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Pharmacist involvement may lower preventable ADEs rates after discharge

Communication, documentation problems result in meds discrepancies

Pharmacist counseling and follow-up are associated with lower rates of preventable adverse drug events (ADEs) after patient discharge from the hospital, a new study indicates.

Previous studies have shown that counseling patients before discharge reduces medication discrepancies and improves adherence, the researchers say. The effects of pharmacist interventions on ADEs after discharge, however, are more unknown. These researchers wanted to identify drug-related problems (DRPs) during and after medical hospitalization and to evaluate the effects of counseling and follow-up by pharmacists on the rate of preventable ADEs, health care utilization, medication nonadherence, and medication discrepancies 30 days after discharge from an acute care hospital.

The researchers believed that pharmacist interventions might reduce the rate of preventable ADEs after discharge — and that's the study's most significant finding, says **Jennifer Kirwin**, PharmD, BCPS, a researcher in the study and assistant clinical specialist at Northeastern University School of Pharmacy in Boston. Thirty days after discharge, preventable ADEs were detected in 11% of patients in the control group (eight patients) and 1% of patients (one patient) in the intervention group.

"Different parts of our results have been shown in other studies, and we were able to [duplicate them] but bring something new," she says. "That was what was most interesting to us in this study."

Four pharmacists involved in study

The researchers conducted a randomized trial of 178 patients being discharged to home from the general medicine service at Brigham and Women's Hospital (BWH) in Boston from April 1, 2002, through March 20, 2003. Two patients were excluded, 92 received pharmacist interventions, and 84 received usual care.

Four pharmacists were involved in this study. Two primarily did inpatient counseling on discharge, Kirwin handled most follow-up calls

to patients after discharge, and the fourth acted as a floater who stepped in for one of the other three pharmacists when the need arose.

The pharmacist intervention on the day of discharge consisted of several parts, the researchers say. "First, discharge medication regimens were compared with preadmission regimens and all discrepancies were reconciled with the medical team's help. Patients were screened for previous DRPs, including nonadherence, lack of efficacy, and side effects. The pharmacist reviewed the indications, directions for use, and potential adverse effects of each discharge medication with the patient and discussed significant findings with the medical team."

During the follow-up telephone call to patients three to five days after discharge, Kirwin compared the patient's self-reported medication list with the discharge list. She also asked about medication adherence, possible ADEs, and adherence with scheduled follow-up and laboratory appointments. Significant findings were entered into the electronic medical record used by all BWH outpatient practices and were communicated to the patient's primary care physician through a standard e-mail template.

Of the total patients involved in this study, the researchers also were able to contact 152 patients 30 days after discharge to see if a preventable ADE had occurred. Fourteen additional patients visited the emergency department (ED) or were readmitted to the hospital.

More communication uncovers discrepancies

One problem the pharmacists found at discharge counseling is that the medical team had often misunderstood the patient's preadmission medication regimen and carried through these inaccuracies to the discharge medication orders. These included 34 missing medications, a different dose or frequency of a medication in 12 cases, and a different medication in the same class in 11 cases; 45 patients (49%) had one or more unexplained discrepancies in their discharge medication orders.

The pharmacists also found that 15 patients (16%) admitted to having had problems with their medication regimens before admission, including possible side effects and difficulties with adherence. Pharmacists suggested 23 changes to discharge medications on other clinical grounds. Overall, pharmacists recommended 80 changes in 55 patients (60%).

During follow-up telephone calls three to five days after discharge (79 patients total), pharmacists noted discrepancies between the discharge medication list and the patient's reported home regimen in 56 patients (71%), according to the study results. In 33 patients (42%), discrepancies represented reported changes by the patients' physicians or were changes in as-needed or over-the-counter medications only. Twenty-eight of the remaining discrepancies in 23 patients (29%) remained unexplained.

Most discrepancies involved changes in dose or frequency or complete omission of a prescribed medication. In addition, possible medication side effects were noted in 37% (29 patients), medication nonadherence in 23% (18), difficulty obtaining refills in 18% (14), and difficulty with medication costs in 11% (9). (These results were published in the March 13 issue of the *Archives of Internal Medicine*.)

In addition to the larger number of preventable

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ADEs 30 days after discharge in the intervention group, the rate of preventable, medication-related ED visits or hospital readmissions was 1% in the intervention group and 8% in those assigned to usual care. The groups did not differ significantly with respect to total ADEs, total health care utilization, patient satisfaction, medication adherence, or duration or severity of ameliorable ADEs, the researchers say. Unexplained discrepancies between discharge medication regimens and self-reported medications 30 days after discharge were common in both control and intervention groups (65% and 61%, respectively).

Problems with communication and documentation were commonly related to medication discrepancies, the researchers say. That's not surprising, Kirwin says. Patients come to the hospital from different geographic regions and then return home after discharge. "It underscored the communications problems we were having."

