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B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 21, 2006. 3 drugs were added in the *Formulary*, and 1 was deleted. 5 drugs were designated nonformulary and not available. There was 1 criteria-for-use change and 1 interchange approved.

◆ ADDED

Desonide Ointment (generic)

Posaconazole
(Noxafil® by Schering Plough)

Tetanus Toxoid Reduced Diphtheria Toxoid Acellular Pertussis Vaccine
(Adacel® by Sanofi Pasteur)*

**Restricted to use by Occupational Health.*

◆ DELETED

Halothane
(Halothane by Hospira)†

†Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Anidulafungin (Eraxis® by Pfizer)

Micafungin
(Mycamine® by Astellas Pharma)

Rosuvastatin
(Crestor® by AstraZeneca)

◆ CRITERIA-FOR-USE CHANGES

Quinine
(Qualaquin® by AR Scientific)‡

‡Restricted to ID Approval for malaria (not leg cramps)

◆ INTERCHANGES

Fluticasone Nasal Spray for Mometasone Nasal Spray
(Nasonex®)§

§Same dose and frequency used. Mometasone is nonformulary and not available.

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THERAPEUTIC INTERCHANGE PROPOSAL

Darbepoetin-epoetin interchange?

Darbepoetin and epoetin are both erythropoietins that stimulate red blood cell formation. Epoetin was marketed in 1989 and was first used for anemia associated with chronic renal failure and cytotoxic chemotherapy. It now has many other labeled and off-labeled uses when red blood cell counts are depressed. Darbepoetin, which was marketed in 2001, is a derivative of epoetin that resulted in a product with a longer half-life. The recommended dosage intervals for darbepoetin are longer than for epoetin. Like epoetin, it was first marketed for anemia associated with chronic renal failure, then for use in patients receiving cytotoxic chemotherapy. It, too, has been used for various off-labeled uses.

Like epoetin, darbepoetin was first marketed for anemia associated with chronic renal failure, then for use in patients receiving cytotoxic chemotherapy.

Both drugs work by the same mechanism to stimulate red blood cell production. At equivalent dosages, the same therapeutic effect is expected. Both drugs can be given at weekly intervals. Although darbepoetin can be given less frequently, which could be an advantage in some practice settings, in the hospital setting where patients have shorter lengths of stay, larger, less frequent dosing may not be cost effective.

A proposal to therapeutically interchange darbepoetin and epoetin is being developed for P&T consideration. The selection of product will be based on the lowest cost. Attending physicians with objections to this possible interchange should submit their concerns in writing to: Secretary, P&T Committee, PO Box 100316. Evidence to support your concerns should be cited or provided in your written submission. Deadline for submissions is January 22, 2007.

DRUG INFORMATION FORUM

Drug Information Service

The Drug Information and Pharmacy Resource Center is available to answer drug-related questions from healthcare professionals from 9:00 am to 5:00 pm, Monday through Friday. This service is available to areas of Shands at UF *not* covered by an outpatient pharmacist, decentralized pharmacist, or clinical pharmacy specialist. Questions can be submitted by calling (352) 265-0408 or by registering and submitting questions via our website at http://www.shands.org/professionals/drugInfo/default.asp.

The Center is staffed by Doctor of Pharmacy Students in the final year of their training. Each answer provided is, however, reviewed and approved by a faculty preceptor. Questions are thoroughly researched and answers fully referenced.

The Center is best used for questions that are not emergent. Since each answer is researched by students and has to be reviewed before an answer is given, there may be a delay that is unacceptable for "stat" requests. Questions that require more thorough research for the available evidence on a topic are ideal to submit.

INSIDE THIS ISSUE

Formulary update, *from page 1*

Desonide ointment is a low-potency topical corticosteroid that was evaluated for formulary inclusion because of frequent nonformulary use. The Dermatology Consult Service often recommends this product.

Desonide ointment is available as a 0.05% concentration, which is equivalent in potency to hydrocortisone 2.5% based on skin blanching studies. Hydrocortisone ointment 2.5% is not listed in the *Formulary.*

There is 1 published study that compares desonide 0.05% and hydrocortisone 1% for atopic dermatitis in children. This study showed more rapid improvement of erythema and induration with desonide based on physician global assessment scales. However, this study did not use equivalent dosages.

Desonide has plain petrolatum as the ointment base, and there are no ingredients associated with sensitivity reactions. It is generic and relatively inexpensive. Since there is no equivalent strength of topical hydrocortisone in the *Formulary*, desonide ointment 0.05% was added.

