetes, it will become exceedingly important that all of these patients receive optimal care," she says. "For optimal care, the American Diabetes Association recommends that patients with diabetes receive care from a multidisciplinary team. Therefore, it may be advantageous to develop more diabetes management clinics throughout the United States such as the one established at the University of Iowa Hospitals and Clinics."

Overall, according to Newkirk, the study showed that care provided by the diabetes clinic with a pharmacist lowered blood glucose by 1.4%, which may translate to lowering the patients' chance of any diabetes related endpoint by 21%. She says this is an important concept because many of the clinic patients were referred after their primary care physician found they were difficult to control.

[Editor's note: Contact Dr. Newkirk at (319) 384-5100 or by e-mail at erin-newkirk@uiowa.edu.] ■

Antidote triggers find unreported ADRs

Research at the University of Pittsburgh has shown that tracking adult ICU use of antidotes such as protamine and phytonadione can signal adverse drug reactions (ADRs). A report on the study was given at the recent American College of Clinical Pharmacists meeting.

Sandra Kane-Gill, PharmD, MSc, tells *Drug Formulary Review* trigger research generally has not included the adult ICU. The primary study objective, she says, was to evaluate positive predictive values of triggers such as protamine, phytonadione, and methylprednisolone for detecting ADRs in the adult ICU. A secondary objective was to compare the number of ADRs detected using triggers to those voluntarily reported.

Kane-Gill says that while the University of Pittsburgh has a voluntary reporting system that produces a reasonable number of ADRs, many people often feel they are too busy to make a report or there are other reasons why reports are not made.

"We wanted to find a way to identify ADRs in a more assertive way," she says.

As a study at King's College Hospital, London, UK, says, triggers can be abnormal laboratory values, medication stops, and prescriptions for certain drugs, all of which can prompt a more detailed search of patient records for information on an ADR. In that study, almost half of prescriptions for trigger drugs were written in response to an adverse drug event, with vitamin K, Beriplex®, naloxone, calcium resonium, and hydroxyzine found to be the most specific.

In Kane-Gill's study, a retrospective chart review was applied to all patients admitted to the medical ICU from July 1, 2005, to June 30, 2006, who received protamine, phytonadione, and methylprednisolone.

So many patients received phytonadione and methylprednisolone that a random sample of 50 patients each from those two groups was evaluated for related ADRs. Only 11 patients received protamine during the study period and all were evaluated.

Objective assessment used for ADRs

A clinical pharmacist doing the chart reviews used an objective assessment instrument to determine that an adverse drug reaction had occurred. The study defined ADRs as undesirable clinical manifestations consequent to and caused by drug administration.

Positive predictive values were calculated as the proportion of triggers that occurred divided by the number of times that triggers occurred and ADRs were confirmed.

The study found positive predictive values of 0.36 for protamine, 0.18 for phytonadione, and 0.0 for methylprednisolone, respectively. Kane-Gill says none of the ADRs detected using the triggers had been reported on the voluntary reporting system.

Protamine and phytonadione make good triggers, she says, because they typically are given in response to an ADR. "If you see that one of these antidotes has been administered," she tells *DFR*, "you can look at the record and are likely to see that an ADR has occurred."

While this research was done with a retrospective chart review, Kane-Gill says it could be done prospectively and the findings could be used to prevent ADRs.

"If clinical pharmacists could get a real-time alert that an antidote has been administered, we could intervene quickly," she says.

[Editor's note: Contact Dr. Kane-Gill at (412) 624-5150 or e-mail her at slk54@pitt.edu.] ■

Hospitals told how to ease high-alert problems

A report in the *Joint Commission Journal on Quality and Healthcare Safety* makes recommendations for hospitals to follow to reduce patient harm related to high-alert medications. The report comes from the Institute for Healthcare Improvement in Cambridge, MA, and gives specific recommendations for anticoagulants, sedatives, narcotics, and insulin.

Improving safety when using anticoagulants:

- Have formatted anticoagulation flow sheets and orders follow patients through transfers from hospital to skilled nursing facility to home;
- Establish an anticoagulant dosing service or clinic for both inpatient and outpatient care;
- Report laboratory results to a provider who can act on them;
- Permit pharmacists to change doses of antithrombotic agents based on laboratory values by following protocols approved by medical staff;
- Limit warfarin starting doses to 2.5 mg or 5 mg depending on patient age and/or comorbidities; and
- Check medication orders for drug interactions.