"Obviously, there are going to be different levels of communication from the hospital physicians to the primary care physicians. [Hospital physicians] don't have access to all the same information. This was definitely a factor in the study."

Preventable ADEs in the study were due to a number of factors, including discrepancies and inappropriate prescribing before discharge, as well as discrepancies, lack of medication access, nonadherence, and inadequate drug monitoring after discharge. Pharmacists in general should note the different reasons for the preventable ADEs, Kirwin says.

"It wasn't always adherence, and it wasn't always a knowledge issue. There were also problems with access to medications. All of these different factors played into it," she says. "When pharmacists work with patients who are recently discharged or transferring settings, they should keep in mind all the potential pitfalls." ■

FDA issues 2005 approvals for drugs, biologic products

CDER's approvals for NMEs decrease from 2004

The FDA recently announced its 2005 approvals for new drug applications (NDAs) and biologic license applications (BLAs).

The Center for Drug Evaluation and Research (CDER), the FDA's organization for setting and ensuring the standards for the safety and effectiveness of drugs and certain therapeutic biologic products, approved 78 new drug applications (NDAs) and two biologic license applications (BLAs) in 2005. Of these 80 approvals, 20 were for New Molecular Entities (NMEs), products that have not previously been marketed. While this represents a relatively low number of NME approvals historically, the FDA says, 15 of these approvals were designated for priority reviews (down from 21 in 2004). The five approved under standard review was 10 fewer than was approved under standard review in 2004. CDER also approved 13 orphan-designated products for the treatment of rare diseases.

The median total approval time for priority review remained the same as 2004 — six months. The median total approval time for standard review decreased slightly from 24.7 months in 2004 to 23 months in 2005.

Significant CDER approvals in calendar year 2005 include:

- Entecavir (Baraclude) for the treatment of chronic hepatitis B virus infection.
- Mecasermin (Increlex) and mecasermin rinfabate (IPLEX) for the long-term treatment of growth failure in children with severe primary growth-factor deficiency.
- Tipranivir (Aptivus), in combination with ritonavir, for the antiretroviral treatment of HIV-1-infected adult patients with evidence of viral replication. These patients already had used many HIV medicines, and had a type of virus resistant to currently available HIV therapy. This new combination therapy provides a new treatment option for patients with limited options.
- Abatacept (Orencia) for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
- Sorafenib (Nexavar) for the treatment of patients with advanced renal cell carcinoma.

In addition, CDER approved 452 generic medications. Generic products approved in 2005 include 13 treatments for HIV/AIDS that will be available for purchase abroad as part of the President's Emergency Plan for AIDS Relief.

CBER approves 18 BLAs in 2005

The FDA's Center for Biologics Evaluation and Research (CBER) approved 18 BLAs in 2005. Six of the 2005 approvals were for vaccines, a category of products that is important because of the potential risks of pandemic influenza and bioterrorism.

CBER oversees the safety and effectiveness of biological products, including vaccines, blood and blood components, human tissues, certain medical devices, and novel products such as cell-, gene-, and tissue-based therapies. CBER's major product approvals in 2005 include:

• Fluarix, GlaxoSmithKline's (GSK's) influenza vaccine for immunization of adults ages 18 and older against influenza caused by virus types A and B. Fluarix, which was approved in just over three months, was the first vaccine to receive the FDA's accelerated approval.

• Two Vaccinia Immune Globulin Intravenous (VIGIV) products to treat certain rare complications of smallpox vaccination. Both products were granted priority review.

• Procleix WNV Assay, the first test to screen blood, tissue, cell, and organ donors for West Nile virus. The test will help protect patients who receive blood and other donated products against West Nile infection. In the past, about 30 patients are believed to have acquired the virus from a blood transfusion, and nine of them died.

• Two new combination vaccines to prevent whooping cough: Boostrix (GSK) for adolescents ages 10-18, and Adacel for ages 11-64. ■

Alert issued on tubing, catheter misconnections

Luer connectors a common component

The Joint Commission on Accreditation of Healthcare Organizations in Oakbrook Terrace, IL, has issued a *Sentinel Event Alert* that asks health care organizations to pay special attention to how tubing and catheters are connected so dangerous misconnection errors can be prevented.

The Joint Commission says nine cases involving tubing misconnections had been reported to its Sentinel Event Database by early April. These cases, which affected seven adults and two infants, resulted in eight deaths and one instance of permanent loss of function. Reports in the media and to organizations such as ECRI (formerly the Emergency Care Research Institute), the FDA, the Institute for Safe Medication Practices, and United States Pharmacopeia (USP) indicate that misconnection errors occur with "significant frequency and, in a number of instances, lead to deadly consequences," the *Alert* says.

