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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 20, 2001. 2 drugs were added in the *Formulary* and 1 drug was deleted. 1 drug that was added was restricted. 1 drug was designated not available.

◆ **ADDED**

Drotrecogin*
(Xigris® by Eli Lilly)

Insulin glargine
(Lantus® by Aventis)

***Restricted to ICUs and order form.**

◆ **DELETED**

Levonorgestrel implants
(Norplant® by Wyeth-Ayerst)

◆ **NONFORMULARY, NOT AVAILABLE**

Darbepoetin
(Aranesp® by Amgen)

Drotrecogin alfa activated is recombinant human activated protein C. The inflammatory and procoagulant host responses to infection are closely related. Proinflammatory cytokines, such as tumor necrosis factor (alpha), interleukin-1 (beta), and interleukin-6, are capable of activating coagulation and inhibiting fibrinolysis. Also, the procoagulant thrombin can stimulate multiple inflammatory pathways. The activation of coagulation, followed by intravascular deposition of fibrin, has been implicated in the development of multiorgan dysfunction and death. Activated protein C is an important modulator of the coagulation and inflammation associated with severe sepsis. Drotrecogin inhibits the coagulation cascade and (possibly) improves outcomes in patients who have severe sepsis.

Drotrecogin was evaluated proactively by the P&T Committee before Food and Drug Administration

(continued on next page)

DRUG INFORMATION FORUM

Acetylcysteine: Not just an antidote anymore

Acetylcysteine (Mucomyst®) possesses activity as a mucolytic, an antioxidant, and an antidote. Historically, acetylcysteine has been most often used as an antidote after acute ingestion of acetaminophen. Acetylcysteine prevents hepatotoxicity associated with high doses of acetaminophen by acting as a substrate for the toxic acetaminophen metabolite.

Today, acetylcysteine is being used in several unique areas of medicine. Acetylcysteine has gained popularity as an antioxidant and a free radical scavenger in the prophylaxis of radiocontrast-induced nephrotoxicity (RCIN). The Drug Information Center has received several questions concerning the use of acetylcysteine in patients who are undergoing procedures requiring radiocontrast agents.

There is some confusion about why these patients are receiving acetylcysteine. Health care professionals have asked if acetylcysteine possesses any cardioprotective effect because it was given to patients undergoing cardiac catheterization. Acetylcysteine does not have any direct cardioprotective effect in these patients. The benefit seen from using acetylcysteine is its ability to prevent reductions in renal function that have been associated with radiocontrast agents used in the procedure.

Risk factors for radiocontrast media-induced nephrotoxicity include chronic renal insufficiency, diabetes mellitus, decreased circulating volume, high doses of contrast media, and high-osmolality radiocontrast agents. Contrast agents reduce kidney function by direct toxic effects on the tubular epithelial cells and by affecting local hemodynamics resulting in vasoconstriction in the kidney.[1] High-osmolality agents are associated with a higher incidence of side effects than low-osmolality agents. However, low-osmolality agents are more expensive than high-osmolality agents.

Preventative strategies are recommended for any patient at risk of developing RCIN. Agents that have been previously studied in humans for prophylaxis of RCIN include those that might mitigate the effects of the radiocontrast media on the tubules or alter the local hemodynamics in the kidney. Drugs that have shown either marginal or no benefit in studies with small sample sizes include mannitol, furosemide, low-dose dopamine, theophylline, atrial natriuretic peptide, and calcium-channel blockers. The addition of mannitol or furosemide to hydration before radiocontrast media administration showed no additional benefit compared to hydration alone in a randomized trial by Solomon and colleagues.[2]

Oxygen-free radicals may play a role in the mechanism of nephrotoxicity caused by radiocontrast media. Acetylcysteine has been hypothesized to act as an antioxidant to scavenge the free radicals and help prevent reductions in renal function. Acetylcysteine has also been found to have vasodilatory properties in animal models.

A study by Tepel and colleagues found that administration of acetylcysteine and hydration before the administration of radiocontrast agents could prevent radiocontrast media-induced nephrotoxicity.[3] In this prospective, placebo-controlled, randomized

(continued on page 4)

INSIDE THIS ISSUE

Formulary update, *from page 1*
approval because the committee determined that it could represent an advantage over existing therapies. Drotrecogin was "tentatively added" in the *Formulary* with stipulations that follow. The evaluation of drotrecogin will continue at the January P&T Committee meeting.

The FDA approved drotrecogin November 21, 2001—the day after the P&T Committee met. It has a labeled indication for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (eg, as determined by APACHE II).