Improving safety when using heparin:

- Establish and implement standardized protocols and dosing;
- Develop guidelines to hold heparin and give reversal treatment of heparin overcoagulation; and
- Reduce the potential for errors and simplifying the process by minimizing the number of available concentrations.

Improving safety when using warfarin:

- Use standardized protocols include vitamin K dosing guidelines when starting and maintaining warfarin therapy;
- Develop an evidence-based protocol to discontinue and restart warfarin perioperatively;
- Make laboratory results available on the unit within two hours or monitoring at the bedside;
- Plot international normalized ratio results versus dose changes on the run chart or control chart; and
- Have patients and families participate in self-management.

Improving safety when using narcotics:

- Standardize protocols to begin and maintain pain management;
- Ensure appropriate monitoring to detect adverse effects of narcotics and opiates;
- Make available protocols and reversal agents that can be given without needing additional physician orders;
- Minimize or eliminate multiple drug strengths when possible;
- Consult pain specialists (specially trained nurses, pharmacists, physicians, or others) when managing physicians are not experienced in pain management;
- Maximize nonpharmacologic intervention for pain and anxiety;
- Have pharmacy or nursing staff program and independently double-check all pumps; and
- Independently double-check patient-controlled analgesia and epidural narcotics on the unit.

Improving safety when using insulin:

- Independently double-check the drug, concentration, dose, pump settings, route of administration, and patient identity before administering any intravenous insulin;
- Use pretyped forms for diabetic and insulin infusion orders;
- Separate look-alike and sound-alike drugs by labeling, time, and distance;
- Prepare all infusions in the pharmacy and standardize them to a single concentration of intravenous infusion insulin;
- Encourage patients who are able to manage their own insulin; and
- Coordinate meal and insulin times.

Improving safety when using sedatives:

- Stock and prescribe only one concentration of oral agents for moderate sedation;
- Use preprinted order forms for narcotics and sedatives;
- Monitor all children who have received chloral hydrate for preoperative sedation before, during, and after the procedure; and
- Make available age- and size-appropriate

resuscitation equipment and reversal agents during procedures performed when a patient is sedated and in other situations where sedatives are administered. ■

Prescribing changes as patients near death

A study intended to determine how prescribing for comorbid illnesses and symptom control changes during the palliative phase of a terminal illness found older people take more medications and says medications for comorbid conditions should be reviewed in the context of their original therapeutic goals.

Published in the *Journal of the American Geriatric Society*, the Australian study reported that chronic comorbid conditions are commonly encountered in people with life-limiting illnesses, with the most frequently seen being cardiovascular diseases, including hypertension; chronic obstructive pulmonary disease; and diabetes. "Management of these comorbid problems needs to be actively reviewed in response to the systemic changes encountered in the palliative phase of a life-limiting illness," the researchers wrote.

The study was conducted in Adelaide, South Australia, where specialized palliative care services funded by the state government provide consultative specialist nursing, medical, and allied health support for general practitioners and community nurses who are the primary point of care. Palliative care services there are organized as regional whole population networks.

Lead researcher **David Currow,** BMed, MPH, says that because one study aim was to improve specialized palliative care delivery, eligibility criteria were broad. All adult patients referred to the service with any form of pain in the preceding three months were eligible after providing written informed consent. Patients who were expected to die within 48 hours or who lived outside the geographic region served by the team were excluded.

As part of the study, enrolled patients underwent community-based nursing reviews at baseline, biweekly for three months, and then at least monthly until death. Data collected included a list of medications taken regularly at each specialist nursing review. Medication reports included generic drug name, dose, route of administration, indication and frequency, and pattern of use (regularly or as needed). Medications were divided into two categories: those for comorbid conditions and those for symptom control for the patients' life-limiting illnesses. Areas of overlap such as antidepressants or anti-epileptic medications (both of which are also frequently used for neuropathic pain) were classed with symptom-control medications.

Logical findings

According to Currow, many of the study findings appear intuitively logical but have not been documented previously. It is clear, he says, that as health care practitioners recognize the palliative phase of life-limiting illnesses, comorbid conditions must be actively managed.

Generally, new medications were added to patients' regimens for symptom control as the primary life-limiting illness progressed. Although there was a statistically significant decrease in medications for comorbid medical conditions, this reduction occurred at the time at which an increase in symptom control medication was noted. That overlap coincides with a period of decreasing function, the researchers said, and future research is needed to define whether the overlap is contributing to an acceleration in declining global function.