Several different types of tubes and catheters are involved in the misconnections reported to the Joint Commission. They include: central intravenous (IV) catheters, peripheral intravenous catheters, nasogastric feeding tubes, percutaneous enteric feeding tubes, peritoneal dialysis catheters, tracheostomy cuff inflation tubes, and automatic blood pressure cuff insufflation tubes. The specific misconnections involved an enteric tube feeding into an intravenous catheter (four cases); injection of barium sulfate (gastrointestinal contrast medium) into a central venous catheter (one case); an enteric tube feeding into a peritoneal dialysis catheter (one case); a blood pressure insufflator tube connected to an intravenous catheter (two cases); and injection of intravenous fluid into a tracheostomy cuff inflation tube (one case).

Many of these misconnection cases and of the more than 300 reported to USP's databases, however, involve luer connectors, the small devices used in the connection of many medical components and accessories. Luer connectors are common to many of these errors because they enable functionally dissimilar tubes or catheters to be connected, the Joint Commission says. Examples of misconnections involving luer connectors include the following:

• Capnography sampling tube to an intravenous cannula.

• Enteral feeding set to a central venous catheter.

• Enteral feeding set to a hemodialysis line.

• Noninvasive blood pressure insufflation tube to a needleless IV port.

• Oxygen tubing to a needleless IV port.

• Sequential compression device hose to needleless "piggyback" port of an IV administration set.

Even with these problems, no standards are currently published that specifically restrict the use of luer connectors to certain medical devices. The solution to reducing these errors, health safety experts say, is to use engineering controls that respect how products and devices are designed and to re-engineer work practices. For example, **Stephanie Joseph**, project engineer for ECRI, recommends that hospitals avoid buying nonintravenous equipment that can mate with the luer connectors on patient IV lines. Clinicians should also trace all lines back to their origin before connecting or disconnecting any devices or infusions.

The Joint Commission has offered recommendations and strategies of its own to help health

care organizations reduce tubing misconnection errors. These are:

- Do not purchase nonintravenous equipment that is equipped with connectors that can physically mate with a female luer IV line connector.
- Conduct acceptance testing (for performance, safety, and usability) and, as appropriate, risk assessment (e.g., failure mode and effect analysis) on new tubing and catheter purchases to identify the potential for misconnections and take appropriate preventive measures.
- Always trace a tube or catheter from the patient to the point of origin before connecting any new device or infusion.
- Recheck connections and trace all patient tubes and catheters to their sources upon the patient's arrival to a new setting or service as part of the hand-off process. Standardize this "line reconciliation" process.
- Route tubes and catheters having different purposes in different, standardized directions (e.g., IV lines routed toward the head; enteric lines toward the feet). This is especially important in the care of neonates.
- Inform nonclinical staff, patients, and their families that they must get help from clinical staff whenever there is a real or perceived need to connect or disconnect devices or infusions.
- For certain high-risk catheters (e.g., epidural, intrathecal, arterial), label the catheter and do not use catheters that have injection ports.
- Never use a standard luer syringe for oral medications or enteric feedings.
- Emphasize the risk of tubing misconnections in orientation and training curricula.
- Identify and manage conditions and practices that may contribute to health care worker fatigue, and take appropriate action. ■

Report: More pharmacists opting for part-time work

The U.S. pharmacy profession could face a worsening shortage of pharmacists in the next decade as more men prepare to retire and more men and women opt for part-time work, according to a new study released in March by the Pharmacy Manpower Project (PMP).

The *National Pharmacist Workforce Study* finds the potential worsening shortfall coming at a pivotal time with pharmacists wanting to spend less time dispensing drugs and more time providing patient-centered services such as immunizations and counseling seniors on proper medication usage and the Medicare Prescription Drug Plan. The study was released at the American Pharmacists Association's Annual Meeting & Exposition and will be published in the May/June 2006 issue of the *Journal of the American Pharmacists Association*.

The number of practicing women pharmacists increased from 31% in 1990 to 46% in 2004. The study finds a large percentage of male pharmacists nearing retirement, with more than four in 10 (41.2%) age 55 and older, compared with only about 10% of women. Meanwhile, more men and women are working part time — 27% of women and 15.5% of men in 2004 (compared to 23.4% and 11.6%, respectively, in 2000).

Although the trend of part-time work is increasing for both men and women pharmacists, the study finds the trend toward more part-time work is being fueled by women. For women ages 31-50, more than 30% are working part time.

The report shows that pharmacists' roles are diverse. In 2004, pharmacists spent 49% of their day dispensing drugs and 32% of their time on activities such as advising patients on drug therapies, evaluating the safety of drug therapy, administering vaccines, and counseling patients on services ranging from self-care to disease management. The results suggest pharmacists would like to spend only 39% of their day dispensing drugs and increase the time spent providing services to patients to 48% of their day.

