

DRUG UPDATE

Volume 24, Number 1

January 2007

FORMULARY UPDATE

The P&T Committee met on November 20, 2006. The following is a summary of the business conducted:

ADDED:

- ◆ Doxercaliferol (Hectorol®)
- ◆ Human Papillomavirus Vaccine (Gardasil®)
- ◆ Zoster Vaccine Live (Zostavax®)

DELETED:

- ◆ Urokinase (Abbokinase®)
- ◆ Halothane (Fluothane®)
- ◆ Paricalcitol (Zemlar®)

CRITERIA FOR USE:

- ◆ Alemtuzumab (Campath®)
- ◆ Cyclosporine (Sandimmune®, Neoral®, Gengraf®)
- ◆ Sirolimus (Rapamune®)
- ◆ Tigecycline (Tygacil®)

Doxercaliferol (Hectorol®) was added to the Shands Jacksonville *Formulary* for the treatment of secondary hyperparathyroidism associated with chronic kidney disease.

Secondary hyperparathyroidism may result in an alteration of the feedback mechanism of parathyroid hormone (PTH) release and can lead to calcium/phosphorus imbalance. Vitamin D analogs are used in pa-

(Continued on page 2)

Medication Use Evaluation

Tigecycline (Tygacil®) should not be used for off-label indications

Tigecycline was added to the Shands Jacksonville *Formulary* and its Criteria for Use were approved by the P&T Committee in August 2006. Tigecycline is a glycylicycline antibiotic, structurally related to the tetracyclines. According to the approved Criteria for Use, tigecycline may be used for 1.) treatment of complicated intra-abdominal and skin and skin structure infections in patients refractory or intolerant to other antibiotics or 2.) treatment of documented *Stenotrophomonas* infections in patients refractory or intolerant to other antibiotics.

Tigecycline is a bacteriostatic drug that has not been studied in other infections (e.g., pneumonia). It covers a wide variety of bacteria including methicillin-resistant *S. aureus*, some gram-negative pathogens (excluding *N. meningitidis* and *P. aeruginosa*), and some anaerobic pathogens [e.g., *B. fragilis*, *clostridium* (but not *C. difficile*)]. The most notable adverse events associated with

tigecycline include nausea (29.5%), vomiting (19.7%), and diarrhea (12.7%).

A recent Medication Use Evaluation (MUE) reviewed 6 patients who received tigecycline from September to October 2006. In 5 of the 6 cases (83%), tigecycline was used in patients with skin and soft tissue infections who were previously treated with other antibiotics. One ventilated patient re-

Tigecycline criteria were revised to discourage its use as empiric treatment for respiratory tract infections.

ceived tigecycline empirically for fever of unknown origin. The patient later had cultures that documented *Pseudomonas aeruginosa* in the blood and lungs. Treatment in this patient was changed to levofloxacin + cefepime to cover this organism. Tigecycline is not recommended for empiric coverage in critically ill patients due to its lack of coverage of *P. aeruginosa*. Additionally, this agent is bacterio-

(Continued on page 4)

IN THIS ISSUE

- ◆ Heparin Prone to Errors

(Formulary Update from page 1)

tients with calcium disarray and elevated PTH and alkaline phosphatase levels despite the use of calcium-containing phosphate binders. Other drugs in this class include paricalcitol (Zemlar[®]) and calcitriol (Calcijex[®], Rocaltrol[®]). Both are listed in the Shands Jacksonville *Formulary*. These agents do not require hydroxylation in the kidney for activation; however, doxercalciferol requires activation by the liver and has a longer half-life. The clinical significance of this characteristic is unknown due to the lack of prospective head-to-head trials. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommends the calcium-phosphorus product (Ca x P) be < 55mg²/dL². When compared to calcitriol and paricalcitol, doxercalciferol is the only product whose labeling carries the same recommendation (i.e., drug discontinuation is recommended for calcitriol and paricalcitol at 75 and 70 mg²/dL², respectively). Other considerations include that 1.) the intravenous dosing of paricalcitol is weight-based, which can be quite cumbersome, and 2.) doxercalciferol oral dosing may be inconvenient secondary to its available capsule strengths. The data for doxercalciferol and paricalcitol regarding mortality rates are similar and both improve survival when compared to calcitriol. When comparing cost, doxercalciferol appears to be less expensive than paricalcitol; however, both are fully reimbursed by Medicare for dialysis patients and

both agents are listed in the Community Care Rx (Medicare Part D) *Formulary*. Calcitriol is the only agent available as a generic, but at therapeutic doses it has been associated with detrimental hypercalcemia and hyperphosphatemia.

