DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

THOMSON™
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

JULY 2004
VOL. 20, NO. 7 • (pages 49-56)

Pharmacists who misfill prescriptions often share lack of working memory

Intervention can redirect actions and reduce errors

The system often is blamed when pharmacists fill prescriptions incorrectly. For example, pharmacists may say they were distracted by a busy workplace, resulting in the "misfilling" of the orders.

A new report, however, says some pharmacists are predisposed to medical errors due to individual factors, such as a lack of working memory. Without working memory, pharmacists are more apt to struggle with multitasking. The good news is that with proper intervention and a goal-setting program, pharmacists can recognize the situation and learn to minimize the likelihood of future medical errors.

This report was presented to the Florida Board of Pharmacy on April 14 by **Carsten Evans**, MS, PhD, assistant dean at Nova Southeastern University (NSU) College of Pharmacy in Fort Lauderdale, FL. The report was the result of a three-year study that analyzed pharmacists who were directed to the NSU program as a result of their misfills. These pharmacists were required to satisfy an educational component that was assigned to them as part of a judgment from the board for making a medication error.

The report introduced two issues that were critical in the development of the NSU medical error remedial program, Evans says. The first issue was a review of the fact that the leading reported cause of medical errors (according to U.S. Pharmacopeia in Rockville, MD) has always been performance deficit. Performance deficit is defined as a cause of error that may not be attributed to any specific cause, a reason for error that cannot be explained, or the person was educated and/or trained and should have known better.

The second issue described the primary factor contributing to error, distraction, as an event that interferes with or interrupts an individual from concentrating on his or her original focus of attention. After defining these two issues, the researchers focused on developing a program based on human behavior, Evans says.

The philosophy of the program design was to determine which measures of individual characteristics predict pharmacists who commit

medical errors. "The measures selected were cognitive attributes such as planning, organizing, the ability to multitask — comprised of working memory, attentional control, and learning speed skills — and personality characteristics of conscientiousness and emotional stability," he says.

The NSU Med-Error Remedial program was first presented to the Florida Board of Pharmacy in May of 2001. It was designed by Evans; Robert Pihl, PhD, professor of psychology and psychiatry at McGill University in Montreal; Jordan Peterson, PhD, professor of psychology at the University of Toronto; and Daniel Higgins, PhD, professor at Harvard University in Boston.

This study compared the pharmacists mandated by a state board of pharmacy for misfill errors to a control group of pharmacists on computerized neuropsychological tasks and personality tests, offered by ExamCorp (www.examcorp.com). The three-year results found no differences in personality, but did find highly significant decrements among members of the medical error group for working memory, attentional control, and verbal organization when compared with the controls.

"We went into this looking for similarities," Evans says. The similarities were simple: The people who make most of the errors have no working memory. "The pharmacists who were randomly selected out of an audience for the control group, for the most part, had working memory."

Working memory is the ability to sustain multiple thoughts at the same time. On the ExamCorp test, it has a scale measure range of 0-99, he notes. "No" or "very little" working memory is considered less than 10 on the scale. It was very common to find the misfill pharmacists score less than 10 over the three-year period. "We have people who have zero working memory who are filling prescriptions," Evans adds.

These pharmacists can be productive when they single-task. Their stress level, and possibility of error rate, increases when they try to handle more than one task at a time. Evans also found that while some people are born with a lack of working memory, some lose it after undergoing major transitions in life.

The results were not gender-based. Age, however, is a factor. "As we age, our brain cells are not replaced as fast and our working memory capacity decreases," he says.

Logistic regression of test scores was highly significant in successfully determining group membership, Evans says. The findings were unrelated to workload. "The results point to the importance of considering individual factors in making errors in the practice of pharmacy. These measures allow us to predict the probability of pharmacists to error and to determine those in need of intervention. Selection and intervention are the two areas where specific steps can be taken to dramatically reduce the risk of pharmacist errors."

Intervention is the last component of the NSU Med-Error Remedial program. Research data show that the program's process can improve working memory and that it is possible to improve organizational and planning skills, Evans says. Interventions are directed approaches toward individual factors in minimizing medical errors. The interventions include testing, discussion of individual results (with the program psychologist), required readings,

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 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@ahcpub.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), $479. 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 $80 each. (GST registration number R128870672.)

Thomson American Health Consultants is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program, #381-000-04-015-H01, will be available **July 8, 2004, to July 7, 2007.**

Thomson American Health Consultants has designated up to 6 contact hours annually for this program. Participants will receive ACPE 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. Drs. Gilchrist, Holder, and Cramer (authors) report no relationships with companies related to the field of study covered in *Drug Criteria & Outcomes.*

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@thomson.com).
Senior Production Editor: **Nancy McCreary**.

Editorial Questions

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

and a unique goal-setting requirement for the participants.

Included in the intervention/training are techniques that can modify risk factors such as individual characteristic job matching, stress-reduction interventions, goal-setting programs, and exercising — both mental and physical. The key is finding ways to relieve stress, Evans says.