Posaconazole is a broad-spectrum triazole antifungal agent with activity against common and rare but emerging fungal pathogens, including those belonging to the zygomycete class, which are refractory to most antifungal agents. Posaconazole is the first oral antifungal that displays significant activity against zygomycetes. Posaconazole is fungistatic by inhibiting ergosterol synthesis and fungal cell wall formation.

Posaconazole has labeled indications for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients aged 13 years of age and older who are severely immunocompromised and for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole or fluconazole. Posaconazole has also demonstrated clinical efficacy, mainly as salvage therapy, in the treatment of a wide variety of refractory invasive fungal infections, including invasive candidiasis, invasive aspergillosis, fusariosis, and zygomycosis. Posaconazole has demonstrated improved outcomes (ie, decreased mortality) when used as prophylaxis in at-risk, severely immunocompromised patients.

Although data are limited, as with all new agents, posaconazole has demonstrated few common adverse effects, with the most common being gastrointestinal complaints and headaches. Since posaconazole is an inhibitor of CYP3A4 liver enzymes, it must be used with caution with drugs that either affect or are metabolized through this pathway.

Posaconazole is available only as a 40-mg/mL oral suspension; there is no intravenous product. All doses must be given with food or a nutritional supplement, preferably high in fat, to increase oral absorption.

Posaconazole was added in the *Formulary* and restricted to approval by the Infectious Diseases Consult Service, Dr. Wingard, or the Antimicrobial Management Program. Posaconazole is an alternative to voriconazole or amphotericin B.

Adacel® was reviewed based on the request of the Department of Occupational Health. Adacel® is the first **tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine** marketed for use in adults and adolescents aged 11-64 years of age.

The pertussis antigen composition of the adolescent and adult tetanus toxoid, diphtheria toxoid, and acellular pertussis (Tdap) formulation is similar to pediatric diphtheria toxoid, tetanus toxoids, and acellular pertussis vaccine (DTaP), but the pertussis antigens are reduced in quantity. The Institute for Safe Medication Practices has warned about possible confusion between Tdap (Adacel®) and DTaP (Daptacel®), which is used for active immunization in infants and children 6 weeks to 6 years old. Daptacel® is not listed in the *Formulary.*

In cases where adults were inadvertently given Daptacel® (instead of Adacel®), there were no adverse effects noted. The efficacy of Adacel® in a primary series or to complete the primary series has not been studied.

During clinical trials the most commonly reported adverse reaction to Adacel® was pain at the injection site, which appeared at a slightly higher rate than in those patients vaccinated with tetanus toxoid combined with diphtheria toxoid (Td).

At this time, Adacel® use will be limited to Occupational Health as part of the standard battery of vaccinations administered to employees. Adacel® is currently under a nationwide supply shortage. Our monthly allocation is only 30 doses per month. Therefore, Adacel® will only be used to vaccinate those employees who are at highest risk of pertussis exposure (as determined by Occupational Health).

Halothane is an inhaled anesthetic gas used for general anesthesia. Halothane has been discontinued by its sole US manufacturer; thus, it was deleted from the *Formulary* and designated nonformulary and not available.

Halothane had been available in the US since 1958. Isoflurane and sevoflurane are inhaled anesthetics listed in the *Formulary* that are similar to halothane.

Anidulafungin and **micafungin** were designated nonformulary and not available after a comprehensive review of echinocandins. Caspofungin remains in the *Formulary* and continues to be restricted to approval by the Infectious Diseases Consult Service, Dr. Wingard, or the Antimicrobial Management Program.

The echinocandins are the newest class of antifungals used in the management of invasive fungal infections. Caspofungin was the first of these agents and was approved by FDA in 2001. Micafungin (2005) and anidulafungin (2006) are newer agents. The Anti-infective Subcommittee thoroughly evaluated the efficacy and safety data of each of these agents and recommended which product warranted inclusion in the *Formulary.*

All 3 agents are considered equivalent in regards to managing invasive candidiasis. For invasive *Aspergillus* infections, only caspofungin and micafungin have published clinical data supporting their role as monotherapy or in combination with other antifungal agents. Limited data suggest that micafungin may be considered a plausible alternative to caspofungin when managing invasive *Aspergillus.* A clinical trial evaluating anidulafungin in invasive *Aspergillus* has finished enrolling patients, but preliminary data are unavailable for analysis.

