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SHANDS at the University of Florida

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Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met February 17, 2004. 3 drugs or dosage forms were added in the *Formulary* and 3 were deleted. 4 drugs or dosage forms were designated non-formulary and not available. New criteria for use were approved for 1 drug.

◆ ADDED

Butalbital + Acetaminophen + Caffeine (eg, Fioricet®)

Insulin Aspart Protamine + Insulin Aspart (Novolog® Mix 70/30 by Novo Nordisk)

Tolterodine ER (Detrol® LA by Pfizer)

◆ DELETED

Beclomethasone Inhaler (eg, QVAR® by Ivax)*

Butalbital + Aspirin + Caffeine (eg, Fiorinal®)*

Liposomal Daunorubicin (DaunoXome® by Gilead Sciences)

*Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Oxybutynin ER (Ditropan® XL by Alza)

Tolterodine (Detrol® by Pfizer)

◆ CRITERIA FOR USE CHANGES

Bivalirudin (Angiomax® by The Medicines Company)**

**Approved for a 1-yr evaluation of labeled indication

(continued on next page)

ANTI-INFECTIVE NEWS

Anti-infective Stewardship Program initiated at Shands

The Shands at UF Executive Committee approved an Anti-Infective Stewardship Program to improve antibiotic utilization and decrease antimicrobial resistance after an increase in vancomycin-resistant enterococcus (VRE) was noted. This program is now ready to formally begin, and the P&T Committee endorsed the strategic plan for this new service at the February P&T meeting.

The program will use institution-specific microbiological and antimicrobial data, data-collection methods, personnel, and policies and procedures to promote the optimal selection, dosing, and duration for anti-infectives.

The Anti-Infective Stewardship Program will use institution-specific microbiological and antimicrobial data, data-collection methods, personnel, and policies and procedures to promote the optimal selection, dosing, and duration for anti-infectives. The goal is to promote the judicious use of anti-infective agents with a primary objective of preventing (or slowing the development of) anti-microbial resistance.

Decreased antimicrobial resistance should result in shorter lengths of stay (LOS), fewer adverse drug events, decreased morbidity and mortality, and decreased indirect costs. More effective use of anti-infectives may result in decreased expenditures on anti-infectives.

Appropriate anti-infective utilization focuses on spectrum of activity, but also pharmacokinetic considerations for an individual patient. Dosages have to be sufficient to treat or prevent an infection, while minimizing the risk of toxicity. Culture and sensitivity results must be monitored and regimens streamlined to the most specific treatment.

These principles will be used by the staff of the Anti-Infective Stewardship Program to work collaboratively with the Shands at UF medical staff to effect change. The Medical Director of this group is Dr. Denise Schain, who is a faculty member of the Division of Infectious Diseases. She will be supported by 2 clinical pharmacists. Dr. Ken Klinker will be the first pharmacist supporting this program. Dr. Ben Staley will join him this summer.

The Anti-Infective Stewardship Program staff will work with the Anti-Infective Subcommittee of the P&T Committee to develop polices and procedures, evaluate resistance patterns, and serve as experts for information on anti-infective pharmacology and pharmacodynamics. The Anti-Infective Subcommittee consists of physicians, pharmacists, and the hospital epidemiologist and represents a broad range of medical services.

This collaboration will provide the foundation that will help prescribers make appropriate anti-infective choices using population-based information, consensus guidelines, and patient-specific information. The

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INSIDE THIS ISSUE

Formulary update, *from page 1*

Butalbital is an intermediate-acting barbiturate that is used in combination with other drugs for the treatment of tension headaches. Although considered "intermediate-acting," the half-life of butalbital is greater than 60 hours in adult patients, which could lead to accumulation with repeated doses. When used intermittently for an occasional tension headache, this is not a concern; however, continuous use could be problematic. Like all barbiturates, butalbital can be habit-forming.

Bultalbital is commonly combined with **caffeine** and either **acetaminophen** (eg, Fioricet®) or **aspirin** (Fiorinal®) for use in the treatment of tension headaches. These products are commonly used in the ambulatory setting, but have limited application in the inpatient setting where more powerful analgesics or sedatives are available. Therapeutic alternatives to Fioricet® should be considered. However, a generic equivalent to Fioricet® will be listed in the *Formulary* for continuity of care. Fiorinal® will no longer be available.