"Once [the pharmacists] find ways to relieve the stress, they can get along in a multitasking situation because they take every task as an individual one. They learn how not to be harassed into doing more than one thing at a time."

The last stage of the goal-setting program helps the pharmacists take charge, gets them organized, and gives them direction, Evans says. "It decreases their stress and anxiety."

The pharmacists usually are happy to find out why they may have been struggling in their jobs. They repeatedly make the errors because they don't like what they are doing, he says, but they don't understand why they don't like it. "They are multitasking when they should be single-tasking. [For instance], they don't like answering the phone when they are trying to talk to people."

These interventions have demonstrated that they can remediate predictive risk factors of pharmacists and improve their level of functioning for these traits, Evans says. The program gives the pharmacists the tools to avoid the situations that got them into trouble. "It actually improves their health," Evans says. "It makes their life in the present more meaningful. If they can put their lives in order, chances are that they can understand their limitations."

These pharmacists appreciate the fact that they become empowered with the knowledge of why they should not work in areas of the pharmacy operation that require stressful multitasking abilities, he adds.

In conclusion, the three-year results of the report have demonstrated that individual differences are an important factor in medical errors, Evans says. "These differences are measurable. Working memory is a critical attribute, and these factors of concern, like working memory, can be remediated." ■

Pharmacists to assess their safety processes

Aggregate survey data available soon

The Institute for Safe Medication Practices (ISMP) in Huntingdon Valley, PA, is encouraging pharmacists to help conduct a self-assessment of their hospitals' medication safety processes. Data from the surveys then will be compiled and analyzed so that participating hospitals can compare their results against demographically similar institutions.

The 2004 ISMP Medication Safety Self-Assessment has recently been distributed to hospitals across the county. ISMP launched the self-assessment in partnership with the Health Research and Educational Trust and the American Hospital Association (AHA), both based in Chicago. The Commonwealth Fund in New York City provided funding for the project.

The self-assessment is an opportunity for hospitals to take a look at their medication practices, says **Allen J. Vaida**, PharmD, FASHP, ISMP executive director. The first self-assessment, which had 194 survey items, was conducted in 2000. The current self-assessment has 231 items. "We added items over the last four years from new things that we have learned," he says.

Hospitals are being asked to convene multidisciplinary teams to respond to the survey and to provide a wide range of perspectives so the data can be as complete as possible. The teams often include representatives from pharmacy, nursing, information technology, administration, and front-line medical staff. The assessments were mailed to the director of pharmacy at each hospital, and pharmacists often spearhead the project, Vaida says.

The self-assessment process runs at least two to three hours over several meetings, he notes.

Members of the team go through the assessment and come to a consensus on the answers. In some instances, members of the team may not be able to answer a question completely. Someone may be asked to find out the information and report it back to the team at the next meeting.

Questions based on experience

More than 1,400 hospitals submitted their survey data to ISMP in 2000, Vaida says. The time seemed right to launch a self-assessment then. The Institute of Medicine had issued its groundbreaking report on the prevalence of medical errors in late 1999, and the self-assessment came out the next spring. Vaida, however, found that he spent much of his time explaining terms and concepts. "People weren't really into the self-assessing even

though we gave it some press."

The climate has since undergone a tremendous change. "Now there is so much more awareness of the importance of self-assessment," he says. The Joint Commission on the Accreditation of Healthcare Organizations, for example, has added goals regarding medication safety. Accounting for this and AHA's promotion of the current assessment, ISMP expects many more hospitals to participate this year.

The self-assessment also should not be viewed as just ISMP's view of good practices, Vaida says. "The assessment itself is based on ISMP's 30 years of experience in trying to safeguard against medication errors."

ISMP receives information from its national Medication Errors Reporting Program, and from its hospital consults, lectures, and work with groups. "[The assessment] is based on solid information of what we consider are safe characteristics. It's not just someone sitting down and saying, 'This is what I think,'" he says. ISMP also relies on the advice of a national advisory board.

Hospitals who have taken the self-assessment have often found their medication practices weren't quite what they thought before they took the survey. "When [team members] talk about how they share information and what information is obtained on patients, they say, 'Are you telling me that pharmacy doesn't have that information? I never knew that. Why don't they have that?' It might be an IT problem," Vaida says. "When you sit down as a multidisciplinary group, many things may open your eyes that you had taken for granted was done everywhere."

The self-assessment also was meant to set some goals for the hospitals. "As you are going through it, you realize some of your shortcomings and what goals you should work on," he says.

Once the survey has been completed, hospitals can then enter their results on-line at the secure ISMP web site, Vaida explains. The assessments have a password, which a hospital representative enters before submitting the data. The password is not identified with any hospital; it exists only for the integrity of the data.

"I can't tell you what the password is from St. Joe's in Atlanta or what their data are in the database. It is completely de-identified," he says.

Hospitals can enter their data through about the third week in September. Then ISMP will compile and analyze the data, after which participants will get the opportunity to compare the aggregate data against their own results.