Medications for comorbid conditions, especially for secondary prevention, may be continued for longer than clinically indicated, Currow says, with a consequent potential risk of iatrogenic harm. He says there may be opportunities to prevent morbidity and even premature mortality in a person with a life-limiting illness, especially in older people, if medications for comorbid conditions are more actively managed. Likewise, judicious use of symptom-control medications is needed because there is the risk from many of these medications for adverse reactions and adverse medicine interactions for which other strategies may lessen potential harm.

Although the study found that clinicians reduced the number of medications for comorbid conditions, there were an increasing number of medications for symptom control introduced that met high-risk criteria. Given the frailty of the population receiving palliative care, the researchers said, and the predictable decline in functional status, minimizing medications that meet the consensus-derived Beers' risk criteria is important.

The study found that adverse drug reactions and interactions increase when more medications are taken. "The risk of an adverse medication

interaction is greater than 80% when more than seven medications are taken regularly," Currow asserts. "Significant drug-drug interactions have been documented in a population receiving palliative care. In the setting of a life-limiting illness, pathophysiological changes such as cachexia can lead to changes in metabolism, excretion, and volume of distribution of long-term medications that need to be considered when assessing their ongoing net benefit. The underlying indications for the management of long-term conditions such as hypertension or diabetes may also change with cachexia-associated weight loss at the end of life."

Don't stop meds completely

The researchers caution they are not suggesting that medications for comorbid conditions should be stopped simply because a person has a life-limiting illness, noting that many medications for comorbid conditions need to be continued judiciously to maintain optimal function and comfort for the patient.

Now that their study established a baseline, the researchers say, other hospital units need to collect similar longitudinal data to compare with these findings. Also, specific work needs to be performed to adapt the Beers' criteria to the palliative care population. And guidelines and frameworks suggested in the literature for managing comorbid illnesses for people with a life-limiting illness need to be prospectively evaluated to define the magnitude of reduction in any adverse outcomes in that population with continually changing physiology. ■

Robot works for patient safety at Nebraska Medical

The newest employee in the remodeled inpatient pharmacy at the Nebraska Medical Center in Omaha is eight feet tall and 36 feet wide and is capable of storing 44,000 medication unit doses. The center has installed a Swisslog PillPick™ system in hopes of ensuring greater patient safety, reducing medication errors, and increasing productivity by giving pharmacists more time to spend consulting with physicians and nurses about patient care and medication safety.

The system packages, stores, and dispenses medications in bar-coded, unit-dose form, and can dispense more than 6,000 unit doses daily.

"Fewer than 1% of acute care hospitals in North America have this technology," said Nebraska Medical Center executive director of pharmacy and pathology services, **Mike Powell**. "The Nebraska Medical Center is fortunate to have such state-of-the-art technology. This system will definitely help eliminate possible medication errors."

Powell said bar-coding has the potential to dramatically reduce medication errors during dispensing and administration. "Accurate dispensing is key to patient safety and automatic packaging based on bar code recognition assures us of that," he said. "The robot also offers compact and efficient storage.

Additionally, bar-codes will help our hospital make sure that the doctors and nurses are administering the right drugs at the appropriate dosages. The reduction of medication errors has an obvious patient impact and has a financial benefit, too. As a general rule, each adverse drug event due to medication errors can add more than $5,800 to the hospital bill of a single patient." He said the added costs come from factors such as longer hospital stays, drugs used to counteract incorrect dosages, and extra nursing and physician costs.

A critical component to bar code implementation happens at a patient's bedside, center officials said. In a typical administration cycle using bedside verification, a nurse will scan the bar code on the unit dose and scan the patient's wristband to ensure that the "five rights" are met: right patient, right drug, right dose, right route, and right time. The nurse also scans the bar code on his or her hospital identification badge to record who administered the drug.

Pharmacy and nursing must work together

It is vitally important that pharmacy and nursing work closely together, said Nebraska Medical Center director of nursing resources and development **Dawn Straub**, RN. "Nurses are at the sharp end of patient care delivery, that point where all preceding work and actions of others culminate into actual intervention to the patient," she said. "Bar coding will help provide patient safety at this point of interaction and give the nurse a safety net."

The PillPick also promotes safety because it is fully automated. After it is filled and verified by a pharmacist, the doses dispensed are not touched by human hands until they are given to a patient. It contains up to a three-month supply of commonly

dispensed drugs.

