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IN THIS ISSUE

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Joint Commission looking for evaluation and action plan for USP 797

Some hospitals spending millions for facilities compliance

The Joint Commission on Accreditation of Healthcare Organizations in Oakbrook Terrace, IL, is concerned that some hospitals are spending too much to comply with the facilities requirements of the United States Pharmacopeia (USP) Chapter <797>, Pharmaceutical Compounding: Sterile Preparations. USP 797 is the standard of practice for compounded sterile preparations.

"We are getting lots of complaints from hospitals about the money that is being spent on facilities," reports **Darryl S. Rich**, PharmD, MBA, FASHP, field representative (surveyor) for the Joint Commission. "We are hearing sums of money in the millions of dollars." Rich spoke at the American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting, held last December in Las Vegas.

"I want you to understand that both the Joint Commission, as well as ASHP — in our panel that we got together — felt that the facility issue is the least important of all the aspects of USP 797," he says. "Whether you choose to be in compliance with the facility requirements is totally up to you. Joint Commission is not requiring you to meet all the requirements of USP 797."

An article soon will be published that addresses this issue, Rich says. "[It] says if you are spending more than $50,000 to fix up your IV room, you need to reevaluate and look very carefully to see if you are using that money appropriately and are not being sold a bill of goods."

The Joint Commission addresses USP 797 under standard MM.8.10: The hospital evaluates its medication management system. For the Joint Commission's purposes, organizations should consider USP best practice as part of that standard, Rich says. Hospitals should do an evaluation of how well they are in compliance with that chapter. Then they should have an action plan for coming into compliance with those elements of the chapter that they feel are appropriate to their organization. "Surveyors are looking for that evaluation and that action plan," he reports.

This standard is a "B" element of performance, so it also requires

some evaluation of the method used to develop the evaluation, to make sure it is complete, thorough, addresses information in the literature, includes the hospital's own data that it may have collected on the subject, as well as shows involvement of medical staff and experts in this area from the organization.

"We are not only looking to see that you have an analysis and action plan but also that it was done appropriately according to the requirements of the standard," Rich says.

Joint Commission surveyors are not evaluating USP 797 directly, he explains. The surveyors, however, will score issues specific to Joint Commission standards. For example, Rich has seen hospitals in which IVs were prepared in the middle of the pharmacy area, not partitioned off in a functionally separate area.

He scored the hospitals for this. "It's not a 797 issue," he says. "The standard has been there two years." ■

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Hospital undertakes review of preprinted MD orders

Multidisciplinary team brings them to standard

Hospitals need to ensure that their preprinted physician orders meet the appropriate standards for both safety and clinical standards. A multidisciplinary team at one hospital reviewed more than 450 of its existing preprinted orders and found that many fell short. Problems included order form content deviating from the published standards for clinical best practice, orders that did not follow pharmacy formulary, and orders that contained inappropriate symbols and abbreviations.

The team at St. Francis Hospital in Milwaukee, a 180-bed, not-for-profit community facility, also found that many of the existing orders had never been reviewed by all departments that were represented on the order. These departments included pharmacy, nursing, and laboratory.

Team members included the owner, clinical nurse specialists, and representatives from pharmacy, radiology, laboratory, and administrative support — with others having ad hoc membership, says **Susan E. Samet**, PharmD, formerly pharmacy clinical manager for Cardinal Health Pharmacy Management at St. Francis. Samet, now pharmacy system clinical manager at CHISTUS Spohn Health System in Corpus Christi, TX, spoke about the "development and implementation of a multidisciplinary review and approval process for preprinted physician order," at the American Society of Health-System Pharmacists Midyear Clinical Meeting, held last December in Las Vegas.

Recommended action for the review of the orders included deleting physician-specific orders and using system-based orders instead, she says. All orders needed to be routinely reviewed, follow a standard format, and undergo annual review and distribution, say Samet and her St. Francis colleague **Debra A. Anczak**, RPh, MS.

The team used the "plan, do, study, act model" for process improvement and initiated several changes to the review and approval process to ensure complete and consistent review and approval of all preprinted orders. The team did

encounter several challenges that included a lack of a standard format for orders, required elements for a complete order, communication of changes between team members, and communication of changes to the staff members.

One solution was to flowchart the process for communication between members and revise it as needed. The process of review also was automated to ensure proper communication of intent between team members. The team developed a standardized order form template and tip sheet that removed all abbreviations, used standardized wording, and included a format for medication orders. To ensure compliance with best practices and safety issues, old orders were taken out of the facility.

The result was that more than 450 order sets were reviewed and approved to bring the hospital into compliance with regulatory standards, as well as ensuring safe clinical best practice for patients, Samet and Anczak say. ■

Learn how to get around rebound headache

Duration not related to time of drug in body

Giving preventive medications to a patient who is overusing acute medication for headache may be a waste of time, according to a presenter at the American Society of Health-System Pharmacists Midyear Clinical Meeting in December.