Fioricet® is commonly prescribed for tension headaches in the ambulatory setting because it is not a controlled substance. Fiorinal®, however, is a Schedule III controlled substance. Because Fiorinal® is a controlled substance and because it contains aspirin, it is rarely used today.

Novolog® Mix 70/30 is a combination of 70% **insulin aspart protamine** and 30% **insulin aspart**. Insulin aspart (Novolog®) is the immediate-acting insulin listed in the *Formulary*. It is administered immediately before a meal and has a short duration of action. The addition of a longer-acting product (ie, insulin aspart protamine) provides a prolonged duration of action.

The *Formulary* has traditionally listed a limited number of combination insulin products. These products are used to simplify diabetes management and allow patients to practice using the insulin on which they will be sent home.

Tolterodine extended-release was added in the *Formulary* for the treatment of patients who are receiving therapy for overactive bladder. This was done after a class review of drugs used for this indication. Patients are often admitted to the hospital receiving these medications. Immediate-release and extended-release tolterodine and extended-release oxybutynin have been frequently requested non-formulary drugs.

Oxybutynin and tolterodine were developed to be selective for the muscarinic receptors in the bladder in order to avoid bothersome systemic antimuscarinic effects associated with less specific antimuscarinic agents. Although superior to older treatments, patients treated with oxybutynin and tolterodine still exhibit classic antimuscarinic adverse effects (ie, dry mouth, dry eyes, headache, dyspepsia, and constipation).

Extended-release dosage forms appear to decrease the incidence of antimuscarinic adverse effects. Tolterodine appears to have a slightly lower incidence of systemic adverse effects; however, this is offset by tolterodine's slightly lower effectiveness compared with oxybutynin.

Published data show that oxybutynin and tolterodine are effective. Extended-release products are at least as effective as the immediate-release products, and have fewer adverse effects. The absolute benefits of these agents compared with placebo are modest. Differences among these agents are slight. Therefore, it was decided to add 1 extended-release dosage form of these agents in the *Formulary*.

Tolterodine ER was selected because it is commonly used in the ambulatory setting. Tolterodine IR and oxybutynin ER were designated nonformulary and not available. Adult Urology and OB-GYN supported these recommendations.

The following recommendations will be used to aid the medical staff in making reasonable conversions for these nonformulary agents. If patients are receiving oxybutynin IR 2.5 mg twice a day or oxybutynin ER 5 mg daily, tolterodine ER 2 mg daily will be recommended. All other patients receiving higher doses of oxybutynin should be converted to tolterodine ER 4 mg daily.

Beclomethasone oral inhaler was deleted from the *Formulary* and designated not available. Several orally inhaled corticosteroids are used chronically for the management of asthma. Fluticasone (Flovent®) has become the predominant agent used in this area. Recently, the Vanceril® brand of beclomethasone oral inhaler was discontinued by its manufacturer. This stimulated an evaluation of whether this agent is still needed in the *Formulary*. An expensive brand of beclomethasone inhaler, QVAR®, can still be purchased.

Beclomethasone oral inhaler was deleted from the *Formulary* and designated not available. Fluticasone oral inhaler is a good alternative.

At doses of fluticasone 110 mcg (ie, 1 inhalation) twice a day, most patients should receive maximum benefits with a low risk of adverse events. Because inhaled fluticasone has a flat dose-response curve, increased doses do not improve therapeutic benefits and may lead to toxicity. Approximately 30% of an inhaled dose of fluticasone is absorbed and large doses have been associated with suppression of the HPA-axis.

Liposomal Daunorubicin was added in the *Formulary* for use in a specific ECOG protocol, which has been closed. Therefore, it has been deleted from the *Formulary*.

Liposomal daunorubicin is a formulation of daunorubicin that was designed in an attempt to maximize the selectivity of daunorubicin for solid tumors in situ. In the circulation, the liposomal daunorubicin helps to protect the entrapped daunorubicin from chemical and enzymatic degradation, minimizes protein binding, and generally decreases uptake by normal (non-reticuloendothelial system) tissues.

The specific mechanism by which liposomal daunorubicin is able to deliver daunorubicin to solid tumors is not known. However, it is believed to be a function of increased permeability of the tumor neovasculature to some particles in the size range of liposomal daunorubicin. Once within the tumor environment, daunorubicin is released over time. Liposomal daunorubicin has a labeled indication for Kaposi's sarcoma in patients with advanced HIV disease.