The correct dose of micafungin to use for invasive candidiasis and invasive *Aspergillus* infections has been a difficult issue to address. Several published trials allowed for dose escalation of micafungin leaving some confusion regarding appropriate dosing. A recent study answered the question of the correct dose of micafungin in invasive candidiasis/candidemia. Micafungin 100 mg IV daily was found to be equivalent to caspofungin 70/50 mg IV daily. This study has not, however, been published in a peer-reviewed journal.

Selecting 1 agent in this category of drugs results in significant savings. After reviewing all of the current data, the current decision was to select caspofungin. However, as new data are released, this decision could be revisited.

Rosuvastatin was reviewed for possible inclusion into the *Formulary* because it is the third most prescribed nonformulary drug prescribed at Shands at UF.

Rosuvastatin is a 3-hydroxy,3-methylglutaryl CoA (HMG-CoA) reductase inhibitor. There are currently 5 HMG-CoA reductase inhibitors

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Formulary update, *from page 2*
listed in the *Formulary* (ie, atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). Rosuvastatin is the most-recent FDA-approved HMG-CoA reductase inhibitor, and the first "statin" approved after cerivastatin (Baycol®) was voluntarily withdrawn from the market. Crestor® was approved by FDA in June 2002.

Rosuvastatin has been proven efficacious and has the largest documented percentage reduction of LDL of any of the marketed HMG-CoA reductase inhibitors. The *STELLAR* trial, consisting of 2431 patients, showed that rosuvastatin lowered LDL cholesterol 8.2% more than atorvastatin, 26% more than pravastatin, and 12% to 18% more than simvastatin across all dosages. The efficacy of rosuvastatin is well established, but its safety has been questioned.

No clinical trials have evaluated the comparative risk of adverse effects of HMG-CoA reductase inhibitors as a primary endpoint. A meta-analysis of 18 controlled trials attempted to quantify the comparative risks of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin, but the results of this analysis are difficult to interpret. This analysis did not find a higher risk of adverse effects with rosuvastatin.

Myopathy, rhabdomyolysis, and renal dysfunction (ie, proteinuria) have been associated with rosuvastatin use, especially at higher dosages. These findings have been observed in the spontaneous reporting of adverse events to FDA. Although it is controversial as to whether rosuvastatin has a greater incidence of adverse effects, there is no obvious therapeutic advantage for rosuvastatin in patients requiring LDL reduction. Thus, the concerns about potential toxicity of rosuvastatin led the P&T Committee to designate it nonformulary and not available.

Approximate equivalent dosages of HMG-CoA reductase inhibitors listed in the *Formulary* are listed in the table below. Most patients should be able to be treated with generic simvastatin or simvastatin in combination with ezetimibe.

EQUIVALENT DOSES OF LIPID-LOWERING AGENTS

ROSUVASTATIN	SIMVASTATIN	LOVASTATIN	ATORVASTATIN	SIMVASTATIN + EZETIMIBE
5 mg	40 mg	80 mg	20 mg	--
10 mg	80 mg	--	40 mg	--
20 mg	--	--	80 mg	20 mg + 10 mg
40 mg	--	--	80 mg*	40 mg + 10 mg

*Although not equivalent (based on percentage LDL reduction), this is the closest dosage for an HMG-CoA Reductase inhibitor (alone).

QuiNINE is a naturally occurring alkaloid that has been used for hundreds of years. Since it was on the market before 1938, quinine, until recently, did not have a new drug application (NDA) filed with FDA. This recently changed when a manufacturer filed the necessary papers with FDA, and now there is only 1 FDA approved prescription quinine product (ie, Qualaquin®).

Qualaquin®'s FDA labeled indication is for the treatment of uncomplicated *Plasmodium falciparum* malaria in regions where resistance to chloroquine has been documented. The labeling explicitly states that it is not approved for the treatment of nocturnal leg cramps. Further, the *Warnings* section of the labeling states the following: "Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Fatalities have also been reported. The risk associated with the use of quinine sulfate in the absence of evidence of its effectiveness for treatment or prevention of nocturnal leg cramps, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition."

In 1995, nonprescription quinine was removed from the market because of questionable efficacy and the potential for rare, but serious, adverse events. However, quinine continued to be used off-label as a prescription drug for leg cramps using a 325-mg dose because there are limited options for this indication. The old 260-mg nonprescription dosage of quinine continued to be prescribed, although no 260-mg dosage form was available.