Consistent with the growing number of prescriptions dispensed in community pharmacies, the workload for pharmacists has increased between 2000 and 2004. Pharmacists report the high workload can negatively affect their work, including activities such as ability to take a break (48%), opportunity to reduce errors (36%), time spent with patients (35%), and ability to solve drug therapy problems (33%).

The most stressful events for pharmacists include inadequate pharmacy technician staffing levels (38%), phone interruptions (37%), and inadequate pharmacists' staffing (34%). Dealing with difficult patients and co-workers are cited by 33% of pharmacists.

Despite the high workload, the study finds a

high level of job satisfaction. More than three-quarters (77%) of pharmacists in 2004 report a high level of job satisfaction compared with 66% in 2000.

Results of the National Pharmacist Workforce Study were compiled using a questionnaire completed by 1,470 practicing pharmacists. The study was commissioned by the PMP, which is a nonprofit corporation consisting of all major national, pharmaceutical professional and trade organizations. Its mission is to serve the public and the profession by developing data regarding the size and demography of the pharmacy practitioner workforce and conducting and supporting research in areas related to that work force.

To see the report's executive summary, go to: www.aacp.org/Docs/MainNavigation/Resources/7296_ExecsummforAACP.pdf. ▼

FDA extends review period for reintroduction of natalizumab

Biogen Idec and Elan announced on March 22 that the FDA had extended the regulatory review period for the reintroduction of natalizumab (Tysabri) for multiple sclerosis by up to 90 days.

Under the Prescription Drug User Fee Act, extensions to the review period for an application can be triggered by a substantive submission from the sponsor. In this case, the information received was determined to be a major amendment to the pending application. The review period for the application was extended by up to 90 days to provide the FDA time to review the new information.

This new submission is a revised Risk Management Plan (RMP), which takes into account the issues discussed, and recommendations offered, by the Peripheral and Central Nervous System Drugs Advisory Committee on March 7 and 8.

The FDA says this application continues to be a high priority. The agency is working intensively to complete review of this new information and will attempt to do so before the end of the 90-day extension period. ▼

ACCU-CHEK Ultraflex Infusion Sets recalled

Disetronic Medical Systems has announced a voluntary nationwide recall of all ACCU-CHEK Ultraflex Infusion Sets because of a potential that tubing could fully or partially separate at the luer lock-tubing connection. In the event a full or partial separation occurs, insulin may leak from the infusion set tubing causing an interruption of insulin delivery, which can cause hyperglycemia.

The symptoms of hyperglycemia include nausea/vomiting, blurred vision, excessive thirst or hunger, frequent urination, fatigue/tiredness/sleepiness, headache, fruity acetone breath, and abdominal pain. Patients experiencing these symptoms are advised to check their blood glucose to ensure that the blood glucose level is within an acceptable range as defined by the patient's health care team and follow the medical advice given by the health care professional or contact their physician.

Under this recall, customers have the option of replacing their ACCU-CHECK Ultraflex infusion sets, or using the ACCU-CHEK Tender or ACCU-CHEK Rapid-D infusion sets. To read the complete MedWatch 2006 Safety summary, including a link to the firm press release, see: www.fda.gov/medwatch/safety/2006/safety06.htm#Disetronic. ▼

AHA issues statement regarding clopidogrel (Plavix) use

Results from a recent clinical trial so concerned some patients using clopidogrel (Plavix) that the American Heart Association issued a statement offering them guidance about the medication.

After results of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial were published on the web site of the *New England Journal of Medicine* (www.nejm.org) on March 12, the heart association says it received a number of questions from patients seeking guidance on whether they need to take action based on the study. (The results were released early to coincide with their presentation at the American College of Cardiology meeting in Atlanta and also appeared in the April 20 printed issue of the *NEJM.)*

The CHARISMA trial investigated whether people with major vascular risks, including various combinations of conventional risk factors and events such as heart attack, stroke, and peripheral arterial disease, do better with two antiplatelet agents or aspirin alone.

The trial did not support the addition of clopidogrel to aspirin therapy in patients with stable cardiovascular disease or in the case of prevention for

those at high risk for cardiovascular disease, says **Ralph Sacco**, MD, a spokesman for the American Heart Association/American Stroke Association, in the statement. "For the total group, no significant reduction in heart attack, stroke, or cardiovascular death was seen with clopidogrel and aspirin vs. aspirin alone, and the combination of clopidogrel with aspirin was associated with a significantly increased risk of moderate (requiring transfusion) or severe bleeding in those taking the combination for primary prevention."

The results suggested a benefit in the subgroup of patients who had already had a heart attack, stroke, or who had symptomatic peripheral arterial disease, but this needs further study before it changes what patients and doctors should do, he continues. "It is important to remember, however, that previous trials have documented the benefits of combined treatment with clopidogrel and aspirin for other groups of patients — those with heart attack or unstable angina (also called unstable coronary syndromes) and those who have had coronary angioplasty with stent placement."