In fact, the six to eight weeks that the preventive medications take to become effective does not begin until the patient is no longer using the headache medications, says **Carla R. Rubingh**, PharmD, assistant professor of the department of pharmacy practice, University of Nebraska Medical Center in Omaha. Rubingh's presentation, "Getting around rebound," was part of the meeting's "Clinical Pearls" section.

Medication overuse is the No. 1 cause of chronic daily headache, she says. Chronic daily headache is defined as headache that occurs more than 15 days in a month. Medication overuse headache can presents as a dull, squeezing pain, usually in the frontal region of the head.

All acute medications used for the treatment of headache can cause rebound, with the possible exception of nonsteroidal anti-inflammatory medications, Rubingh says. To avoid this, no acute medication should be used more than three days per week. "This is not the number of doses. This is the number of days."

Patients may wonder why they quit taking a medication such as Excedrin for two weeks, and their headache did not get any better. The duration of rebound headache is not related to the duration of the drug in the body, Rubingh says. "You cannot calculate how long it should take for the drug to wash out of the body."

Physiological changes occur in the brain depening what drug the patient is overusing, she explains. "Rebound can last anywhere up to a year."

Because of this, all patients should be monitored for the frequency of the use of these medications and the doses it takes to get relief. Administration of preventive therapy should be done at the time you start to taper [the overused medications], Rubingh says. Support medications can be started at that time, too.

Most important is patient education. Patients, she says, should be told at the beginning that these drugs should not be used more than three days a week. ■

Abstracts highlight drug information, NICU benefits

Here's a snapshot of two Professional Posters presentation abstracts from the American Society of Health-System Pharmacists Midyear Clinical Meeting in December.

• **Implementation of a web-based, multisite drug information service database,** Amy F. Wilson, PharmD, and Cathy L. Bartels, PharmD, FAAIM, assistant professor and associate professor, respectively, of pharmacy practice for the Drug Information Service at Creighton University School of Pharmacy and Health Professions in Omaha, NE. Creighton University Medical Center School of Pharmacy and Health Professions (SPAHP) supports three full-time drug information services in Omaha. A high-tech drug information database was implemented in 2005 to assist in the effective management and efficient collaboration between and among the services. The goal of the project was to provide a searchable database of questions and responses received by the various drug information services.

To do this, a computer consultant development company was contracted to develop the database.

The database was designed to allow users to enter the question, along with a verbal or written response, and document the resources used to answer the questions, as well as any notes for clarification. The system has capabilities to produce PDF files ready for electronic e-mailing, as well as autogeneration of cover sheets for fax transmission. Because the majority of question intake and responses are done by pharmacy clerkship students, the database requires faculty approval, via password, before responses can be completed.

Implementation of the database has allowed the drug information services to evolve toward a paperless environment, providing storage for all drug information requests and responses. The database has improved efficiency of the services, avoiding time being spent researching previously answered questions. In addition, reporting capabilities of the system have allowed monthly service reports to be generated and shared with administration.

• **Persistence of improved medication use safety in the NICU after adding a neonatal pharmacist,** Pauline Chan, RPH, MBA, BCPP, pharmacy manager, and Ronald Floyd, PharmD, at Sharp Mary Birch Hospital for Women in San Diego. After implementing nearly all published recommendations, guidelines, and actions for prevention of medication error in pediatrics, the pharmacists decided in 2002 that the medication error rate could be further reduced only by bringing pharmacists knowledgeable about neonatal pharmacology and pharmacotherapy into close proximity with prescribers and nursing staff. They reported that in 2003 — as compared to earlier years — a neonatal pharmacist providing coverage from 0700 to 1530 hours on weekdays to the neonatal intensive care unit (NICU) at Sharp Mary Birch Hospital for Women was associated with statistically significant changes in medication use process error detection, prevention, and reporting. The improvements over baseline have been maintained throughout 2004.

Data documenting the impact of the pharmacists' efforts to improve the safety of medication prescribing, dispensing, and delivery were collected from the Clinical Pharmacy Intervention system on the Sharp Intranet for 2004. These data were compared to those from 2002 through 2003, which were collected in the same manner.

The average monthly number of clinical interventions reported by pharmacists for the NICU increased significantly between 2002 and 2003, more than doubling the rate from 24 to 58. For 2004, this higher level of average monthly clinical interventions was maintained at 57. For 2004, as well as for 2003, the number of reported potential adverse drug events also increased over baseline. While all types of clinical interventions increased, those involving the antibiotic and miscellaneous categories appeared to increase more than did those involving total nutrient admixture (TNA).