"Simply put, the more human intervention, the greater probability for error," Powell said. "This automated system minimizes handling by pharmacy staff, reducing the potential for human error.

After just one month of operation, Center staff were seeing "amazing results," according to director of pharmaceutical and nutrition care **Chris Shaffer**. "One big difference is the phones aren't constantly ringing in the pharmacy any more because nurses aren't calling about missing medication doses," Shaffer said. "We estimate the PillPick system will eliminate about 17,000 phone calls a year." Shaffer also said the system eliminates the tedious and time-consuming tasks of handling and packaging unit-dose medications, freeing pharmacists to spend more time consulting with physicians and nurses on patient care.

"Research shows that when pharmacists round with physicians, medication errors are reduced by up to two-thirds," Shaffer said. ■

Correction

In a story in the August 2007 *Drug Formulary Review*, the name of former University of Utah researcher **Shobha Phansalkar** was inadvertently misspelled. We regret this error.

NEWS BRIEFS

First responders helped by inhaled corticosteroids

Prophylactic use of inhaled corticosteroids reduced respiratory symptoms and improved quality of life for emergency responders working at the World Trade Center in New York on Sept. 11, 2001, according to a report given at CHEST 2007, the international scientific assembly of the American College of Chest Physicians.

The report was given by **David Prezant**, MD, FCCP, from Montefiore Medical Center in the Bronx, NY, who has been monitoring first responder respiratory status. He said a group of 156 firefighters who responded to Ground Zero began taking inhaled budisonide (AstraZeneca's Rhinocort® and Pulmicort®) two weeks after the attack. They experienced fewer respiratory symptoms and improved quality of life within four to six weeks of treatment compared with other workers who did not take the inhaled steroids, he said.

Some 3,000 firefighters originally enrolled in the study, but only 156 completed a minimum of four weeks of budesonide treatment.

Prezant told Reuters Health the subjects had a significant amount of fear over taking the drug, with many of the firefighters confusing it with anabolic steroids. Another significant number said they had not experienced symptom relief and stopped using their inhalers after a few days.

Those who completed the recommended amount of treatment showed "some clinical and statistically significant changes in symptoms and without any side effects," according to Prezant. He said forced vital capacity improved over 18 months, while the forced expiratory volume in one second declined in the first two years among those who did not take budesonide.

"The important thing to remember is that with any kind of disaster like that, there are going to be a lot of respiratory irritants and particulate matter," Prezant said.

He said prophylactic inhaled corticosteroids may be useful for those fighting wildfires and other emergency responders with prolonged exposure to particulate matter, but warned that patients need to be informed about the need for taking at least four weeks of treatment and need to be taught about adverse effects. Informed consent is necessary, he said, because this is an off-label use of the medications.

COMING IN FUTURE MONTHS

- New erythropoietin labeling
- Sensitivity to pharmacist interventions
- Pharmacist impact on medication reconciliation
- Pharmacist intervention in ED stroke care
- Reducing medication discrepancies
- The pharmacist's role in reducing pain

FDA expands age range for Menactra use

FDA has expanded the approved age range for Sanofi-Pasteur's bacterial meningitis vaccine Menactra® to include children ages 2-10 years. Menactra was first approved January 2005 for people 11-55 years old. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends meningococcal vaccination for children ages 2-10 who are at increased risk of developing meningococcal disease, such as those who have had their spleen removed or whose spleen is not functioning; those with a terminal complement component deficiency; and those who expect to travel outside the United States where the disease is common. Until now, the only vaccine available in the United States for use in children age 2-10 was Sanofi-Pasteur's Menomune™.

Menactra's effectiveness was measured in clinical trials with people ages 2- 55 years. It was shown to produce an immune response one month after vaccination. Its safety was evaluated in eight clinical studies that included a total of 10,057 participants who received Menactra and 5,266 participants who received Menomune.

The most common adverse events reported in the studies were pain at the injection site and irritability. Diarrhea, drowsiness, and lack of appetite also were common.

While not observed in the clinical trials, Guillain-Barré syndrome was noted as a possible but unproven risk in some adolescents following immunization with Menactra, occurring in an estimated one in one million vaccine recipients. FDA said that as a precaution, people who have previously been diagnosed with Guillain-Barré syndrome should not be given Menactra.