Although no head-to-head studies have been performed, paricalcitol and doxercalciferol seem similar in their ability to suppress intact parathyroid hormone. **The oral and IV formulations of doxercalciferol were added to the *Formulary*. Both formulations of paricalcitol were deleted.**

Human Papillomavirus Vaccine (Gardasil[®]) is a recombinant vaccine of the human papilloma virus (HPV) types 6, 11, 16 and 18. This vaccine is indicated for females aged 9-26 for the prevention of the following diseases: genital warts, cervical cancer, and dysplastic or precancerous lesions. Clinical studies have shown the vaccine to greatly reduce the incidence of cervical cancer and precancerous lesions when compared to placebo. The FDA has approved Gardasil for use in females aged 9 to 26; however, the Advisory Committee on Immunization Practices (ACIP), an advisory group to the CDC, recommends routine vaccination for 11-12 year-old girls, and endorses administration in girls as young as 9. They also recommend vaccination in women 13-26 who have not yet received or completed the vaccine series. Gardasil is administered as a series of 3 doses given intramuscularly. Common adverse reactions include injection site reactions and headache. **Gardasil was added to the *Formulary* for use in the Ambulatory Care Clinics.**

Because the vaccine is administered in a 3-dose series, the HPV vaccine should not be administered to patients admitted to the hospital. **(Zostavax[®])** is a vaccine containing live, attenuated varicella-zoster virus that is indicated for the prevention of herpes zoster (i.e., shingles) and post herpetic neuralgia in immunocompetent patients greater than 60 years old. Clinical studies show that when this vaccine was compared to placebo, patients experienced fewer instances of herpes zoster with diminished pain and duration of symptoms, and decreased incidence of post herpetic neuralgia. This vaccine is administered subcutaneously as a one-time dose, and adverse reactions of Zostavax include injection site reactions including mild varicella-like rash. This vaccine is not indicated for the prevention of chickenpox. The varicella live vaccine (Varivax) should be used to vaccinate against this primary infection. **Zostavax was added to the *Formulary* for use in the Ambulatory Care Clinics.**

Urokinase (Abbokinase[®]) is a thrombolytic agent that was restricted to use by Radiology for thrombolysis of acute posterior/basilar artery occlusions. Recently, manufacturing of this product has ended due to the wide availability of alternative agents. Similar *Formulary* medications include alteplase (Activase[®]), reteplase (Retavase[®]), and tenecteplase (TNKase[®]). **Urokinase was deleted from the *Formulary*.**

Halothane (Fluothane[®]) is an inhalational anesthetic agent used

(Continued on page 3)

(Formulary Update from page 2)

for general anesthesia induction and maintenance; however, it is no longer manufactured due to its replacement in most institutions by newer, first-line agents. Alternative agents on the *Formulary* include isoflurane (Forane[®]), desflurane (Suprane[®]) and sevoflurane (Ultane[®]). **Halothane was deleted from the *Formulary*.**

The Criteria for Use for Alemtuzumab (Campath[®]) were revised to delete the statement requiring administration in a monitored environment (e.g., CVICU) with premedications (e.g., acetaminophen, diphenhydramine, and methylprednisolone). Since most patients receive alemtuzumab under anesthesia, this requirement is no longer needed.

The **Criteria for Use for Cyclosporine (Sandimmune[®], Neoral[®], Gengraf[®])** were revised to state that dosage adjustments may be based on cyclosporine plasma, whole blood, or assay concentrations. Also, it was noted that there is a distinction between the different brands of cyclosporine. Cyclosporine, USP (Nonmodified) (Sandimmune[®]) is not bioequivalent to cyclosporine, USP (Modified) (Neoral[®], Gengraf[®]); therefore, these two formulations should not be used interchangeably without physician supervision.

Sirolimus (Rapamune[®]) Criteria for Use were revised to include tacrolimus, mycophenolate, and azathioprine as part of the immunosuppressive regimen for prophylaxis against organ rejection in renal transplant recipients.

Medication Safety

Heparin prone to errors

Medication errors with heparin have received a considerable amount of attention in the press. In November 2006, three premature infants died at a Midwestern hospital when a pharmacy technician loaded the wrong strength of heparin into Pyxis, the automated medication dispensing machine, in the Neonatal Intensive Care Unit (NICU). One milliliter, 10,000 unit/mL heparin vials were placed into the Pyxis instead of the 1 mL, 10 units/mL vials. Additionally, none of the six nurses involved noticed the heparin withdrawn from the machine was 10,000 times the usual concentration. Depending on the vendor used, these two products may look similar.