This reflects the NICU pharmacists' ability to affect prescribing within the context of the clinical environment, their increased awareness of specific clinical situations from immediate nursing communication, as well as pharmacy's previous close scrutiny of TNAs, the pharmacists say. ■

■ Research News ■

Study indicates problems with using corticosteroids in the ICU.

Health care practitioners may currently favor the use of corticosteroids in the intensive care unit (ICU), especially in the setting of sepsis and relative adrenal insufficiency. A new study, however, associates corticosteroid use in the ICU with increased rate of infection, more time spent in the ICU and on ventilators, and possibly increased mortality.

The researchers who conducted the study, which was published in the February issue of the *Archives of Surgery*, say that the increasing use of corticosteroids by practitioners for treatment of sepsis has led to an increasing level of comfort with the use of corticosteroids for other indications in the critically ill. The study was designed to evaluate the morbidity and mortality related to corticosteroid use in the trauma ICU.

To conduct their study, the researchers queried a trauma database for the years 2002 to 2003 for all patients admitted to the trauma and burn ICU of a Level 1 trauma center. The computerized pharmacy orders were then queried for each patient for the use of methylprednisolone, hydrocortisone, dexamethasone, and prednisone. The process identified 100 patients who had received corticosteroids while in the trauma ICU.

The corticosteroid recipients were then matched by age and injury severity score to a control group of 100 patients treated in the ICU

during the same period but without corticosteroids. The researchers used the Statistical Analysis System software to assess the links between corticosteroid use and each of seven outcomes (pneumonia, bloodstream infections, urinary tract infection, other infections, ICU length of stay (LOS), ventilator length of stay, and death) with univariate analysis. They also conducted multivariate regression analysis (logistic regression and ordinary least squares), controlling for age, APACHE II (Acute Physiology and Chronic Health Evaluation II) score, and medical history.

The researchers found no significant difference between the two groups for Glasgow Coma Scale score, APACHE II score, and medical history. In univariate analysis, the corticosteroid group had a significant increase in pneumonia (26% vs. 12%), bloodstream infection (19% vs. 7%), and urinary tract infection (17% vs. 8%). In multivariate models, corticosteroid use was associated with an increased rate of pneumonia and bloodstream infection. There was a trend toward increased urinary tract infection, other infections, and mortality. Patients in the ICU who received corticosteroids had a longer ICU LOS by seven days and longer ventilator LOS by five days.

Overall, the researchers conclude, "caution must be taken to carefully consider the indications, risks, and benefits of corticosteroids when deciding on their use."

These researchers have clearly articulated the results of a well-designed case-control study, say **Michael F. Rotondo**, MD, FACS, and **Paul J. Schenarts**, MD. They published their comments in the journal in an "invited critique" of the study. Rotondo is professor of surgery, vice chairman for clinical affairs, and chief of trauma and surgery critical care at the Brody School of Medicine at East Carolina University in Greenville, NC. Schenarts is an assistant professor of trauma and surgical critical care at the school.

The researchers' findings of significantly increased rates of pneumonia, bloodstream infections, urinary tract infections, ventilator days, and ICU length of stay serve as a warning to those who advocate increased steroid use, the reviewers say. "It is also noteworthy that these results may have been even more significant, had their institution not already implemented a series of protocols designed to limit infections."

"If one considers the indications for the use of steroids in the ICU, the benefits may not outweigh the risks," Rotondo and Schenarts say. Literature does not fully support the use of steroids to treat traumatic optic injury and also does not provide guidance for steroid use in "relative" adrenal insufficiency. In addition, steroids may not alter reintubation rates in those with airway edema, they say. Furthermore, steroid use in sepsis remains controversial, and steroids have not been used as much in the treatment of spinal cord injury.

"Given the paucity of documented benefit," they conclude, "the infectious risks of steroids need to be carefully considered before initiation of therapy." ■

Steroids taken with protease inhibitors linked to complications

A study by researchers at the National Institutes of Health (NIH) indicates that a steroid medication taken with an HIV protease inhibitor may increase the risk of bone damage in HIV-infected patients as well as increase the risk of Cushing's syndrome.

Published in the Dec. 15 issue of the *Journal of Acquired Immune Deficiency Syndrome*, the study showed that ritonavir, a protease inhibitor used to treat HIV patients, taken with prednisone, significantly increased the concentrations of prednisolone in the systems of healthy volunteers.

Researchers gave 10 healthy volunteers a 14-day course of low-dose ritonavir. They also gave the volunteers three doses of prednisone. One dose of prednisone was given before ritonavir was started as a baseline. A second dose was given after four days on ritonavir and a third dose was given after 14 days on ritonavir. Blood samples were taken after each dose of prednisone to determine steroid levels.

Prednisolone concentrations were 41% higher than the baseline amount after the drugs were taken together four days into the ritonavir regimen and 30% higher after the drugs were taken together 14 days into the regimen.