Sacco emphasizes that patients currently taking clopidogrel, aspirin, or the combination for approved indications should not stop their medications. Patients with questions about the medications should talk to a health care professional. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***New indication for tacrolimus (Prograf) by Astellas Pharma US***. The FDA has approved tacrolimus (Prograf), a drug that suppresses the body's immune reaction, for the prevention of graft rejection in the recipients of heart transplants. Tacrolimus capsules and tacrolimus for injection, the first products approved in the United States for heart transplantation in eight years, had been previously approved for the prevention of graft rejection in the recipients of liver and kidney transplants.

Tacrolimus acts by a mechanism similar to cyclosporine, another immunosuppressant used to prevent transplant rejection. Tacrolimus, therefore, offers an alternative to cyclosporine for use in certain combination immunosuppressive regimens in liver, kidney, and heart transplantation.

The safety and effectiveness of tacrolimus-based and cyclosporine-based immunosuppression in heart transplantation were compared in two trials, one of which was conducted in Europe and one in the United States. In the European trial, the survival of patients and grafts 18 months after the transplantation in the tacrolimus group (91.7%) was similar to the cyclosporine group (89.8%). In a U.S. study, patient and graft survival at 12 months after transplantation in the tacrolimus group (93.5%) was similar to the cyclosporine group (86.1%).

The use of tacrolimus is associated with increased risk or neurotoxicity, renal function impairment, infection, and post-transplant diabetes mellitus. Like most combination immunosuppressive regimens used in solid organ transplantation, the use of tacrolimus-based combination immunosuppression is associated with an increased risk of malignancies, notably of nonmelanoma skin cancers.

• ***New indication for zanamivir for inhalation (Relenza) by GlaxoSmithKline.*** The FDA has approved the use of zanamivir for inhalation (Relenza) for prophylaxis of influenza in adults and children 5 years of age and older. Zanamivir, an antiviral medication, was previously approved for the treatment of influenza A and B virus infections in adults and children. Oseltamivir phosphate (Tamiflu) previously was approved for both prevention and treatment of flu; this approval of zanamivir for prevention provides Americans with another option for the prevention of influenza A and B infections.

The effectiveness of zanamivir in preventing seasonal influenza has been demonstrated in four large-scale studies comparing the drug with placebo. In all of these studies, the most common events during treatment with zanamivir in adults

COMING IN FUTURE MONTHS

- FDA MedWatch warning on Pfizer's Macugen
- CT hospital uses McKesson's Robot Rx
- Poison control developments
- ICU barriers to glucose control
- Scripps Health Plan diabetes case management program

and adolescents were ear, nose, and throat infections, headaches; diarrhea, nausea, vomiting, nasal irritation, bronchitis; cough, sinus infections, and dizziness. In children, the most common side effects were ear, nose, and throat infections, vomiting, and diarrhea. Less common reported events included rashes and allergic reactions, some of which were severe.

Bronchospasm, including deaths, were reported in some patients after the initial approval of zanamivir. Most of these patients had asthma or chronic obstructive pulmonary disease. Zanamivir, therefore, is not recommended for treatment or prophylaxis of seasonal influenza in individuals with underlying airways disease such as asthma or chronic obstructive pulmonary disease.

• ***New capsule form for generic zidovudine by Aurobindo Pharma LTD***. The FDA has issued the first generic approval for the capsule dosage form of zidovudine to treat HIV/AIDS to be marketed in the United States. The tablet and oral solution dosage forms of zidovudine were previously approved for sale in the United States when the patent on those dosage forms expired in September 2005. This approval for the capsule formulation of the drug follows the expiration of GlaxoSmithKline's patent on its capsule form of the product marketed under the trade name Retrovir.

Zidovudine is in the class of drugs called nucleoside reverse transcriptase inhibitors. This antiretroviral drug is intended to be used with other anti-retroviral agents for the treatment of HIV-1 infection.

The agency's approval of zidovudine means that there are no existing patents and/or exclusivity preventing the approval of generic versions of this product. As with all FDA-approved generics, this product must meet all of FDA's manufacturing quality, and clinical safety and effectiveness standards for U.S. marketing. More information on HIV and AIDS is available on-line at FDA's web site: www.fda.gov/oashi/aids/hiv.html. ■

IN THE PIPELINE

• Enanta Pharmaceuticals has initiated a Phase II clinical trial for the treatment of community-acquired pneumonia in the United States and Canada for EDP-420, an investigational bridged bicyclic macrolide antibiotic for the treatment of **community-acquired respiratory tract infections**.

• Nuvelo has been granted fast-track designation by the FDA for its lead product candidate, alfimeprase, for the treatment of **acute peripheral arterial occlusion**.

• Genta has announced that the first patient has been entered into a new clinical study that will evaluate the bioactivity and safety of the company's lead **anticancer** drug, oblimersen sodium (Genasense) injection, administered by intermittent subcutaneous injection.