The Institute for Safe Medication Practices and the Food and Drug Administration recently published recommendations to avoid these errors.^{1,2} These include: minimize look-alike packages and labels, do not stock items on nursing units that require further preparation before administration, and assess medications and strengths that are stocked in cabinets that serve high-risk populations. Both agencies also recommend bar coding for bedside scanning to confirm accuracy of the patient, drug and dose.

Shands Jacksonville Department of Pharmacy has recently reviewed our procedures for heparin use in the pediatric and NICU areas. An assessment of all of our heparin products was done to ensure that the vials do not look similar, and that the different heparin concentrations stocked in these areas were reduced. Additionally, a double-check process is in place where a pharmacist checks all of the medications for loading into the Pyxis before they leave the pharmacy.

Heparin is designated a high risk medication by the Joint Commis-

sion on Accreditation of Healthcare Organizations (JCAHO). Not only can stocking and recognition errors occur with heparin, but errors involving calculation of drip rates, bolus dosing, and errors in appropriate monitoring have been reported.

The Shands Jacksonville Nurse/Pharmacy Council created recommendations to reduce heparin errors.³ Some of these recommendations that involve prescribers include:

- ◆ Heparin drips should be ordered using the preprinted heparin drip protocol form: all three sections (i.e., bolus, initial infusion rate, and therapeutic range/bolus doses) must be completely filled in by the prescriber; otherwise the order must be clarified prior to initiation.
- ◆ Heparin boluses must be given from a separate vial, not from the infusion bag and documented in the MAR.
- ◆ Patients with heparin-induced thrombocytopenia (HIT) must NOT receive any heparin, including flushes. HIT is not a dose-related phenomenon.
- ◆ Heparin is metabolized by the liver; therefore, caution must be used in patients with significant hepatic disease. DVT prophylaxis doses (e.g., 5000 units SC q8h) can result in significant anticoagulation in the presence of end-stage liver disease.

References:

1. Anon. Infant heparin flush overdose. ISMP website. Available: www.ismp.org?Newsletters/acutecare/articles/20060921a.asp?ptr=y. Accessed: 1/20/2007.
2. Anon. Preventing fatal heparin overdoses. FDA Patient Safety News: Show #58 December 2006. FDA website. Available: www.accessdata.fda.gov/psn/transcript.cfm?show=58#7. Accessed: 1/20/2007.
3. Anon. Safe use of heparin. Special Edition Nurse/Pharmacy News. Shands Jacksonville Infonet. Available: intrashands1.umc.ufl.edu/Pharmacy/publications/NPN_Jan_07_vol_4_num_1.pdf. Accessed: 1/20/2007.

DRUG UPDATE

Volume 24, Number 1
January 2007

SHANDS Jacksonville is a major affiliate and teaching hospital of the University of Florida Health Science Center/Jacksonville.

Prepared by the Therapeutic Policy Management Division, Department of Pharmacy and the Pharmacy and Therapeutics Committee, Shands Jacksonville. Drug Information Services 904-244-4185. Copyright 2006. All rights reserved. No portion of the *Drug Update* may be reproduced without the written consent of the editor.

*Pharmacy and Therapeutics
Committee Chair*
Malcolm T. Foster, M.D.

Director, Department of Pharmacy
Thanh Hogan, Pharm.D.

Contributing Editors:
Bernadette Belgado, Pharm.D.
Amy Rockwell, Pharm.D.
Ashley Schields, Pharm.D., BCPS

(Tigecycline from page 1)

static, rather than bactericidal. Clinical evidence is not available regarding tigecycline's efficacy for off label indications such as pneumonia or urinary tract infections.

The overall compliance rate to the established Criteria for Use was 83%. Most cases were appropriately used for treatment of skin/soft tissue infections after a trial of other antibiotics. Few adverse events were reported in these patients. One of the six patients (17%) reviewed required anti-emetics for relief of nausea/vomiting during tigecycline therapy. This patient also received opiates, which may have contributed to their nausea. One patient discharged on tige-

cline via home health care reported abdominal pain in a subsequent clinic visit; however, the patient had multiple medical problems and it was unclear if pain was due to tigecycline therapy or other issues.

As a result of this MUE, the criteria for tigecycline were revised to discourage its use as empiric treatment for respiratory tract infections and other unapproved indications until additional data is available. Tigecycline; however, may be considered if a pathogen with documented sensitivity to tigecycline is confirmed and there are no acceptable alternative agents. The Criteria for Use also includes a cautionary note stating that tigecycline does not cover *P. aeruginosa* infections.

Reference:

Tygacil (tigecycline). Wyeth Pharmaceuticals Inc; Philadelphia (PA): June 2006.

Remember to report
Adverse Drug
Reactions (ADRs):

- ◆ Call the ADR hotline 244-4185
- ◆ Contact your pharmacist