The study team included researchers at the NIH Clinical Center and the National Institute of Allergy and Infectious Diseases. The team plans to continue studies of the blood levels of individuals on steroids and other HIV medications. ▼

HHS agencies announce initiative to improve cancer therapy

The Food and Drug Administration (FDA), the National Cancer Institute (NCI), part of the National Institutes of Health, and the Centers for Medicare & Medicaid Services (CMS) today announced the Oncology Biomarker Qualification Initiative (OBQI) — an agreement to collaborate on improving the development of cancer therapies and the outcomes for cancer patients through biomarker development and evaluation. This initiative is the first time these three Department of Health and Human Services (HHS) agencies have focused together on biomarkers as a way of speeding the development and evaluation of cancer therapies.

The goal of OBQI is to validate particular biomarkers so that they can be used to evaluate new, promising technologies in a manner that will shorten clinical trials, reduce the time and resources spent during the drug development process, improve the linkage between drug approval and drug coverage, and increase the safety and appropriateness of drug choices for cancer patients.

Under the OBQI, biomarker research will be focused in four key areas: standardizing and evaluating imaging technologies to see in more detail how treatments are working, developing scientific bases for diagnostic assays to enable personalized treatments, instituting new trial designs to utilize biomarkers, and pooling data to ensure that key lessons are shared from one trial to another. By working with academic and industry scientists, as well as professional organizations, the OBQI teams can foster the development of key information on biomarkers through clinical trials.

The first OBQI project to be implemented will serve to validate and standardize the use of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scanning. PET scans are used to characterize biochemical changes in a cancer. Under the collaboration, researchers will use FDG-PET imaging technology in trials of patients being treated for non-Hodgkin's lymphoma, to determine if FDG-PET is a predictor of tumor response. Data resulting from this type of evidence-based study will help both FDA and CMS work with drug developers based on a common understanding of the roles of these types of assessments. ▼

Bayer, FDA warn of administration errors for nimodipine (Nimotop)

Bayer and the FDA have notified health care professionals of changes to the prescribing information for nimodipine (Nimotop), including a boxed warning to notify prescribers about medication administration errors. Nimodipine is approved for oral administration to improve neurological outcome after subarachnoid hemorrhage.

When administered intravenously or parenterally, it can cause serious adverse events, including death. Nimodipine must not be administered intravenously or by any parenteral route. For more information, see: www.fda.gov/medwatch/safety/2006/safety06.htm#Nimotop. ▼

Hypoglycemia, hyperglycemia linked to gatifloxacin (Tequin) use

Bristol-Myers Squibb Co. has announced labeling changes for gatifloxacin (Tequin), an antibiotic indicated for the treatment of patients with pneumonia, bronchitis, uncomplicated gonorrhea, and various infections including infections of urinary tract, kidneys, and skin.

The labeling changes, announced by the gatifloxacin manufacturer in a letter to health care professionals, update the prescription information as a result of continued reports of serious cases of hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar) in patients receiving gatifloxacin. Since the approval of gatifloxacin in 1999, there have been rare cases of life-threatening events reported globally in patients treated with the drug. Most of these events were reversible when properly managed, but a few had fatal outcomes.

Information about the risks of low blood sugar and high blood sugar was added to the Warnings section of the U.S. labeling in 2002. The new changes strengthen the existing warning on hypoglycemia and hyperglycemia, add a contraindication for use in diabetic patients, and include information identifying other risk factors for developing low blood sugar and high blood sugar, including advanced age, renal insufficiency, and concomitant glucose-altering medications while taking gatifloxacin. ▼

Bosentan label revised to include liver function monitoring

Actelion and the FDA have notified health care professionals of changes to the bosentan (Tracleer) prescribing information based on cases of hepatotoxity reported. Bosentan is indicated for the treatment of pulmonary arterial hypertension. The notification underscored the need to continue monthly liver function monitoring for the duration of bosentan treatment and the need to adhere to the recommended dosage adjustment and monitoring guidelines described in the product labeling.

For more information, see: www.fda.gov/medwatch/safety/2006/safety06.htm#Tracleer. ▼

Study of natalizumab-treated patients shows no new PML cases

An independent clinical and laboratory study of more than 3,000 people treated with the drug natalizumab (Tysabri) for multiple sclerosis (MS), Crohn's disease, and rheumatoid arthritis has found no evidence of new cases of progressive multifocal leukoencephalopathy (PML). The laboratory component of the study was coordinated by the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH), working in conjunction with the NIH Clinical Center. Clinical and neuroradiological experts from other institutions also participated. Results of the study were published in the March 2 issue of the *New England Journal of Medicine*.