• EntreMed has initiated Phase II studies with MKC-1, a novel, orally active, small molecule cell cycle inhibitor with a unique mechanism of action. Patients with **advanced or metastatic breast cancer** who have failed conventional therapies are expected to be enrolled.

• BioMarin Pharmaceutical has announced that the FDA has granted fast-track designation for sapropterin dihydrochloride (Phenoptin) for **phenylketonuria**.

• Affymax has initiated a Phase II clinical trial of Hematide, a synthetic peptide-based erythropoiesis-stimulating agent, to treat **anemia in cancer** patients.

• Schering-Plough reported that the FDA has granted fast designation to its investigational oral hepatitis C protease inhibitor (SCH 503034), currently in Phase II clinical development for the treatment of **chronic hepatitis C virus infection**. ■

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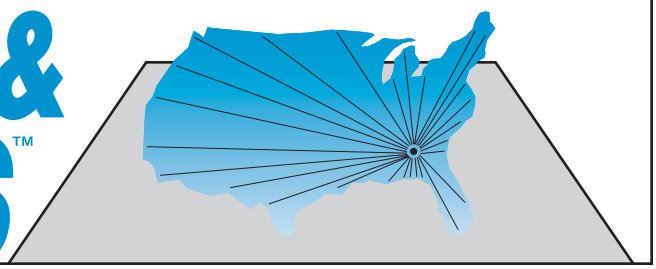

Medications Used in Radiological Emergencies

By **Lydell Collier**, PharmD Candidate, Harrison School of Pharmacy, Auburn (AL) University
Richard Cramer, PharmD, Drug Information Coordinator, Huntsville (AL) Hospital

Since Sept. 11, 2001, terror has become a common word in the American vocabulary. A recent addition are the words "dirty bomb." A dirty bomb is a conventional explosive mechanism that contains radioactive material in a radiological dispersal device. Dirty bombs are more likely to spread radionuclides in a localized area, and the identity of the radionuclides is unpredictable. The elements that compose a dirty bomb could be products stolen or obtained from nuclear power plants, defense facilities, nuclear pharmacies, medical facilities, and industrial facilities using radionuclides. Most experts in emergency planning believe that a dirty bomb is more likely to be a weapon of choice if the United States is attacked by terrorists.

The FDA has approved potassium iodide tablets, insoluble Prussian Blue, Ca-DTPA, and Zn-DTPA to protect the body or enhance the elimination of radioactive or nonradioactive material from the human body. All of these drugs are part of the national pharmaceutical stockpile of drugs. This article will examine these four drugs as well as other medications that could be used in the case of a radiological emergency.

Potassium Iodide (KI)

Iodine, which can be made radioactive and used in a dirty bomb, is important in the body's synthesis of thyroid hormones, and its deficiency in the normal diet is a cause of hypothyroidism. The body is not able to tell the difference between the radioactive and nonradioactive forms of this element. Thus, when presented with a radioactive form of iodine, the body may convert it to iodide and use it to synthesize thyroid hormones, which will be radioactive. The radioactive hormones will be distributed, metabolized, and excreted in the same manner as the nonradioactive hormones, but will deliver a radiation dose to tissues while it remains in the body.

Thyroid uptake of iodide is an active transport process. Once the gland is saturated, any excess iodine will be rapidly excreted. Therefore, by providing the body with sufficient nonradioactive iodide immediately before or at the time of ingestion of any radioactive iodine, the thyroid's absorption of the radioiodine will be prevented or minimized, thus protecting the body from the radioactive form of iodide.

KI tablets are relatively inexpensive and available in strengths of 65 and 130 mg. Recommendations for dosing of KI tablets can be found in **Table, this page**. KI should be taken as soon the patient has been exposed to the radioactive iodine and still may have some protective effect even if it is taken three to four hours after exposure. Because the radioactive iodine will be present in the initial blast and

Table:
KI dosage by age group

Age Group	KI Dosage
Adults age 18 and older	130 mg
Age 12-18 and older and weight more than 150 lbs	130 mg
Age 12-18 and older and weight less than 150 lbs	65 mg
3-12 years and older	65 mg
1 month to 3 years	32 mg
Birth to 1 month	16 mg

decays quickly, a single dose of KI usually is all that is required. The only FDA-approved forms of KI for radiation emergencies include: IOSAT, ThyroShield, and Thyrosafe. Contraindications for emergency use of KI include iodine allergy, dermatitis herpetiformis, and hypocomplementemic vasculitis. Gastrointestinal symptoms, skin rash, confusion, numbness, and eosinophilia represent the majority of adverse effects reported from KI use.