For example, each question has a weighted score. The weighted scores that hospitals received from ISMP help for comparison purposes, reports Vaida. "The assessment is broken up into about 20 sections. A hospital could look at it and say, 'How did I score in the section that asks about formulary safety? Also, how did the rest of the nation score in that? Was I higher or lower?'"

ISMP will break down the information by demographics so hospitals can compare their data to similar institutions. Hospitals will be able to compare by factors such as the number of inpatient beds, type of organization (for-profit, not-for-profit), location (urban, rural), and teaching or nonteaching. ISMP also has the baseline 2000 data.

Some multihospital systems and state quality collaboratives also are interested in finding out how they score as a group, he adds. "[They'll say], let's look at the range. Some of us are doing it well, some not as well in certain categories. Let's start trying to share some best practices."

For the survey to adequately help improve medication safety practices, hospitals must participate, Vaida says. "The important thing is that we are looking for a solid response to this. If we don't know what people need help with, and what some of the issues are, we can't help."

After the first self-assessment, ISMP developed education programs, one of which was the Pathways for Medication Safety. The three tools in the pathways were designed specifically from the results of the first self-assessment, Vaida says. "It was done in collaboration with the Health Research and Educational Trust of AHA and ISMP."

ISMP also had a large advisory group and received funding that allowed it to offer the tools completely free (see www.medpathways.info). "We put that together looking at where the hospitals had their shortcomings," Vaida says. "We hope we can do something like that this time, too." ■

Here's a look at the ISMP 2004 Self-Assessment

Here are some of the items included in the Institute for Safe Medication Practices (ISMP)'s 2004 Medication Safety Self Assessment. This section is listed under Core Characteristic #1: "Essential patient information is obtained, readily available in useful form, and considered when prescribing, dispensing, and administering

medications." Hospitals need to use this scoring system to respond to the items below:

A - There has been no activity to implement this item.

B - This item has been formally discussed and considered, but it has not been implemented.

C - This item has been partially implemented in some or all areas of the organization.

D - This item is fully implemented in some areas of the organization.

E - This item is fully implemented throughout the organization.

1(1). Prescribers and nurses can easily and electronically access inpatient laboratory values while working in their respective inpatient locations.

1(2). Pharmacists can easily and electronically access inpatient laboratory values while working in their respective inpatient locations.

2(1). Prescribers and nurses can easily and electronically access outpatient laboratory values while working in their respective outpatient locations.

2(2). Pharmacists can easily and electronically access outpatient laboratory values while working in their respective outpatient locations.

3(1). Prescribers and nurses can easily and electronically access both inpatient and outpatient laboratory values while working in their respective inpatient and outpatient locations.

3(2). Pharmacists can easily and electronically access both inpatient and outpatient laboratory values while working in their respective inpatient and outpatient locations.

4. A pharmacist or prescriber routinely adjusts doses of medications that may be toxic in patients with renal or liver impairment. ■

Docetaxel (Taxotere) extends life in advanced prostate cancer patients

The results of two recent Phase III clinical trials indicate that docetaxel (Taxotere) extends life in advanced prostate cancer patients who are resistant to hormone therapy, supporting the Food and Drug Administration's approval of docetaxel injection, in combination with prednisone, for the treatment of patients with advanced metastatic prostate cancer **(see FDA Approvals for more information, p. 55)**.

The results of the trials were presented at the annual meeting of the American Society of Clinical Oncology in New Orleans on June 7. One three-year international trial found that docetaxel decreases the chance of dying by 24% in these patients. Researchers randomly assigned 1,006 hormone-resistant prostate cancer patients to receive intravenous docetaxel (every three weeks or weekly) or the current standard chemotherapy drug, mitoxantrone. Patients receiving docetaxel every three weeks survived 2.4 months longer on average than those receiving mitoxantrone or docetaxel weekly.

"The study's statistics are very robust. Two months may not sound like much time to most people, but the study shows that prostate cancer responds to docetaxel and this opens up the door to explore more options," says **Mario Eisenberger**, MD, co-chair of the study and the R. Dale Hughes Professor of Oncology at the Johns Hopkins Kimmel Cancer Center in Baltimore. The study results also show significant improvements in pain relief and lowering prostate specific antigen blood levels. Aventis Pharmaceuticals, maker of docetaxel, funded the study.

Results echoed in second study

Researchers in the second study randomized 770 patients to one of two treatment arms: docetaxel 60 mg/m^2 every three weeks and estramustine 280 mg three times daily for five days or mitoxantrone 12 mg/m^2 every three weeks and prednisone 5 mg twice daily.

The researchers found that the docetaxel-based regimen reduced patients' risk of death by 20%. The trial investigators also reported a 27% increase in disease progression-free survival and a 55% increase in objective response rate in the patients taking docetaxel. In addition, the majority of these patients had a PSA decline of more than 50%.

"These results demonstrate the first major therapeutic advance in prostate cancer and offer hope for millions of men worldwide," says **Daniel P. Petrylak**, MD, associate professor of medicine at Columbia University College of Physicians & Surgeons in New York City and director of the Genitourinary Oncology Program at New York-Presbyterian Hospital.