Natalizumab, an immune system-modifying drug, was approved by the FDA in November 2004 to treat relapsing-remitting MS. Studies have shown that it can substantially reduce the frequency of relapses in that disease. However, the drug was withdrawn from the market and from clinical trials in February 2005 after the manufacturer identified two cases of PML in MS patients who had received the drug. A person with Crohn's disease who had received natalizumab also was diagnosed with PML. The current study was conducted to determine whether other people treated with natalizumab were at risk of PML. Symptoms of PML include mental deterioration, problems with vision, speech, balance, and movement and, in most cases, coma, and death.

Although the study did not find any evidence for new cases of PML, the researchers cannot say for certain that the patients who received natalizumab will not develop the disease in the future. The risk associated with longer-term treatment with natalizumab also is unknown.

The study also did not formally include patients who were treated with natalizumab outside of clinical trials. However, since PML is a very severe disease, it is likely that any PML in other patients who received natalizumab would have been diagnosed, the researchers say. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Anidulafungin (Eraxis) by Pfizer.*** The FDA has approved anidulafungin (Eraxis) to treat certain infections caused by *Candida,* a yeast-like fungus that can cause serious infections in hospitalized patients or patients with compromised immune systems.

Anidulafungin, a new molecular entity that has never been marketed in the United States, is an antifungal drug that is administered intravenously, and is used to treat *Candida* infections in the esophagus (candidiasis), bloodstream (candidemia), and other forms of *Candida* infections, including abdominal abscesses and peritonitis.

Anidulafungin was generally well tolerated in clinical studies. The most commonly reported adverse events were mild diarrhea, mild elevations in laboratory tests of liver enzymes, and

COMING IN FUTURE MONTHS

- One hospital's experience in preparing for USP 797
- Notes from APhA's Annual Meeting and Exposition
- Dual blockade of the renin-angiotens in system in diabetic nephropathy
- Optimize reconciliation of medication administration records for high-risk medicines
- A model for justifying clinical pharmacy services

headache. Some patients experienced infusion-related reactions, most of which were mild. In a few patients with significant underlying medical conditions who were on multiple concomitant medications, there were reports of serious hepatic abnormalities.

• ***New indication for cetuximab (Erbitux), manufactured by ImClone Systems and distributed and marketed by Bristol-Myers Squibb Co.*** The FDA has approved cetuximab (Erbitux) for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck (SCCHN) that cannot be removed by surgery (unresectable SCCHN). This is the first drug approved for head and neck cancer that has shown a survival benefit in this population. Cetuximab also was approved for monotherapy to treat patients whose head and neck cancer has metastasized despite the use of standard chemotherapy.

This is the second indicated tumor type for cetuximab, previously approved by the FDA for use in combination with irinotecan for patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer who are refractory to irinotecan therapy and as a single-agent for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan therapy.

Cetuximab, which received a priority review, is the first drug approved to treat head and neck cancer since methotrexate became available in the 1950s. Approval of cetuximab in combination with radiation therapy was based on a study that showed it prolonged survival by 20 months compared to treatment with radiation alone. Approval of cetuximab monotherapy was based on evidence of tumor shrinkage in 13% of patients, lasting on average of six months.

Commonly reported side effects of cetuximab were infusion reactions (fever, chills), skin rash, fatigue/malaise, and nausea. The common side effects associated with radiation such as sore mouth, trouble swallowing, and radiation skin changes were similar in frequency in patients receiving cetuximab plus radiation and those receiving radiation alone.

• ***New indication for rituximab (Rituxan) by Genentech.*** The FDA has approved rituximab (Rituxan) for use in the first-line treatment of patients with diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens. Rituximab previously has been approved as a single agent for use in relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL).

The approval was based on efficacy and safety data from three randomized, controlled, multicenter studies of rituximab in combination with CHOP or other anthracycline-based chemotherapy induction regimens in 1,854 previously untreated (first-line) patients with diffuse large B-cell lymphoma (DLBCL). In each study, hazard ratios for the time-to-event comparison, as well as the overall survival benefit, favored the rituximab-containing arms. ■

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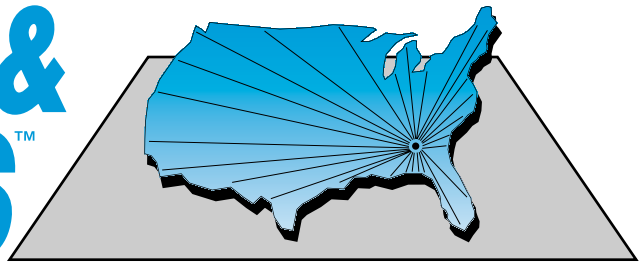

Exenatide (Byetta) Drug Evaluation

Part 2 of 2: Clinical trial summary, Cost comparison, and Recommendation

By **Steven Higginbotham**, PharmD Candidate
Harrison School of Pharmacy, Auburn (AL) University

Clinical trial summary

***Trial 1*:** Buse JB, Henry RR, Han J, et al. **Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with Type 2 diabetes.** *Diabetes Care* 2004;27:2,628-2,635.