Change in Humate-P storage approved

FDA has approved a change in storage conditions for CSL Behring's Humate-P, a treatment for bleeding in certain patients with hemophilia A or von Willebrand disease. The treatment can now be safely stored for up to two years at 77° F. Previously, it required refrigerator-level temperatures for that length of storage.

Humate-P is manufactured from human plasma obtained from screened and tested U.S. donors.

Reported adverse reactions include allergic reactions such as hives, rash, chest tightness, swelling, and shock. ■

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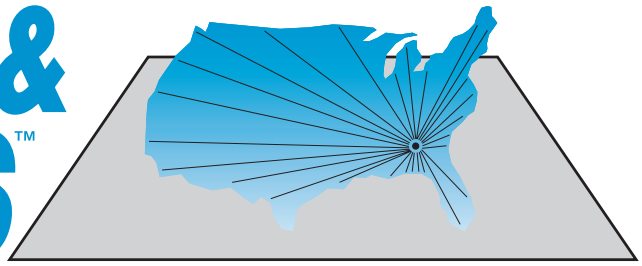

Phosphate laxatives: The renal risk

By **Wade Williams**, PharmD Candidate, Auburn University Harrison School of Pharmacy

Oral sodium phosphate (OSP) products are commonly used for bowel cleansing, but many health care professionals are not aware of a serious adverse effect associated with these drugs. Acute phosphate nephropathy, a type of acute renal failure, is a missed cause of renal failure in patients with post oral sodium phosphate therapy. OSP products are commonly prescribed as a method of bowel cleansing prior to colonoscopy, radiographic procedures, and surgery. This method of bowel cleansing has been determined as the cause for acute renal failure in more than 20 documented cases where renal biopsies were taken, and many more cases without biopsies have shown an association with OSP products.

Oral products containing sodium phosphate include Fleet® Phospho-soda®, Fleet Accu-Prep®, Visicol®, and OsmoPrep™. The bowel cleansing doses of OSP solutions (two 45 mL doses prior to procedure) and Visicol (40 tablets) provide similar amounts of sodium phosphate: about 60 g per dose. OsmoPrep (tablet) is the latest OSP product and was approved in March 2006; the 32-tablet dose contains 48 g of sodium phosphate, and no cases of acute phosphate nephropathy have been associated with this product yet.

What is acute phosphate nephropathy?

Acute phosphate nephropathy is a type of nephrocalcinosis. Nephrocalcinosis is characterized as renal parenchymal calcium deposits that contribute to renal insufficiency and is usually linked to conditions associated with hypercalcemia. Acute phosphate nephropathy presents as acute renal failure with minimal proteinuria and bland urine sediment in patients recently receiving oral sodium phosphate. Calcium-phosphate crystal deposition in the distal tubules and collecting ducts along with acute or chronic renal tubular injury is seen in renal biopsy.

In the doses needed for bowel cleansing, oral sodium phosphate can cause decreased intravascular volume and hyperphosphatemia. Decreased intravascular volume stimulates reabsorption of water from the renal tubules, further increasing the phosphate concentration in renal tubular fluid. The abnormally high calcium phosphate concentration in the renal tubular fluid causes precipitation of calcium phosphate crystals in the kidney that leads to nephropathy.

Supporting data

A case series study describing 21 biopsy-proven cases of acute phosphate nephropathy in patients who were treated with OSP products for bowel cleansing was published in Nov. 2005; 16 of the 21 patients had a history of hypertension, and 14 were on an ACE inhibitor or angiotensin receptor blocker (ARB). The mean age was 64 years with 17 of the patients being female; only four patients had pre-existing renal insufficiency. One patient received Visicol tablets, and all other patients received Fleet Phospho-Soda or a generic equivalent. One patient received 120 mL of OSP solution over 12 hours, which significantly exceeds the recommended dose; however, all other patients received the standard dose. Average baseline serum creatinine was 1.0 mg/dL, and increased to an average of 3.9 mg/dL at a median of one month after colonoscopy. The time to discovery of acute renal failure post colonoscopy ranged from one day to five months.

Several other cases have been published showing renal failure following oral sodium phosphate treatment for bowel cleansing. A 76-year-old man received multiple doses of OSP solution and developed acute renal failure with a peak phosphorus level of 15.8 mg/dL. Hemodialysis quickly decreased phosphorus levels and renal function returned to normal one month later. Reports of OSP solution and tablets have been published as well. In addition, 20 cases have been reported to the FDA with half of those implicating the tablet dosage form.