Bivalirudin is a direct thrombin inhibitor. It has an FDA-labeled indication for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). The approved criteria for use of bivalirudin were modified to include general use in PTCA, but this is limited to an evaluation period. After 1 year, bivalirudin will be re-evaluated by the P&T Committee.

The criteria for the use of bivalirudin were changed at the request of the interventional cardiologists. Their request was based on the results of the *Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2* (ie, the REPLACE-2 trial). The interpretation of this study is controversial, however.

The primary endpoint of REPLACE-2 was a combination of efficacy (death, MI, urgent revascularization) and safety (bleeding). A triple-endpoint using just the efficacy components was a secondary analysis. A drug that is less efficacious, but safer could look better using the quadruple-endpoint. *(continued on next page)*

Formulary update, *from page 2*

The triple-endpoint favored heparin plus a GP IIb/IIIa inhibitor (OR = 1.09 [95% CI 0.90 to 1.32]). Thus, bivalirudin could be no more than 9% worse using the quadruple endpoint, but could be as much as 32% worse using the triple-endpoint. There were also more non-Q-wave MIs in the bivalirudin-treated patients.

Bleeding was lower in the bivalirudin group, but the "drivers" in this finding were vascular access puncture and GI bleeding. The bleeding endpoint included major and minor bleeding. If only major bleeding was used, the bleeding between the groups would have been similar.

Whether bivalirudin should replace heparin plus a GP IIb/IIIa in "lower risk" patients depends on the interpretation of the quadruple endpoint, the definition of bleeding, the dosage range of heparin used, and an economic consideration. Using bivalirudin instead of a GP IIb/IIIa inhibitor should result in significant cost savings.

PATIENT EDUCATION

Preventing nosebleeds from nasal steroids

Winter in Florida is ending. Soon everything will be in bloom and allergens will be beginning their annual onslaught. Seasonal allergic rhinitis is prevalent in this area.

Nasal corticosteroids are first-line treatments for seasonal allergic rhinitis. Nasal steroids are more effective than oral histamine blockers and they are associated with few systemic adverse effects. Nosebleeds (epistaxis) are the most common complaints from patients who use nasal steroids. Patients are usually willing to tolerate this local reaction to avoid systemic adverse effects while achieving superior therapeutic results.

A recent meta-analysis concludes that there is no clear evidence that suggests that one nasal steroid is superior to another. Fluticasone nasal inhalation is the product that has been selected for inpatient use at Shands at UF because it is commonly used by patients in the ambulatory setting. Inpatients should be able to convert to fluticasone during their hospitalization. Regardless of the product used, the incidence of nosebleeds has been reported to range between 17% to 23%.

Recently, a simple technique was reported that may decrease the incidence of nosebleeds associated with nasal steroids. An abstract presented at the American College of Allergy, Asthma, and Immunology Annual Meeting suggests that using the opposite hand when spraying the steroid in the opposite nostril may be beneficial. Spraying the nasal steroid with the right hand in the left nostril (and left hand in the right nostril) directs the drug away from the septum, where most nosebleeds occur.

Although nasal steroids are considered equivalent in terms of efficacy and safety, aqueous solutions may be preferable to products containing chlorofluorocarbons (CFCs). These products may dry the nasal mucosa and predispose the patient to nosebleeds. Also, the CFC-containing nasal inhalers are being phased out because of the potential effects of CFCs on the environment (ie, depletion of ozone in the atmosphere).

Anti-infective news, *from page 1*

Anti-Infective Stewardship Program will be contacting individual prescribers of targeted agents, but this will be complemented with educational programs.

In addition to the increasing incidence of VRE, several observation trends help justify the implementation of this new program. Additional areas of increasing resistance include extended-spectrum beta-lactamase (ESBL) resistance and increased prevalence of methicillin-resistant Staphylococcus aureus (MRSA). The increasing prevalence of Clostridium difficile infections is a direct consequence of antibiotic misuse. Data also show overuse of broad-spectrum antibiotics and increasing antibiotic costs.

Antifungals will also be a focus. Excessive antifungal prophylaxis with fluconazole has resulted in resistant fungal infections—and the increasing use of newer antifungal agents, like caspofungin, to treat resistant fungal organisms.