Both sets of researchers say that docetaxel had a manageable safety profile. ■

NEWS BRIEFS

Decision tool available on tablet splitting

Tablet splitting — the practice of splitting a medication tablet of a higher dosage to obtain lower dosage units — is becoming more widespread. Some patients choose to do it, and some insurers expect patients to do it. However, what might look like a cost-saving approach isn't right for every product nor for every patient, cautions the American Pharmacists Association (APhA) in Washington, DC. The decision to split tablets must consider both the product and the patient.

Certain tablets may be difficult to split, for example. They may have coatings or be controlled-release tablets that may be impossible to split. In addition, many elderly patients may lack the skill or dexterity to split a tablet properly.

APhA's Strategic Directions Committee (SDC), therefore has reviewed the available literature and input from practitioners regarding the impact of the splitting of tablets on patient care. The SDC developed questions for pharmacists and decision makers to consider when evaluating the appropriateness of tablet splitting for individual patients and products. The guidelines can be found in the May/June issue of the *Journal of the American Pharmacists Association*.

The Committee also recommends that the U.S. Food and Drug Administration and the United States Pharmacopeia study the splitting of tablets to provide data on the appropriateness of tablet splitting from a scientific basis. ▼

Severe sufferers prefer brand name meds

As the severity of a medical condition increases, the likelihood that consumers will choose a generic medication dramatically decreases, according to a survey released at the Medco Health Solutions 2004 Drug Trend Symposium in Orlando, FL.

Seventy-nine percent of people would use generic medications to treat minor conditions such as a cold or the flu, and 76% of people would use a generic to treat heartburn, says a random household survey of 1,000 adult consumers nationwide conducted in April by marketing research firm ReedHaldyMcIntosh for Medco. However, only 56% agreed to use generics to treat asthma, and only 52% would use generics to treat diabetes. For treating heart disease, the number of people who would use a generic medication fell to less than 50% (47%) — despite the fact that generic medications are the medical equivalent of their brand-name counterparts.

The survey offers some insight into factors that drive brand-name use. Fifty-seven percent of respondents said they would be more likely to use a generic medication if they saw it advertised, despite the fact that generics have a lower cost. The survey also found that when presented with the same copay for using either a brand-name medication or a generic, 59% would choose the brand, while 33% would choose the generic (the remainder were undecided). As the cost of the copay rose for the brand-name medication, people were more likely to choose a generic, underscoring the importance of designing drug plans that take advantage of cost-saving opportunities for both employers and employees. ▼

Study: Medicare drug plan is confusing to elderly

A survey released by the Kaiser Family Foundation in Washington, DC, shows that seniors are confused about the outcome of the Medicare prescription drug debate and the prescription drug law. While about two-thirds of seniors report following the debate closely, just 15% say they understand the new prescription drug law very well and almost seven in 10 don't know that it passed and was signed into law.

The survey found that as of Feb. 8, 64% of seniors (49% of the public) said they followed the Medicare prescription drug debate very closely or somewhat closely. However, most seniors say they don't understand the new law. Only 15% of seniors (7% of the public overall) say they understand the law very well; 24% of seniors (26% of the public) say they understand it somewhat well; and 60% of seniors (64% of the public) say they understand it not too well or not well at all.

Of particular note, 68% of seniors don't know the law was passed by the Congress and signed by the president; 27% think the law did not pass, and

41% say they did not know whether it was passed. Some 32% of seniors correctly say the law was passed and signed. Awareness is even lower for the general public (23% say it was passed and signed).

The drug benefit will not take effect until 2006, but currently a majority of seniors have an unfavorable impression of the law. Based on their personal knowledge about the law, 55% of seniors (38% of the public) say their impression is unfavorable, compared with 17% of seniors (25% of the public) who say it is favorable. Some 28% of seniors (37% of the public) say they don't have any impression of the new law.

Findings from the survey are available on the Kaiser Family Foundation web site at: www.kff.org/kaiserpolls/pomr022604pkg.cfm. ▼

Applications available for safety award

The American Society of Health-System Pharmacists (ASHP) Research and Education Foundation in Bethesda, MD, and the Cardinal Health Foundation in Dublin, OH, have announced the availability of applications for the inaugural Award for Excellence in Medication-Use Safety. The award program honors a pharmacist-led multidisciplinary team that makes significant institutionwide system improvements relating to medication use. The award, the first of its kind, recognizes on a national level pharmacy professionals who have assumed a leadership role in promoting safety in the medication-use process. Applications are currently available at a dedicated web site, www.excellenceinmeduse.org. The applications are due by Aug. 2.

The competition will honor three finalists chosen by a panel of judges who will visit each finalist's site this fall. The winner will receive a $50,000 award, and the other two finalists will receive $10,000 each. Primary emphasis for the award criteria will focus on achievements in the following areas: medication-use system initiative/scope, planning and implementation, measurable outcomes and impact, and innovation and applicability. The award winners will be announced Dec. 1, 2004, with presentations to follow at the ASHP Midyear Clinical Meeting in Orlando, FL, on Dec. 5-9. ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• ***Azacitidine (Vidaza) by Pharmion Corp.*** The FDA has approved azacitidine (Vidaza) injection for the first treatment of patients with myelodysplastic syndrome (MDS). The product was given fast-track status and a priority review. Azacitidine also is an orphan product. This approval gives Pharmion a seven-year period of exclusive marketing for the drug.