The literature identifies patients that may be at a higher risk of acute phosphate nephropathy: patients with impaired renal function, reduced intravascular volume, or electrolyte abnormalities. Also, patients currently taking ACE inhibitors, ARBs, diuretics, or NSAIDs are believed to be at an increased risk. ACE inhibitors, ARBs, and NSAIDs can all decrease renal perfusion by dilation of renal arterioles. This becomes particularly problematic with volume depletion in which further reductions in perfusion exist, and diuretics may also cause volume depletion. Use of these medications should be monitored when considering a phosphate laxative.

FDA recommendations

- Avoid use of OSP in patients with kidney disease, impaired renal function of perfusion, dehydration, or uncorrected electrolyte abnormalities.
- Avoid exceeding recommended OSP doses and avoid concomitant use of laxatives containing sodium phosphate.
- Use OSP with caution in patients taking diuretics, ACE inhibitors, ARBs, and NSAIDs.
- Encourage patients to take the correct OSP dose and drink sufficient quantities of clear fluids during bowel cleansing.
- Obtain baseline and post-procedure labs (electrolytes, calcium, phosphate, BUN, and creatinine) in patients who may be at increased risk for acute phosphate nephropathy, including those with vomiting and/or signs of dehydration.
- Use hospitalization and intravenous hydration during bowel cleansing to support frail patients who may be unable to drink an appropriate volume of fluid or may be without assistance at home.

Options

Since there is no way to avoid bowel cleansing prior to colonoscopy, alternatives are needed for patients that are not good candidates for OSP products. Polyethylene glycol (Golytely®, Colyte®) is a safe and effective option, and it requires the patient to drink a large volume of fluid, which would reduce the risk of volume depletion. Many physicians and patients prefer the ease of OSP products; however, polyethylene glycol may offer a safer option for some patients.

Magnesium citrate is another option for bowel cleanings; however, this laxative is completely excreted renally and should also be used with extreme caution in patients with renal deficiency. Magnesium citrate may also cause a significant shift in fluid and electrolytes, and it is believed that an osmotically balanced product, such as polyethylene glycol, may be a safer alternative.

Conclusion

Acute phosphate nephropathy and chronic renal impairment are serious conditions that can occur with OSP bowel cleansing; however, these events are rare. OSP products for bowel cleansing involve a large phosphate load, fluid shifts, possible dehydration, and a rare adverse effect that can be devastating. Practitioners should be aware of the risk profile of OSP products and be able to determine which patients might be at an increased risk for nephropathy.

References

1. Markowitz G, Stokes MB, Radhakrishnan J, et al. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: An underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005;16:3389-3396. Epub 2005 Sep 28.
2. Orias M, Mahnensmith RL, Perazella MA. Extreme hyperphosphatemia and acute renal failure after a phosphorus-containing bowel regimen. *Am J Nephrol* 1999;19:60-63.
3. Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003;349:1006-1007.
4. Fleet Laboratories. Available at: www.phosphosoda.com.
5. Clark LE, Dipalma JA. Safety issues regarding colonic cleansing for diagnostic and surgical procedures. *Drug Saf* 2004;27:1235-1242.
6. Food and Drug Administration. Food and Drug Administration Science Background Paper: Acute phosphate nephropathy and renal failure associated with the use of oral sodium phosphate bowel cleansing products. Available at: www.fda.gov/cder/drug/infopage/OSP_solution/backgrounder.htm. Accessed on: Nov. 6, 2007. ■

New FDA Approvals

FDA recently announced these approvals: The first generic versions of Novartis' anticonvulsant Trileptal® (oxcarbazepine) have been approved by FDA for use alone or in combination with other medications in treating **partial seizures** in adults and children ages four and older.

Oxcarbazepine tablets in 150 mg, 300 mg, and 600 mg strengths are being manufactured by Roxane Laboratories, Inc., Glenmark Pharmaceuticals Limited, and Sun Pharmaceutical Industries Limited.

FDA said labeling of the generic products may differ from Trileptal because parts of the Trileptal labeling are protected by patents and/or exclusivity.

Serious skin reactions have been reported in children and adults associated with Trileptal use. Common side effects reported with Trileptal include dizziness and drowsiness.

FDA has approved Johnson & Johnson's Doribax™ (doripenem injection, 500 mg intravenous infusion) for treating **complicated urinary tract and intra-abdominal infections**. The agency said Doribax has been shown to be active against several strains of bacteria.