Objective: To evaluate the ability of exenatide to improve glycemic control in patients with Type 2 diabetes who have not achieved control with maximally effective doses of a sulfonylurea.

Study design: A triple-blind, randomized, placebo-controlled, 30-week study conducted at 101 sites in the United States.

Treatment regimen: After a four-week, single-blind, placebo lead-in period, 377 subjects were randomized and began four weeks of 5 mcg subcutaneous exenatide twice daily (before breakfast and dinner; in arms A or B) or placebo. The exenatide dose for arm B was then increased to 10 mcg twice daily while arm A remained at 5 mcg twice daily for the duration of the study.

Study population

• The study included males and females (age range 22-76 years) with Type 2 diabetes.

• Of the 377 patients randomized, 123 received a placebo, 125 received exenatide 5 mcg BID, and 129 received exenatide 10 mcg BID.

Inclusion criteria

• Type 2 diabetes treated with maximum doses of a sulfonylurea for at least three months prior to screening.

• Fasting plasma glucose level < 240mg/dL, body mass index (BMI) 27-45 kg/m^2, and Hb_{A1c} 7.1-11%.

• Stable weight (±10%) for three months prior to screening.

• No clinically relevant abnormal laboratory test values (for Type 2 diabetes) defined as > 25% outside normal range.

• Females were either postmenopausal, surgically sterile, or used contraceptives for at least three months prior to screening.

Exclusion criteria

• Use of metformin, thiazolidinediones, meglitinides, α-glucosidase inhibitors, exogenous insulin, or weight-loss drugs within three months prior to screening.

• Therapy with corticosteroids, drugs that alter GI motility, transplantation medications, or investigational drugs.

• Evidence of any clinically significant comorbid condition.

Study endpoints

Primary endpoint

— Evaluation of glycemic control based primarily on Hb_{A1c}.

— Safety profile based on adverse events, clinical lab test, physical examination, 12-lead electrocardiogram, and vital signs.

Secondary endpoint

— Fasting plasma glucose concentrations.

— Changes in weight.

— Fasting concentrations of circulating insulin, proinsulin, and lipid.

Results

• More patients being treated with exenatide achieved an $Hb_{A1c} \leq 7\%$ than those receiving placebo (10 mcg group 41.3%, 5 mcg group 32.6%, placebo 8.8%; $P \leq 0.0002$).

• No clear safety concerns were identified.

• Fasting plasma glucose concentrations were decreased in the exenatide groups and increased in

the placebo group. [10 mcg (-0.6 ± 0.3), 5 mcg (-0.3 ± 0.2), placebo (+0.4 ± 0.3); P < 0.05 vs. placebo for the 10-mcg arm only].

• All patients experienced weight loss during the study period, with the exenatide group losing the most [10 mcg (-1.6 ± 0.3 kg), 5 mcg (-0.9 ± 0.3 kg), placebo (-0.6 ± 0.3 kg)].

• No significant differences in fasting insulin concentrations in any of the groups.

• There was a significant decrease in proinsulin reduction compared with baseline and placebo.

• No significant changes in lipids were noted in any of the groups.

Strengths

• Balanced, randomized, and placebo-controlled.

• Triple-blinded

• Conducted at 101 sites across the United States.

• Two separate laboratories were used to analyze blood test.

• Used intention-to-treat analysis.

• Accounted for dropouts.

• Several outcomes measured.

• All baseline measurements were similar.

Weaknesses

• Only 260 of the original 377 completed the trial.

• Diet and exercise were not controlled.

• Self-administered injection.

Authors' conclusions

• Exenatide reduced Hb_{A1c} and was associated with sustained weight loss.

• Exenatide generally is well tolerated and appears to be a safe drug.

• Long-term use of exenatide is likely a good choice for Type 2 diabetics who are uncontrolled with sulfonylurea agents.

***Trial 2*:** Defronzo RA, Ratner, Han J, et al. **Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes.** *Diabetes Care* 2005;28:1,092-1,100.

Objective: To evaluate the ability of exenatide to improved glycemic control in patients with Type 2 diabetes who failed to achieve control with maximally effective doses of metformin.

Study design: A 30-week, triple-blind, randomized, placebo-controlled study consisting of 336 patients at 82 sites across the United States.

Treatment regimen: All patients were given placebo for the first four weeks of the study. Patients were then given either exenatide 5 mcg or placebo BID for four weeks. Thereafter, patients either received exenatide 5 mcg, 10 mcg, or placebo for the remainder of the study. All patients continued metformin.