Azacitidine is thought to work by restoring normal growth and differentiation of bone marrow cells. The safety and effectiveness of azacitidine, in the treatment of all subtypes of MDS, were established in a randomized, controlled trial and in two nonrandomized studies in a total of 268 patients. About 15% of patients in the three trials had complete or partial responses to azacitidine. Responses consisted of complete or partial normalization of blood counts and of immature cell percentages in the bone marrow. In responders, the need for transfusions was eliminated.

The most common adverse events reported in clinical trials included nausea, anemia, thrombocytopenia (low platelets in blood), diarrhea, fatigue, irritation at the injection site, and constipation.

• ***New indication for docetaxel (Taxotere) by Aventis Pharmaceuticals***. The FDA has approved docetaxel (Taxotere) injection, in combination with prednisone, for the treatment of patients with advanced metastatic prostate cancer. This is the first drug approved for hormone refractory prostate cancer that has shown a survival benefit.

Docetaxel works by inhibiting tubulin, a protein essential to cell division, thus preventing cancer cells from dividing and growing in number.

The safety and effectiveness of docetaxel

COMING IN FUTURE MONTHS

- ■ Taking fewer drugs may help lung transplant patients
- ■ Know which patients may be noncompliant
- ■ Patients confused about food-drug interactions
- ■ Trending of adverse drug reactions related to analgesic use
- ■ The questions regarding the potential of statins

was established in a randomized, multicenter global clinical trial with more than 1,000 patients comparing chemotherapy with docetaxel and prednisone to mitoxantrone and prednisone in men with metastatic, hormone-refractory prostate cancer. Docetaxel, in combination with prednisone, given every three weeks, showed a survival advantage of approximately 2.5 months over the control group in the trial.

The most common adverse events reported were nausea, alopecia, and bone marrow suppression. In addition, fluid retention and peripheral neuropathy, known effects of docetaxel, were also observed.

• ***Paricalcitol injection (Zemplar) by Abbott Laboratories for pediatric use***. The FDA has approved paricalcitol injection (Zemplar) for use in children and adolescent hemodialysis patients, ages 5-19, with secondary hyperparathyroidism (SHPT). Paricalcitol initially was introduced in 1998 and currently is used to treat SHPT in the majority of adult dialysis patients in the United States.

The safety and effectiveness of paricalcitol were examined in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric patients, ages 5 to 19 years, with chronic renal failure on hemodialysis. Nearly all had received some form of vitamin D therapy prior to the study.

Paricalcitol is contraindicated in patients with vitamin D toxicity, hypercalcemia, or hypersensitivity to product ingredients. ■

IN THE PIPELINE

• Guilford Pharmaceuticals has initiated a Phase III clinical development program for Aquavan injection, a novel **sedative/hypnotic** that is a proprietary water-soluble prodrug of propofol.

• Vicuron Pharmaceuticals has completed enrollment in three Phase III clinical trials involving more than 1,500 patients designed to support registration of once-weekly dalbavancin for the treatment of **skin and soft-tissue infections**.

• Coley Pharmaceutical Group has completed the planned enrollment for its Phase II, randomized clinical study of the company's lead TLR Therapeutic, CPG 7909 (ProMune), for the treatment of **non-small cell lung cancer**.

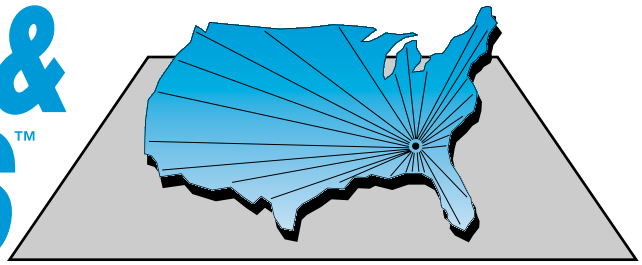
• InterMune has initiated a Phase II clinical trial of the combination of interferon alfacon-1 (Infergen) and interferon gamma-1b (Actimmune) for the treatment of patients chronically infected with **hepatitis C virus** who have failed to respond to therapy with pegylated interferon alpha-2 plus ribavirin.