There are several types of antimicrobial control programs in the United States. Antimicrobial management services (or Anti-Infective Stewardship Programs) extend the use of other control measures (ie, formularies, restrictions, streamlining programs, and IV-to-PO programs) to provide individualized recommendations based upon a review of patient-specific data. Published information from these programs have demonstrated encouraging results in controlling antimicrobial resistance and improving patient outcomes.[1,2] Decreasing antimicrobial resistance takes time. However, persistence and cooperation from the medical staff can be effective.

Carling and colleagues recently published their 7-year experience with a "multidisciplinary antibiotic management program" at a teaching hospital in Boston.[3] This program showed a decrease in nosocomial infections caused by *Clostridium difficile*, a decrease in nosocomial infections caused by resistant Enterobacteriaceae, and a favorable impact on the rate on VRE. These improved outcomes occurred with a 22% decrease in the use of broad-spectrum antibiotics and a 15% increase in patient acuity levels.

By targeting specific drugs, the Shands at UF Stewardship Program hopes to have similar results. Antibiotic drugs and categories that will initially be targeted include: vancomycin, carbapenems, ciprofloxacin, and cefepime. A streamlining program will target all broad-spectrum antimicrobials 72 hours after therapy is initiated. Antifungal prophylaxis in critically ill patients will also be targeted.

Prescribers will be contacted with suggestions to improve prescribing. When inappropriate use of antibiotics is identified and a pharmacist cannot convince the prescriber to change therapy, the Stewardship's Medical Director will discuss the patient with the prescriber. When necessary, the process will be taken up the medical staff chain of command to effect change.

Over the last several months a pilot project to improve imipenem use has shown a decrease in the amount of imipenem used. This project showed that 50% of the imipenem use was consistent with consensus guidelines of the Anti-Infective Subcommittee. Of the 50% that was inappropriate, therapy was successfully changed approximately 60% of the time after a pharmacist contacted the prescribers. This intervention decreased overall inappropriate use from 50% to about 20%. This was done before the Stewardship was formalized, but shows the promise of this approach.

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PAIN MANAGEMENT

Opioid allergies...Why are most alerts wrong?

Patients are frequently labeled as being allergic to opioids (ie, morphine, codeine, and meperidine). Sometimes these labels are wrong because the patient did not experience an "allergy." They experienced an adverse effect that is misclassified as an allergy.

Published data suggests as many as 9 out of 10 patients labeled with an opioid allergy do not have true allergy.[1-4] These patients can be treated with the drug suspected of causing an allergy without a problem.

Patients considered allergic to an opioid present a therapeutic challenge. Pain cannot always be controlled with non-opioid alternatives (eg, NSAIDs).

If a patient is labeled with an allergy to codeine or morphine, prescribers may want to use a synthetic opioid. Synthetic opioids like meperidine or fentanyl have disadvantages. Meperidine is short-acting and is associated with central nervous system adverse effects, like seizures, even in patients with good renal function. Fentanyl is a potent alternative to morphine, but many practitioners are not comfortable using this agent. Fentanyl is also not available as a tablet or capsule.

Most of the time, a substitute for morphine or another opioid is unnecessary. A simple medication history usually reveals the patient simply experienced an adverse effect, not an allergy. Patients who experienced nausea, vomiting, constipation, or somnolence are not "allergic." These adverse drug reactions do not preclude the use of morphine.

Patients who experience pruritus, a rash, or even urticaria may not have experienced an allergic reaction to morphine. Morphine, codeine, and other opioids are potent stimuli for the degranulation of mast cells. This results in the direct release of histamine, and is not an allergy.

Histamine causes the pruritus, rash, and even urticaria. Pre-treatment with an antihistamine can prevent this type of reaction. Rash and pruritus do not preclude the use of an opioid. It is unclear whether urticaria is an allergy or an adverse effect. It could be caused by histamine or be an IgE-mediated allergy. Depending on the availability of other alternatives, morphine is usually avoided in these patients.

True IgE-mediated allergic reactions to morphine are extremely rare. In fact, true allergies are so rare they should be reported in the literature.[5] Skin testing cannot be used because of the direct effect on mast cells;[6] however, morphine-specific IgE antibody determined by radioimmunoassay (RAST) can enable a more accurate diagnosis.

When a patient has an opioid allergy noted in their chart, the odds are they are not truly allergic. By doing a thorough medication history, pain management options can be expanded. If a patient is not allergic, document the rationale for changing the patient's allergy information in the progress notes, and write an order to have the allergy removed from the chart and the hospital information system.

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