An expert ad hoc group of ICU and infectious disease physicians and pharmacists was established to determine appropriate criteria for use. A draft of a Drotrecogin Order Form was developed to promote appropriate prescribing and to facilitate collecting information that will allow the monitoring of the use of this drug. The Drotrecogin Order Form can be found on the Shands intranet at http://intranet.shands.org./pharm/xigrisform.pdf.

Drotrecogin should be administered intravenously at an infusion rate of 24 mcg/kg/hr for a total duration of infusion of 96 hours. A 96-hour course of drotrecogin costs approximately $7000—more for larger patients. Therefore, the impact of drotrecogin on pharmaceutical expenditure could be great. The Resource Utilization Committee (RUC) has required that quarterly reports on use and cost of drotrecogin be presented.

Hemorrhage is a major concern with drotrecogin. When drotrecogin is used in a wider patient population than in the published clinical trials, a higher rate of bleeding should be anticipated. Drotrecogin is contraindicated in patients who have active internal bleeding, or who are more likely to bleed because of certain medical conditions including recent stroke, recent head or spinal injury, or severe head trauma. In the event of clinically important bleeding, the infusion of drotrecogin should be stopped immediately.

Also, the efficacy of drotrecogin may not be as impressive in practice as it was in the clinical trials since it will probably be used in a wider population of patients (eg, transplant recipients). Therefore, patient selection will be very important to balance safety and efficacy.

Drotrecogin orders must be written by attending physicians from the BICU, CICU, MICU, PICU, and SICU using the Drotrecogin Order Form. Since a decision to use drotrecogin can be delayed as much as 24 hours, requiring an attending to complete the order form should not result in adverse consequences.

Insulin glargine is a long-acting recombinant analogue of human insulin with a labeled indication for both type 1 and type 2 diabetes in patients greater than 6 years of age. It is only used in patients with type 2 diabetes who require insulin.

Insulin glargine is a chemically modified analog of human insulin that is not water-soluble at a neutral pH. When administered subcutaneously, insulin glargine precipitates and is slowly released over 24 hours. Essentially, it is a sustained-release form of insulin.

◆

The Drotrecogin Order Form can be found on the Shands intranet at http://intranet.shands. org./pharm/xigrisform.pdf and orders must be written by attending physicians from the BICU, CICU, MICU, PICU, and SICU using the Drotrecogin Order Form.

Insulin glargine is given once a day at bedtime as a subcutaneous injection. It is not intended for intravenous administration and should not be mixed with any other insulin. Although there are no current recommendations as to the reductions needed in insulin glargine dosing in renal and hepatic impairment, it should be used cautiously and monitored carefully in these patients. A review of drug-induced hypoglycemia published in the *New England Journal of Medicine* concluded that patients should have their maintenance doses of daily insulin reduced upon admission to avoid the occurrence of hypoglycemia due to fasting and decreased caloric intake. These recommendations should be considered for insulin glargine, although these recommendations were based on older forms of insulin.

Clinical trials show that insulin glargine is at least as effective at lowering fasting plasma glucose levels compared with NPH insulin. Insulin glargine has been associated with less nocturnal hypoglycemia compared with NPH insulin.

Insulin glargine costs 3-times as much as NPH or Lente insulin, but use should be relatively low. Patients started on insulin glargine in the hospital will not be able to take this vial home. Unlike other forms of insulin, insulin glargine is a prescription product and must have an appropriate prescription label. There is no mechanism for this labeling at this time, and the vial that the patient is using as an inpatient cannot legally be sent home with the patient.

There is a medication safety hazard associated with Lantus® insulin. Reports at other hospitals have shown confusion between Lantus® and Lente insulin when orders are not written clearly. Pharmacy and nursing education efforts have already been instituted. An article was also placed in the October issue of the *Drugs & Therapy Bulletin* to alert the medical staff about this possible problem.

Levonorgestrel implants are silicone rubber tubes that are implanted in a superficial plane of the upper arm and that slowly releases the progestin, levonorgestrel, over up to a 5-year period providing a constant method of contraception. This method is reversible upon removal of the implants.

Approximately 1 year ago, Norplant® implants were removed from the market because of quality control issues. They remain unavailable at this time. The OB-GYN department used Norplant® as a birth control method for noncompliant patients before their discharge. Depot medroxyprogesterone is now used, but it must be administered every 3 months. Women who had Norplant® implanted before it was removed from the market last year were advised to use a back-up, barrier or other nonhormonal method of contraception, such as a condom, spermicide, a diaphragm, or IUD. No new implants have been placed since this warning.