Prussian Blue (Radiogardase-Cs)

The FDA approved insoluble Prussian Blue, also known as ferric ferrocyanide, as an agent to delay the absorption of cesium-137 (Cs-137) and thallium (Tl) from the gastrointestinal tract. Cs-137 is produced during fission reactions and is a likely component of a dirty bomb. Thallium causes gastrointestinal, neurological, and ocular toxicity in both its stable and radioactive forms. Thallium is absorbed through the skin, and non-radioactive salts have been used as depilatory drugs or as insecticides and rodenticides.

Soluble salts of cesium and thallium are absorbed from the gastrointestinal tract and enter the enterohepatic circulation, prolonging their presence in the body. They are distributed consistently throughout body tissues. Cs-137 has a half-life of 30 years and will produce a continual radiation dose to all body tissues.

Insoluble Prussian Blue is not absorbed when it is taken orally, and about 99% is excreted in the feces. If it is administered immediately after the ingestion of cesium or thallium, Prussian Blue combines with the radiated metal ion to form an insoluble compound that is excreted in the feces, reducing the absorption of these compounds into the body. Continued administration greatly reduces reabsorption of cesium or thallium from the enterohepatic pathway.

Prussian Blue is given in 500 mg capsules that can be swallowed whole; patients who cannot swallow pills can break the capsules and mix the contents in food or liquid. Breaking open the capsules will cause the patients' mouths and teeth to be blue during the time of treatment, and patients should be warned that their feces also will have a blue color. Adverse effects reported with the use of Prussian Blue include mild constipation, gastric distress, and hypokalemia.

The dose of Prussian Blue depends on the person's age and the amount of contamination in the body. The appropriate daily dose of Prussian Blue should be based on the suspected level of internal contamination (e.g., low: 3 g daily; intermediate: 3-10 g daily; high: 10-20 g daily). The drug is usually given three times a day for a minimum of 30 days. Recommendations for thallium are similar to those for Cs-137, but an initial loading dose of 3 g should be administered.

DTPA (diethylenetriaminepentaacetate)

The FDA has approved two chelating agents, pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA), for treatment of internal contamination with plutonium, americium, or curium to increase the rate of elimination of these agents from the body. All forms of these elements are radioactive and could be present in a dirty bomb, especially plutonium and americium. Both calcium and zinc in the DTPA is exchanged with the transuranium element, and the transuranium-DTPA complex is stable and excreted in the urine. Neither drug is effective for uranium or neptunium exposure.

Both chelating agents can be delivered through continuous intravenous (IV), but they cannot be used simultaneously. Each administration IV dose of Ca- or Zn-DTPA should be 1 g for adults or 14 mg/kg for children, and doses should not be fractionated. An inhaled version can be prepared for those whose lungs have been contaminated by radioactive material. The route of administration may be either slow intravenous push of the drug over a period of three to four minutes, intravenous infusion (1 g in 100-250 mL D_5W, Ringers Lactate, or normal saline), or inha-lation in a nebulizer (1:1 dilution with water or saline). Ca-DTPA is more effective than Zn-DTPA, but it is more likely to result in the chelation of other essential metals, such as zinc, magnesium, and manganese, and cause depletion of these minerals.

Therefore, Ca-DTPA should be administered for the first 24 hours as soon as possible after the ingestion or inhalation of the radioactive elements, followed by Zn-DTPA. The chelating effects of these compounds are similar after the first 24 hours. Therapy may continue for a few days up to several months or longer, depending on the type and extent of exposure and results of excretion testing. These drugs should not be taken by patients who have kidney disease or bone marrow complications.

Ca-DTPA should be used cautiously in patients with hemochromatosis, as deaths have been reported in patients receiving up to four times the recommended dose. Adverse effects include headaches, lightheadedness, chest

pain, metallic taste in the mouth, nausea, diarrhea, injection site reactions, and itching. Cough and wheezing have been reported in patients receiving the inhalation route.

Monitoring for both drugs include baseline blood and urine samples, CDC with differential, BUN, serum electrolytes and chemistries, and blood and urine radioassays. Serum zinc and CBC should be monitored more closely in patients receiving more than one dose of Ca-DTPA. A quantitative baseline estimate of total internalized transuranium elements and measures of radioactivity elimination should be obtained. Radioactivity in blood, urine, and feces should be measured weekly during therapy. In pregnancy, multiple doses of Ca-DTPA appear to be teratogenic due to depletion of zinc body stores; therefore, treatment of pregnant women should begin and continue with Zn-DTPA.

Both medications are available in 1 g vials for distribution by the Radiation Emergency Assistance Center/Training Site.

Colony-Stimulating Factors (Cytokines)

Granulocyte colony-stimulating factors (G-CSF) are produced by recombinant DNA technology with the purpose of stimulating the growth of white blood cells. Three recombinant colony-stimulating factors (filgrastim, pegfilgrastim, and sargramostim) are currently licensed for use in patients with neutropenia. Pegfilgrastim is a long-acting formulation of filgrastim. Filgrastim and sargramostim have been used in radiation accident victims.