Study population

• Males and females (age range 19-78 years) with Type 2 diabetes being treated with metformin monotherapy were included.

• Of the 336 patients, 113 were given placebo, 110 exenatide 5 mcg, and 113 exenatide 10 mcg.

Inclusion criteria

• Type 2 diabetes being treated with monotherapy.

• Fasting plasma glucose level < 240mg/dL, BMI 27-45 kg/m^2, and Hb_{A1c} 7.1-11%.

• Metformin dose was > 1,500 mg/day for three months prior to the study.

• Stable weight (± 10%) for three months prior to screening.

• No clinically relevant abnormal laboratory test values (for Type 2 diabetes) defined as > 25% outside normal range.

• Females were either postmenopausal, surgically sterile, or used contraceptives for at least three months prior to screening.

Exclusion criteria

• Use of sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors, exogenous insulin, or weight-loss drugs within three months prior to screening.

• Therapy with corticosteroids, drugs that alter GI motility, transplantation medications, or investigational drugs.

• Evidence of any clinically significant comorbid condition.

Study endpoints

Primary endpoint

— Glycemic control assessed by efficacy and safety.

Secondary endpoint

— Patients (%) achieving $Hb_{A1c} \leq 7\%$ by week 30.

— Effect of exenatide on glucose concentrations.

— Weight changes.

— Concentrations of insulin, fasting proinsulin, and lipids.

Results

• Forty percent of subjects in the 10 mcg group, 27% in the 5 mcg group, and 11% in the placebo group reached an $Hb_{A1c} \leq 7\%$ by week 30. This was statistically significant (P < 0.001).

• Fasting plasma glucose levels were lower in the exenatide groups [10 mcg (-10.1 ± 4.4 mg/dL), 5 mcg (-7.2 ± 4.6 mg/dL), placebo (+14.4 ± 4.2 mg/dL), P < 0.005].

• All patients with baseline BMI ≥ 30 kg/m^2 lost weight over the study period. Patients in the exenatide group lost slightly more that those in

the placebo group. In patients with a baseline BMI < 30 kg/m^2, only those in the exenatide group lost weight (approximately 1-3 kg).

• No significant changes in insulin concentrations were noted.

• A significant reduction in proinsulin was observed in the exenatide group vs. placebo.

• No lipid changes were noted in any group.

Strengths

• Balanced, randomized, and placebo-controlled.
• Triple-blinded.
• Conducted at 82 sites across the United States.
• Intent-to-treat analysis was used.
• Dropouts were explained.
• Baseline measurements were similar.
• Multiple outcomes were measured.
• Only people using metformin were included.

Weaknesses

• Relatively small number of participants.
• Diet and exercise were not controlled.
• Self-administered injection.

Authors' conclusions: Exenatide was effective in lowering Hb_{A1c} in patients who failed to achieve glycemic control with metformin monotherapy. Exenatide was not associated with weight gain or increased risk of hypoglycemia.

***Trial 3*:** Whitehouse FW, Kruger DF, Fineman MF, et al. **A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes.** *Diabetes Care* 2002;25:724-730.

Objective: To assess the effects of mealtime pramlintide on long-term glycemic and weight control in patients with Type 1 diabetes.

Study Design: A 52-week, double-blind, randomized, placebo-controlled, multicenter study involving 480 patients.

Treatment regimen: Patients were started on either 30 mcg pramlintide or placebo preprandial QID. After 20 weeks, the pramlintide patients were re-randomized to 30 or 60 mcg pramlintide QID if decreases from baseline Hb_{A1c} were less than 1%. Of the 342 patients who completed the 52-week study, 236 (~70%) volunteered to participate in a one-year, open-label extension in which all received 30 or 60 mcg pramlintide QID.

Study population: 16- to 70-year-old males and females with a history of Type 1 diabetes.

Inclusion criteria

• Type 1 diabetes for at least one year.

• C-peptide concentration ≤ 1 and a baseline Hb_{A1c} value between 7% and 13%.

• Hypoglycemia- and hyperglycemia-free for at least two weeks.

• Insulin dose not adjustedby ± 10% during the one week prior to the study.

• Women were surgically sterile, postmenopausal, or using effective contraception.

Exclusion criteria:

• Clinically significant ischemic heart disease, hypertension (> 150/95), gastrointestinal disease, renal disease, and unstable diabetic neuropathy.

• Treatment with drugs known to alter gastrointestinal motility (e.g., erythromycin, metoclopramide, cisapride, cholestyramine, or colestipol).

• Treatment with drugs that alter glucose metabolism (e.g., thiazide diuretics, corticosteroids, bile sequestering resins, acarbose, or metformin).

Study endpoints:

Primary endpoint

— Relative change in Hb_{A1c} from baseline to week 52.