Because of lack of availability and the need to re-evaluate this product should it become available again, Norplant® was deleted from the *Formulary*. Its formulary status can be reconsidered if it is re-released to the market.

Darbepoetin is a hyperglycosylated analogue of recombinant human erythropoietin. The extra carbohydrate chains result in amino acid substitutions, giving darbepoetin an increased circulating half-life compared with erythropoietin. Darbepoetin's half-life is 2 to 3 times longer than that of epoetin.

(continued on next page)

Formulary update, *from page 2*

Instead of 3-times a week administration, darbepoetin can be given weekly. Instead of weekly administration, darbepoetin can be given every other week. This could result in less nursing and pharmacy time and, potentially, fewer patient office visits in the outpatient setting.

Clinical trial data show that darbepoetin has similar effectiveness and adverse effects compared to epoetin. Thus, the main advantage of darbepoetin is that it can be given less frequently than epoetin.

Darbepoetin is less expensive than epoetin for large dosages, but more expensive for lower dosages. Therefore, adding it in the *Formulary* should not increase pharmaceutical expenditures, but it is difficult to estimate the actual effect.

Reimbursement is a critical issue with darbepoetin. Currently, there is no Medicare reimbursement code for darbepoetin when it is used in a hospital-based clinic.

If darbepoetin is administered in a physician-owned clinic, it can be billed on an HCFA 1500 Form (superbill) using a miscellaneous code (ie, code J-3490), which is used for all new drugs, provided that it is used only for an approved indication and that additional explanatory text is provided. Very specific explanatory text is required to justify the use of a drug when a miscellaneous code is used. If not done correctly, the clinic will not receive any reimbursement. Poor reimbursement could be financially devastating.

Darbepoetin cannot be billed in a hospital-based clinic. If it were used, there would be no reimbursement for this expensive agent.

When the temporary C-code is assigned, darbepoetin can be billed in a hospital-based clinic, but only for the approved indications. In other words, if someone used it in the Shands Infusion Center or the BMT outpatient clinic for a cancer-related indication, there would be no reimbursement.

Darbepoetin is not available in the Shands Outpatient Pharmacy at this time. Once the reimbursement issues have been clarified, the formulary status of darbepoetin will be reconsidered. Until that time, it has been designated not available in the inpatient setting as well.

PHARMACOTRIVIA

Making sense out of "MAbs"

Does it seem like generic names are getting more difficult to remember—and pronounce? There is a method to this madness, and this article will try to explain the generic names of monoclonal antibodies or "MAbs."

A drug company can request that a generic name be assigned to a drug after an investigational new drug application (IND) has been submitted to the Food and Drug Administration (FDA). The United States Adopted Name (USAN) Council assigns generic names. Since generic names are nonproprietary, they are not subject to proprietary trademark rights and are entirely in the public domain. Generic names are selected using principles that are designed to be logical and assure safety and consistency.

Although generic names are supposed to be brief, easy to pronounce, and easy to remember, that is not the general perception—particularly for monoclonal antibodies. Most generic names have few syllables. Monoclonal antibodies' generic names often have 4 or more syllables. Once you understand the principles used to establish the generic names of monoclonal antibodies, each syllable provides information about these biological agents.

The rules for naming monoclonal antibodies were established by the USAN Council in conjunction with the FDA, the US FDA Center for Biologics Evaluation and Research (CBER), and the World Health Organization's (WHO) International Nonproprietary Names (INN) Committee. The first guideline is easy to remember: all monoclonal antibodies end in mab.

By working backward from the "mab" suffix to the prefix of the generic name, you can detemine how the MAbs are created and what they are used for. In front of "mab" is the animal source used to create the antibodies. The following letters are approved as product source identifiers.

a = rat
e = hamster
i = primate
o = mouse
u = human
xi = chimera
zu = humanized

Currently, all monoclonal antibodies on the US market come from a chimeric or humanized source (*see table below*). Chimera means the fusion of 2 genetically distinct types of cells. This term comes from Greek mythology where the chimera was a monster with a lion's head, a goat's body, and a serpent's tail. Chimeric antibodies are usually the fusion of mouse and human antibodies. Humanized refers to the manipulation of animal genes (usually mouse) to create antibodies that appear to be human (ie, < 10% mouse).

In front of the source in the name of a monoclonal antibody is the disease or target of that antibody. The current list of diseases or targets includes the following.

bac = bacterial
cir = cardiovascular
col = colon (tumor)
got = gonad/testis (tumor)
gov = gonad/ovary (tumor)
les = infectious lesions
lim = immune (immunomodulator)
mar = mammary (tumor)
mel = melanoma (tumor)
pr(o) = prostate (tumor)
tum = tumors (miscellaneous)
vir = viral

Thus far, the only monoclonal antibodies that have been marketed are targeted at the cardiovascular system, miscellaneous tumors, viruses, or are immunomodulatory. In an attempt to make these generic names pronounceable, often the last consonant of the target syllable is dropped (eg, lim truncated to li).