Just like a cancer patient who has received chemotherapy or radiation therapy, a person who has received a high dose of radiation may experience bone marrow destruction. Since G-CSF has been used successfully for cancer patients to stimulate growth of white blood cells, making them less vulnerable to infections, it is expected to help patients who have bone marrow damage from very high doses of radiation in much the same way. G-CSF can speed up the process of white blood cell creation, reducing the time that the patient is vulnerable to infection.

Colony-stimulating factors are safe for most adults. Side effects include fever, diarrhea, skin rash, and weakness, with the most common side effect being mild-to-moderate bone pain. The treatment plan is to give 5 mcg/kg of patient weight of filgrastim daily for up to two weeks, either by injection or intravenous infusion or sargramostim at 250 $\mu g/m^2$ per day administered subcutaneously. A third and final option is to give 6 mg pegfilgrastim subcutaneously once weekly in patients weighing more than 45 kg.

Amifostine (Ethyol)

Amifostine is in a class of drugs known as radioprotectants. Radioprotectants are used to protect tissues against oxidative damage at the cellular level.

Amifostine is known as a broad-spectrum cytoprotective agent because it protects against a large array of cytotoxic therapies in multiple organ systems. The drug becomes dephosphorylated in the tissue to its active form, which is a free thiol. When in its active form, amifostine is taken up into the cells and acts as a free radical scavenger.

Amifostine was approved by the FDA for use as a protectant for normal tissues during radiotherapy of head and neck cancers. The use of this drug is limited by its side effects, which include nausea, vomiting, and hypotension. At concentrations necessary to protect against acute radiation injury, these side effects are significant, thus making its use as a prophylactic for acute radiation injury questionable. Also, there is no evidence that amifostine provides any protective value when given after exposure to ionizing radiation. Therefore, it is likely that the best use would be for first responders entering a contaminated area.

Androstenediol (Neumune)

Androstenediol, one of the drugs still under development by Hollis-Eden, is being created for the treatment of ARS (acute radiation syndrome). ARS is caused when the body is exposed to high doses of radiation. When this occurs, the patient may experience severe loss of neutrophils, or thrombocytopenia. This is potentially life-threatening because of the lethal effect of high doses of whole body radiation on the bone marrow that produces these cells.

Androstenediol (5-androstenediol), is an immune-regulating hormone that stimulates myelopoiesis and increases the number of circulating platelets and certain white blood cells of the innate immune system. These changes may last for several weeks after treatment and result in enhanced resistance to infection and significantly better survival rates. It can be given prophylactically 24 hours before exposure or two to four hours after exposure. Preliminary findings in monkeys show that androstenediol significantly reduced the duration of neutropenia as well as

occurrence of severe thrombocytopenia in treated animals.

Conclusion

In the event of a radiation emergency, there are some key points regarding contamination for the medical management of radiation casualties. The first is that all patients should be medically stabilized from their traumatic injuries before radiation injuries are considered. Additionally, exposure from a source outside the person does not make that person "radioactive." Thus, they are of no hazard to medical staff. This is different from a nuclear blast type of event where the patient needs to be isolated to prevent others from being exposed to radiation. Third, the amount of nausea, vomiting, diarrhea, and skin erythema may be an indication of the amount of radiation that a person has received.

For decontamination, the majority of surface radiation may be removed with soap, warm water, and a washcloth. All patients who have been exposed to radiation should be monitored for dehydration, electrolyte imbalances, infections, gastrointestinal destruction, and bone marrow suppression.

This article examines just a few of the antidotes available in case of a radiation emergency. Many other products are in various stages of development and in competition for government support. In today's society, it is important that health care officials and providers are aware of the dangers a radiologic emergency would present. It is even more important that we have a basic knowledge of the antidotes mentioned in this article to provide quality health care to those who may be affected by such a tragic event.

Resources

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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.

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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.

17. Which of the following FDA-approved drugs is part of the national pharmaceutical stockpile of drugs?
    A. Potassium iodide tablets
    B. Insoluble Prussian Blue
    C. Ca-DTPA
    D. Zn-DTPA
    E. All of the above

18. By providing the body with sufficient nonradioactive iodide immediately before or at the time of ingestion of any radioactive iodine, the thyroid's absorption of the radioiodine will be prevented or minimized, thus protecting the body from the radioactive form of iodide.
    A. True
    B. False

19. Soluble salts of cesium and thallium:
    A. are absorbed from the gastrointestinal tract.
    B. enter the enterohepatic circulation, prolonging their presence in the body.
    C. are distributed consistently throughout body tissues.
    D. All of the above

20. The FDA has approved two chelating agents, pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA), for treatment of internal contamination with:
    A. plutonium.
    B. americium.
    C. curium.
    D. All of the above