• Millennium Pharmaceuticals has initiated a multicenter Phase II clinical trial of bortezomib (Velcade) for Injection in combination with rituximab in patients with **relapsed or refractory indolent (follicular and marginal zone) non-Hodgkin's lymphoma**. ■

DFR now offers free CE

Thomson American Health Consultants is pleased to announce its accreditation by the Accreditation Council for Pharmacy Education to provide continuing pharmacy education. With this accreditation status, *Drug Formulary Review* will begin offering continuing education credits with the July issue for the monthly *Drug Criteria & Outcomes* supplement. Readers can earn up to 6 credit hours annually by participating in this education activity. The continuing education test questions and instructions can be found on page 4 of the *Drug Criteria & Outcomes* supplement. If you have any questions about this program, please contact Managing Editor, Paula Cousins at (816) 960-3730 or paula.cousins@thomson.com. ■

DRUG CRITERIA & OUTCOMES™



Iron Complex Evaluation

By **Bradley Gilchrist**, PharmD, Clinical Pharmacist; **Nathan Holder**, PharmD, Clinical Pharmacist; and **Richard Cramer**, PharmD, Drug Information Coordinator
Department of Pharmacy, Huntsville (AL) Hospital

Product Introduction

1. Iron sucrose injection (Venofer) is dissociated by the reticuloendothelial system into iron and sucrose. The iron is transferred from the blood into iron stores that are located in the liver and bone marrow. The iron binds with ferritin and then is available for use by the body.
2. Sodium ferric gluconate complex (Ferrlecit), referred to as iron gluconate, is a stable macromolecular complex. The iron is more readily available for use because the complex does not have to be degraded.
3. Iron dextran (DexFerrum/Infed) is absorbed after injection into the capillaries and the lymphatic system. Circulating iron dextran is removed from the plasma by the reticuloendothelial system where the complex is split into iron and dextran. The iron binds to ferritin and then is available to replenish the depleted iron stores.

Indications

- Iron sucrose — treatment of iron deficiency in patients who receive chronic hemodialysis and supplemental erythropoietin therapy.
- Iron gluconate — treatment of iron deficiency in patients who receive chronic hemodialysis and supplemental erythropoietin therapy.
- Iron dextran — treatment of microcytic hypochromic anemia resulting from iron deficiency in which oral administration is infeasible or ineffective.

Contraindications

- **Iron sucrose:** Patients with evidence of iron overload, known hypersensitivity to iron sucrose or any of its inactive compounds, and anemia not caused by iron deficiency.
- **Iron gluconate:** Anemia not associated with iron deficiency, and known hypersensitivity to sodium ferric gluconate complex or any of its inactive compounds.
- **Iron dextran:** Hypersensitivity to iron dextran, all anemias that are not involved with iron deficiency, and hemochromatosis.

Dosage and administration

1. **Iron sucrose**
   - Of three U.S. studies used to evaluate iron sucrose, two did not require patients to receive a test dose. The third required a test dose of 2.5 mL (50 mg) diluted in a 50 mL normal saline (NS) infusion over three to 10 minutes.
   - The recommended dosage for repletion therapy for iron deficiency in hemodialysis patients is 5 mL iron sucrose (equivalent to 100 mg elemental iron) given by intravenous (IV) injection over five minutes or infusion over 15 minutes during the dialysis session. Doses can be given no more than three times per week. Give a minimum of 10 doses to achieve 1,000 mg elemental iron.
   - Iron sucrose must be injected directly into the dialysis line by slow injection or infusion.
     — ***Slow IV injection:*** Iron sucrose may be administered directly into the dialysis line at a rate of 1 mL (20 mg iron) undiluted solution per minute (five minutes per vial) not exceeding one vial (100 mg) per injection.
     — ***Infusion:*** Iron sucrose may be administered by infusion (into the dialysis line for hemodialysis patients), which can

reduce the risk of hypotension. Each vial must be diluted in 100 mL NS, immediately prior to infusion, and given over at least 15 minutes.

2. **Iron gluconate**
   - Test dose currently is not recommended.
   - Recommended dose for repletion of iron in patients on hemodialysis is 125 mg (10 mL) in 100 mL NS over one hour in hemodialysis. Most patients require a cumulative dose of 1 g elemental iron over approximately eight sequential dialysis treatments to achieve a favorable response.
   - Iron gluconate may be administered either as an infusion or as a bolus or IV push at a rate no faster than 12.5 mg/min.
3. **Iron dextran**
   - IV or intramuscular (IM) iron dextran test dose (given prior to initial dose).
   - Dosages:
     — Dose (mL) = 0.0442 (Desired hemoglobin (Hb)-Observed Hb) × lean body weight (LBW) + (0.26 × LBW).
     — Iron replacement for blood loss: Replacement iron (mg) = blood loss (mL) x hematocrit.
   - Test dose: Patients should be given a test dose of 0.5 mL for IV or IM iron dextran. The IV dose should be given gradually over 30 seconds. The manufacturer recommends that an hour should pass before administration of the rest of the dose.
   - IV bolus may be given at rate of ≤ 50 mg/min or diluted in 250-1,000 mL NS and infused over one to six hours.

Note: Iron sucrose and iron gluconate cannot be given as total drug infusions (i.e., their doses must be separated over several visits).