In order to create a unique name, a distinct compatible syllable is selected as the starting prefix. There is no rule for this selection, although you can guess where these syllables are derived. For example, does the starting prefix in abciximab come from being a Fab fragment (ie, fAB) or from antibody (ie, Ab)?

Using your new understanding of the generic names of monoclonal antibodies, look at the generic names in the table that lists all currently

(continued on page 4)

TABLE. MONOCLONAL ANTIBODIES ON THE US MARKET

Generic Name	Unique Prefix	Target	Source	Monoclonal Antibody	Brand Name
Abciximab	Ab	ci [r]	xi	mab	ReoPro®
Alemtuzumab	Alem	tu [m]	zu	mab	Campath®
Basiliximab	Basi	li [m]	xi	mab	Simulect®
Daclizumab	Dac	li [m]	zu	mab	Zenapax®
Gemtuzumab	Gem	tu [m]	zu	mab	Mylotarg®
Infliximab	Inf	li [m]	xi	mab	Remicade®
Palivizumab	Pali	vi [r]	zu	mab	Synagis®
Rituximab	Ri	tu [m]	xi	mab	Rituxan®
Trastuzumab	Tras	tu [m]	zu	mab	Herceptin®

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Drug information forum, *from page 1*
study, 600 mg of acetylcysteine or placebo was administered orally twice daily to 83 patients with chronic renal insufficiency undergoing a computed tomography (CT) procedure. Patients were included in the study if they had a serum creatinine above 1.2 mg/dL or a creatinine clearance less than 50 mL/min. Acetylcysteine or placebo was administered on the day before and the day of the procedure. Hydration with 1/2 normal saline (0.45% NS) for 12 hours before and after the procedure was also given to each patient. A nonionic, low-osmolality contrast agent (iopromide) was used.

Only 1 of 41 patients (2.4%) in the acetylcysteine group experienced acute reductions in renal function (defined as an increase in serum creatinine of 0.5 mg/dL or more) compared with 9 of 42 patients (21.4%) in the control group. This was an absolute reduction in the rate of RCIN of 19%. This is a number needed to treat of only 5.3 patients to prevent a case of RCIN. The study concluded that prophylactic administration of acetylcysteine and hydration decreased the incidence of reduced renal function in high-risk patients undergoing procedures that require radiocontrast agents.

Comparable adverse effects were experienced in both groups and included gastrointestinal discomfort and dizziness. This clinical trial showed a benefit to patients receiving both acetylcysteine and hydration compared to hydration alone, which is in contrast to earlier trials with other agents that showed no improved benefits for patients.

Acetylcysteine is an old drug that has gained some renewed interest because of its antioxidant properties. Despite the small numbers of patients in clinical trials performed in patients receiving radiocontrast agents, acetylcysteine is being used in this patient population. The dose of acetylcysteine for RCIN prophylaxis is 3 mL (600 mg) of a 20% solution. The inhalation solution is given orally undiluted. Unfortunately, acetylcysteine has a very bad taste and smells similar to rotten eggs. The cost of this dose of acetylcysteine is minimal. Knowledge about the current evidence to support the use of acetylcysteine in these patients, the correct dose to be used, and any adverse effects is essential when making evidence-based medicine decisions.

by Kalen Porter, PharmD

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Pharmacotrivia, *from page 3*
marketed monoclonal antibodies, except muromonab-CD3. (Muromonab-CD3 or Orthoclone OKT3® was named before the current guidelines were established). Can you guess what these products are used for?

Alem**tu**zumab (CLL), gem**tu**zumab (AML), ri**tu**ximab (non-Hodgkin's Lymphoma), and tras**tu**zumab (breast cancer) are all used to treat miscellaneous **tumors**. Basi**li**ximab and dac**li**zumab are used to prevent the rejection of transplants because of their **immunomodulatory** effects. Inf**li**ximab is used for its immunomodulatory effects in Crohn's disease or in rheumatoid arthritis. Ab**ci**ximab is used in percutaneous coronary interventions to prevent **cardiovascular** complications. Pali**vi**zumab is used in premature neonates to prevent respiratory syncytial **virus** (RSV) infections.

Often we just give up and use the brand name for biologicals. Brand names are shorter and easier to pronounce, but brand names of MAbs will not provide as much information about the agent as the generic name.