In several multicenter, multinational studies, doripenem was shown to have a cure rate comparable to the currently prescribed medications levofloxacin (Ortho-McNeil's Levaquin®), for complicated urinary tract infections, and meropenem (AstraZeneca's Merrem®), for complicated intra-abdominal infections.

The most common adverse reactions reported were headache, nausea, diarrhea, rash, and phlebitis. Also, allergic reactions have occurred and some may require immediate treatment.

FDA said doripenem's safety and effectiveness in pediatric patients have not been established. And it has not been studied in pregnant women and should only be used during pregnancy if clearly needed.

Bristol-Myers Squibbs' intravenous infusion Ixempra™ (ixabepilone), a new **cancer treatment**, has been approved by FDA for use in patients with metastatic or locally advanced breast cancer who have not responded to certain other cancer drugs. FDA evaluated ixabepilone under priority six-month review. It was approved for use in combination with capecitabine (Roche's Xeloda®) in patients who no longer benefit from two other chemotherapy treatments, including an anthracycline such as doxorubicin or epirubicin, and a taxane such as paclitaxel or docetaxel.

Ixabepilone also was approved for use alone in patients who no longer benefit from an anthracycline, a taxane, and capecitabine.

FDA said ixabepilone has been shown to bind to cancer cell microtubules, structures within cells that help to support and shape them and also play a role in cell division.

The drug's safety and effectiveness in combination with capecitabine were evaluated in 752 patients in a randomized clinical trial comparing the combination to capecitabine alone. The combination therapy demonstrated improvements in delaying cancer progression or death compared to capecitabine alone, the agency said. Safety and efficacy of ixabepilone administered alone were evaluated in a study of 126 patients. Clinically significant tumor shrinkage occurred in 12% of the patients.

Ixabepilone's significant side effects include peripheral neuropathy and bone marrow suppression. Other commonly observed toxicities included constipation, nausea, vomiting, muscle pain, joint pain, fatigue, and general weakness. Ixabepilone should not be taken by women who have had severe allergic reactions to drugs that contain cremophor or its derivatives, or by women who have had baseline bone marrow suppression determined by low white blood cell or platelet count.

The combination of ixabepilone and capecitabine should not be given to patients with moderate or severe liver impairment due to increased risk of toxicity and death.

FDA has approved Merck's Isentress™ (raltegravir) tablets for treating **HIV-1 infection** in combination with other antiretroviral agents in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

FDA said raltegravir is the first agent of a drug class known as HIV integrase strand transfer inhibitors. It is designed to interfere with the enzyme that HIV-1 needs to multiply.

When used with other anti-HIV medicines, raltegravir may reduce the amount of HIV in the

blood and may increase white blood cells to help fight off other infections. Agency approval of raltegravir is based on data from two studies in 699 HIV-1 infected patients with histories of extensive antiretroviral use. A greater proportion of the patients who received raltegravir in combination with other anti-HIV drugs experienced reductions in the amount of HIV in the blood, compared with patients who received placebo in combination with other anti-HIV drugs.

The most common adverse events reported with raltegravir were diarrhea, nausea, and headache. Blood tests also showed abnormal elevated levels of a muscle enzyme in some patients receiving the drug.

Patients taking raltegravir may still develop infections, including opportunistic infections or other conditions that may develop in patients living with HIV-1 infection. Its long-term effects are not known and its safety and effectiveness in children younger than age 16 have not been studied. It also has not been studied in pregnant women. FDA said women who are taking HIV medications when they get pregnant are advised to talk with their doctor or other health care professional about use of this drug during pregnancy and about registering with the antiviral pregnancy registry if they use it. ■

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.

21. Oral sodium phosphate (OSP) products are commonly prescribed as a method of bowel cleansing prior to:
    A. colonoscopy.
    B. radiographic procedures.
    C. surgery.
    D. All of the above

22. Acute phosphate nephropathy is a type of nephrocalcinosis, which is characterized as renal parenchymal calcium deposits that contribute to renal insufficiency and is usually linked to conditions associated with hypercalcemia.
    A. True
    B. False

23. The use of OSP should be avoided in patients with:
    A. kidney disease.
    B. impaired renal function of perfusion.
    C. dehydration.
    D. uncorrected electrolyte abnormalities.
    E. All of the above

24. Which of the following is the safest option in patients with renal impairment?
    A. Magnesium citrate products
    B. Polyethylene glycol products
    C. Oral sodium phosphate products
    D. All of the above

DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

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