Efficacy

- **Iron sucrose** — Iron sucrose has successfully raised hemoglobin and hematocrit in several small studies, mostly against placebo. One study comparing IV iron sucrose to oral ferrous sulfate showed that patients who received IV iron sucrose had a better response than the oral iron group. Almost all studies took place in patients who were receiving maintenance hemodialysis.
- **Iron gluconate** — Iron gluconate has effectively raised hemoglobin and hematocrit levels vs. oral iron therapy. These studies were well-controlled large trials that included mostly iron-deficient hemodialysis patients. In one study, after one month, iron gluconate and oral iron increased hematocrit by 3.8% and 0.2% and hemoglobin by 1.3% and 0.4%, respectively.
- In the one study comparing iron sucrose and iron gluconate, the two iron products had relatively the same effect on hemoglobin in patients who also were on epoetin. This study used doses that were different from what is recommended by the manufacturer for both products.
- **Iron dextran** — Iron dextran has proven effective in patients who are iron-deficient. It has been effective in various populations, not only those undergoing hemodialysis or who have end-stage renal disease.

Safety

The safety profile of iron dextran is dependent upon its administration **(see Table 1)**. When given as a daily IM or IV injection (100 mg), the adverse effect profile is quite low. The IV bolus infusion is associated with a greater frequency of side effects. Serious side effects can be reduced with the administration of a test dose.

There has been recent concern that iron sucrose is more often associated with increased risk of infection. Recent studies have demonstrated the promotion of bacterial growth in iron-overloaded patients attributed to free, unbound iron in the serum. Presence of free iron in the serum has also been identified as a source of inhibition of neutrophil killing capacity. Other trials, however, have not been able to demonstrate an association between

Table 1: Adverse Event Comparison

Adverse event	Iron sucrose injection	Iron dextran	Iron gluconate
Hypotension	36%*†	1-2%	2%
Cramps/leg cramps	23%*†	None reported	10%
Nausea	> 5%	> 10%	2%
Anaphylaxis/hypersensitivity	< 1%*	Black box warning	3%
Headache	> 5%	> 10%	7%
Vomiting	> 5%	> 10%	2%
Diarrhea	> 5%	< 10%	2%
Flushing	None reported	> 10%	1%

*Data from clinical studies are limited due to small sample sizes. Differences in populations studied may produce different results.

†Includes cases regardless of relation to iron sucrose administration.

supersaturated transferrin or IV iron administration and risk of infection.

Drug/lab and drug/drug interactions

- Parenteral iron preparations should not be administered with oral iron preparations because the absorption of oral iron is decreased.
- Drug interactions with iron gluconate have not been studied.
- Iron dextran has a decreased effect when used with chloramphenicol.
- Iron dextran can cause falsely elevated serum bilirubin levels and falsely decreased serum calcium levels.
- Iron dextran can interfere with bone scan tests. After an infusion of iron dextran, bone scans have been reported to show a reduction of bony reuptake, marked renal activity, and excessive blood pool and soft-tissue accumulation.
- Do not mix parenteral iron preparations with other medications or add to parenteral nutrition solutions.
- Drug interactions would be expected to be similar among parenteral iron products.

Monitoring parameters

- Monitor hematologic parameters and iron indices (hemoglobin, hematocrit, transferrin saturation, and ferritin).
- Maintain transferrin saturation between 20% and 50%.
- Withhold iron therapy if ferritin level is greater than 800 ng/mL or if transferrin saturation is 50% or more.
- Serum iron values may be obtained 48 hours after IV dosing.
- Goals of therapy include a target hemoglobin level of 11.0-12.0 g/dL, hematocrit level of 33%-36%, transferrin saturation 20% or more, and ferritin 100 ng/mL or more.

Comparison

Iron dextran may be given as a total daily dose due to its slow release. Iron sucrose and iron gluconate cannot be given as a total daily dose because they release iron more rapidly. Iron sucrose and iron gluconate do not require a test dose (physician's discretion), whereas iron dextran does require a test dose before administration. Iron gluconate, iron sucrose, and iron dextran each have had reports of anaphylactic reactions; iron dextran carries a black box warning as a result.

Iron gluconate is more expensive per dose than iron sucrose, but the amount of elemental iron in each dose of iron gluconate is greater than that in iron sucrose **(see Table 2)**. Iron dextran is a relatively inexpensive iron product compared to the other two products ($215 per 1,000 mg dose).

Iron dextran has been used safely and efficaciously for years and can be administered as a single daily dose. Additionally, it is significantly less expensive than the two newer agents. However, iron dextran is associated with a slightly higher incidence of allergic reactions, including life-threatening anaphylaxis. When comparing the other two IV products, we also must examine the efficacy, cost, and nursing time. Iron gluconate is typically given as a series of eight 125 mg injections, while iron sucrose is given as a series of ten 100 mg injections. The increased number of injections required for iron sucrose could increase cost even more due to increased nursing time and extra patient visits. Also, iron gluconate appears to have more studies supporting its efficacy than iron sucrose.

Recommendation

Iron sucrose and iron gluconate have both been used as alternative parenteral iron products at Huntsville Hospital for use in patients who are not able to receive iron dextran, such as those patients with a known allergy to it. Based on available data, iron gluconate and iron sucrose seem to be similar iron replacement products. The results found are not completely reliable due to the small sample sizes of each study.