Based on the current evidence, the P&T Committee restricted quinine's use to the treatment of malaria, which requires approval of Infectious Diseases. The use of quinine for the treatment of nocturnal leg cramps will no longer be permitted.

Fluticasone nasal spray will now automatically be interchanged for orders for **mometasone nasal spray.** Both are commonly used nasal corticosteroids used for the treatment of rhinitis, but fluticasone is now available as a generic.

Nasal corticosteroids are generally considered equivalent when given at an equivalent dosage. The dose and dosage interval for fluticasone and mometasone nasal sprays are the same, thus the same dose and interval will be used for fluticasone.

MEDICATION SAFETY

Promethazine: resolve to dilute

Phenergan® (promethazine), first approved by the Food and Drug Administration in 1951, is commonly prescribed for its antiemetic, antimotion sickness, sedative, and antihistamine properties. Even after 55 years of use, it is important to emphasize that great care should be taken in the administration of intravenous (IV) promethazine. In August, the Institute for Safe Medication Practices (ISMP) published a statement concerning the safe use of IV promethazine to avoid severe tissue damage.[1]

In a previously published case report, a woman was admitted for flu-like symptoms and during the course of her stay, she was prescribed IV promethazine.[1] As the promethazine was being injected, the patient cried out in pain. Her fingers and arm turned "purple and blotchy." The IV promethazine was not diluted prior to injection and extravasation into the local tissue occurred. Because of this incident, the woman had to have her thumb, index finger, and the top of her middle finger amputated.

Intravenous preparations of promethazine have a pH between 4 and 5.5. At this pH range, the surrounding tissue can become severely damaged if extravasation from the IV site occurs during administration. The consequences of this damage can range from pain and burning upon administration to local tissue necrosis necessitating amputation. Because the outcomes can be so harmful, education about the proper use of IV promethazine and safeguards to prevent adverse effects are invaluable.

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Medication safety, *from page 3*

So, what is Shands doing to decrease the likelihood that a similar occurrence will happen here? Education about the risks associated with IV promethazine use is the first step. With increased awareness should come increased caution.

Decreased morbidity associated with administering IV promethazine may be achieved by infusing at a slower rate, increasing monitoring of the patient after administration to assess for adverse events, and proper reporting of those events.[1] Reporting such adverse effects allows a more accurate determination of their prevalence so that better methods for minimizing risks can be developed and instituted.

Shands at UF has also implemented steps to help reduce risks. When promethazine is obtained from a SureMed® cabinet, a cautionary alert prompts the user to dilute the vial into a volume of 10 mL of normal saline before administration. Studies have shown promethazine to be compatible with and stable in normal saline. Also, the 50-mg/mL vial of promethazine will not be stocked anywhere in the hospital so a 25-mg/mL vial has to be used.

Additional measures of protection that are recommended by the ISMP are to use large, patent veins during administration to minimize contact with the surrounding tissue. Also, consider administering promethazine over a 10-15 minute interval rather than as a slow, IV push.

Another suggested option is to remove IV promethazine from the *Formulary*. This is not an action that the P&T Committee is considering at this time since there is widespread and established uses for IV promethazine in our patient populations, and steps are being implemented proactively to decrease the risks associated with its use.

There are instances where a smaller dose can be just as efficacious as a larger dose.[2] This supports administering 6.25 mg or 12.5 mg instead of 25 mg or 50 mg. By reducing the amount given, the exposure can also be decreased along with the risks for severe tissue damage.

So how should extravasation be addressed if it occurs? Currently, there are no treatments that have been proven to be successful. Ganglionic blockade using 10 mL of 0.75% lidocaine hydrochloride and 0.125% bupivicaine hydrochloride has been used in a previous case report and appeared to aid in pain control and help facilitate range of motion.[3] Heparinization has also been used to help manage extravasation as part of the acute management scenario.[4]

By discussing the risks associated with using IV promethazine and by taking proactive measures to mitigate those risks, our patients can have more favorable outcomes. Recently, a family member of mine was admitted to a hospital in another state. She also was admitted for flu-like symptoms. Promethazine was prescribed and was injected intravenously without first being diluted. She experienced severe pain and phlebitis secondary to promethazine, which emphasized to me the importance of system changes and education about this topic.

Extravasation of promethazine can cause tissue necrosis leading to amputation. By recognizing this potential hazard, measures can be put into place to minimize the chances that extravasations will occur.

By Michael Dunham, PharmD

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