— Number of patients with an Hb_{A1c} < 7% or < 8% depending on baseline.

Other endpoints

— Absolute changes in Hb_{A1c} and body weight from baseline to week 52.

— Relative change in insulin use from baseline.

Results

• Of the 480 patients enrolled, 342 completed the study.

• Patients in the pramlintide group has significant mean reductions in Hb_{A1c} (0.67%) compared with placebo (0.16%) from baseline to week 13 (P < 0.0001). A significant placebo-corrected treatment difference was sustained in favor of pramlintide through week 52 (-0.39 vs. -0.12%, P = 0.0071).

• Percent of patients who achieved an Hb_{A1c} of < 7% in patients who had a baseline ≥ 7% (25 vs. 11.3% for placebo, P = 0.01).

• Percent of patients who achieved an Hb_{A1c} of < 8% in patients who had a baseline ≥ 8% (58.6 vs. 35.1% for placebo, P = 0.04).

• Patients in the pramlintide group had a sustained mean reduction in weight; patients in the placebo group had a mean increase in weight.

• There was a slight increase of insulin use in both groups (+2.3% for pramlintide and +10.3% for placebo at week 52, P = 0.0176).

• There was no significant increase in the incidence of severe hypoglycemia in either group.

Strengths

• Double-blind, randomized, placebo-controlled, multicenter.
• All baseline values were similar.
• Used intent-to-treat analysis.
• Hb_{A1c} and weight were analyzed using a

two-way ANOVA (analysis of variance).

• Dropouts were accounted for.

Weaknesses

• Insulin use was not controlled.

• Self-administered injection.

• Diet and exercise was not controlled.

Authors' conclusions: Use of pramlintide at mealtime as an adjunct to insulin improved long-term glycemic control. Pramlintide did not cause weight gain or increase the incidence of severe hypoglycemia in Type 1 diabetics.

Cost comparison

Exenatide (Byetta)

• 300 mcg/1.2 mL pen containing 60 5-mcg doses — $147/month or $4.90/day (5 mcg BID).

• 600 mcg/2.4 mL pen containing 60 10-mcg doses — $172.50/month or $5.75/day (10 mcg BID).

• A pen containing a month's supply of drug will have to be used for each patient; the company does not plan to manufacture a multidose vial.

Pramlintide (Symlin)

• 3 mg/ 5mL vial — $79.50.

• Type 1 diabetics $2.39- 4.77/day (30-60 mcg TID).

• Type 2 diabetics $4.77-9.54/day (60-120 mcg TID).

Recommendation

Exenatide and pramlintide both mimic natural peptides in the body that have a role in glucose control. Although both drugs have very similar effects on the body, they act by very different mechanisms. Trials indicate that both drugs effectively improve long-term glycemic control and do not cause weight gain. Exenatide is indicated for use in Type 2 diabetes, whereas pramlintide is indicated for Type 1 and Type 2 diabetes. Both drugs are given as SQ injections at multiple times throughout the day (BID for exenatide and TID-QID for pramlintide). Similar side effects have been observed with the drugs and they are both safe. The monitoring and storage requirements are similar for both drugs as well.

Pramlintide can be twice as expensive as exenatide. A month's supply of exenatide will likely have to be purchased for each patient regardless of the length of stay because of the lack of a multidose vial. Because of the different mechanisms of action and slightly different indications, both drugs will be needed on the formulary. Pramlintide is a complicated drug to initiate; therefore, a protocol must be created for its use.

CE *Questions*

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

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

This CE program will improve participants' ability to:

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

13. Exenatide and pramlintide have very similar effects on the body, but act by very different mechanisms.
    A. True
    B. False

14. Exenatide:
    A. improves long-term glycemic control.
    B. does not cause weight gain.
    C. is for use only in Type 2 diabetes.
    D. All of the above

15. Pramlintide is indicated for use only in Type 2 diabetes.
    A. True
    B. False

16. Which of the following statements is false?
    A. Both exenatide and pramlintide must be administered as SQ injections multiple times throughout the day.
    B. Similar side effects have been reported with both exenatide and pramlintide.
    C. Exenatide can be twice as expensive as pramlintide.
    D. Regardless of length of stay, a month's supply of exenatide must be purchased for each patient.

Resources

• Amylin Pharmaceuticals. Byetta [package insert]. San Diego: April 2005.

• Amylin Pharmaceuticals. Symlin [package insert]. San Diego: March 2005.

• Klasco RK, ed. DRUGDEX® System. Thomson MICROMEDEX, Greenwood Village, CO (Edition expires 2005). Accessed June 13, 2005.

• Personal Communication with Keith Moss. Pharmacy Buyer. Huntsville (AL) Hospital System Pharmacy. June 2005.

• Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with Type 2 diabetes. *Diabetes Care* 2003;26:784-790. ■