Both iron sucrose and iron gluconate have been used without major administration problems in this hospital and the regional outpatient setting. Recently, iron gluconate has been used much more than iron sucrose in this region. Because of increased use of the product and other reasons discussed in this evaluation, iron gluconate is the hospital formulary agent and will be used in place of iron sucrose. Iron dextran will continue to be an IV iron formulary agent.

Table 2: Cost Comparison

Generic name	Brand name	Vial size	Dose	Cost per dose
Iron sucrose	Venofer	20 mg/mL 5 mL vial	100 mg (1 vial/dose)	$40
Iron dextran	InFeD	50 mg/mL 2 mL vial	100 mg (1 vial/dose)	$21.50*
Iron gluconate	Ferrlecit	12.5 mg/mL 5 mL vial	125 mg (2 vial/dose)	$50

*This cost is for a smaller daily dose, not a higher complete dose such as 1,000 mg.

Resources

• American Regent Laboratories. *Venofer Formulary Monograph.* Shirley, NY; 2003;1-32.

• American Regent Laboratories. *Venofer Package Insert.* Shirley, NY; 2003.

• Schein Pharmaceutical. *InFeD Package Insert.* Florham Park, NJ; 2003.

• Watson Pharma. *Ferrlecit Package Insert*. Florham Park, NJ; 2003.

• Iron sucrose. *Drug Facts and Comparisons.* St. Louis: Facts and Comparisons; 2001:36a-36b.

• Iron dextran. *Drug Facts and Comparisons.* St. Louis: Facts and Comparisons; 2000:33-35.

• Sodium ferric gluconate complex. *Drug Facts and Comparisons.* St. Louis: Facts and Comparisons; 2000:35-36.

• Personal communication. Cindy Hall, Buyer. Huntsville (AL) Hospital System; February 2004.

• Charytan C, Levin N, Al-Saloum M, et al. Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis associated anemia: North American clinical trial. Clinical study report, 1999. *Am J Kidney Dis* 2001;37:300-307.

• Van Wyck DB, Cavallo G, Spinowitz BS, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. *Am J Kidney Dis* 2000;36:88-97.

• Silverberg DS, Blum M, Agbaria Z, et al. Intravenous ferric saccharate as an iron supplement in dialysis patients. *Nephron* 1996;72:413-417.

• Van Zyl-Smit R, Moosa MR, Potgieter CD, et al. A multicentre study to investigate the tolerance, safety, and efficacy of intravenous iron sucrose in hemodialysis patients with anemia. Clinical study report, 1997 and data on file: American Regent Laboratories; Shirley, NY. Abstract in *Kidney Int* 1999;55:2130.

• Macdougall IC, Chandler G, Elston O, et al. Beneficial effects of adopting an aggressive intravenous iron policy in a hemodialysis unit. *Am J Kidney Dis* 1999;34:S40-S48.

• Silverberg DS, Iaina A, Peer G, et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 1996;27:234-238.

• Hussain R, Christi SH, Navqi S. Experience of iron saccharate supplementation in haemodialysis patients treated with erythropoietin. *Nephrology* 1998;4:105-108.

• Iron dextran. Drug information handbook. Hudson (Cleveland): Lexi-Comp; 2000:643-644.

• Ferric gluconate. Drug information handbook. Hudson (Cleveland): Lexi-Comp; 2000: 688-689.

• Patruta SI, Edlinger R, Sunder-Plassman G, et al. Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency. *J Am Soc Nephrol* 1998;9:655-663.

• Parkkinen J, von Bonsdorff L, Peltonen S, et al. Catalytically active iron and bacterial growth in serum of hemodialysis patients after IV iron-saccharate administration. *Nephrol Dial Transplant* 2000;15:1827-1834.

• Deicher R, Ziai F, Cohen G, et al. High-dose parenteral iron sucrose depresses neutrophil intracellular killing capacity. *Kidney Intl* 2003;64:728-736.

• Hoen B, Paul-Dauphin A, Hestin D, et al. EPIBAC-DIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 1998;9:869-876. ■

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 certificate of completion requires a passing score of 70% or higher. When a passing test and evaluation form are received, a certificate 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.

1. Which of the following products is indicated for the treatment of microcytic hypochromic anemia resulting from iron deficiency in which oral administration is infeasible or ineffective?

A. Iron sucrose
B. Iron gluconate
C. Iron dextran
D. All of the above

2. In the one study comparing iron sucrose and iron gluconate:

A. Both products had relatively the same effect on hemoglobin in patients who were on epoetin.
B. The doses differed from those recommended by the manufacturers.
C. Both A and B are correct.

3. Iron dextran:

A. Has a decreased effect when used with chloramphenicol.
B. Can cause falsely elevated serum bilirubin levels and falsely decreased serum calcium levels.
C. Can interfere with bone scan tests.
D. All of the above

4. Goals of therapy include:

A. Hemoglobin level of 11.0-12.0 g/dL.
B. Hematocrit level of 33%-36%.
C. Transferrin saturation 20% or more.
D. Ferritin 100 ng/mL or more.
E. All of the above