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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 20, 2007. 2 drugs were added in the *Formulary*, and 4 drugs or dosage forms were deleted. 5 drugs or dosage forms were designated nonformulary and not available. Criteria for use were changed for 3 drugs.

◆ ADDED

Ambrisentan (Letairis® by Gilead Sciences)*

**Restricted to patients approved for the Letairis Education and Access Program*

Anidulafungin (Eraxis® by Pfizer)†

†Restricted to approval by the ID Consult Service, Dr. Wingard, or the Antimicrobial Management Program

◆ DELETED

Aprotinin (Trasylol® by Bayer)‡

Caspofungin (Cancidas® by Merck)‡

Itraconazole, Intravenous (Sporanox® by Ortho Biotech)‡

Ranitidine Effervescent Tablets (Zantac® Efferdose by Glaxo-SmithKline)‡

‡Nonformulary and Not Available

◆ NONFORMULARY AND NOT AVAILABLE

Ramelteon (Rozerem® by Takeda Pharmaceuticals)

◆ CRITERIA-FOR-USE CHANGES

Altretamine (Hexalen® by MGI Pharma)§

§Requires a Chemotherapy Order Form; Nonformulary.

Ceftriaxone (Rocephin® & generics)**

***Resticted:Cannot be used in infants 28 days old or less*

Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra® by Sanofi Pasteur)††

††Can be used in patients from 2–55 years of age

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PRESCRIBING

Discontinue stress, discontinue stress ulcer prophylaxis

Stress ulcers are superficial lesions involving the mucosal layer of the stomach that appear after major stressful events.[1] Critically ill patients admitted to intensive care units (ICUs) are at an increased risk for suffering from complications related to stress ulceration.[2] As such, stress ulcer prophylaxis (SUP) is appropriate for many critically ill patients.

SUP is defined as any medication used to prevent formation of stress ulcers and includes antacids, sucralfate, prostaglandin analogues, histamine H_2-receptor antagonists, and proton-pump inhibitors (PPIs). Although these therapies are considered effective, there are disadvantages associated with their use. A higher gastric pH is associated with gastric microbial growth, tracheobronchial colonization, and nosocomial pneumonia.[3] Unnecessary use of acid suppression therapy has been associated with the development of community-acquired pneumonia, as well as community-acquired *Clostridium difficile* infections.[4,5] Both studies were conducted in outpatients and found an association between the use of acid suppression therapy and infection.[4,5] In addition, long-term PPI use, particularly at high-doses, has been associated with an increased risk of hip fracture (ie, osteoporosis).[5] SUP also increases the number of medications a patient receives, as well as the cost of their treatment.[3]

Several risk factors have been identified for the development of stress ulcers, including respiratory failure, coagulopathy, hypotension, sepsis, hepatic failure, renal failure, surgery, burns, and major trauma.[2] A prospective, multi-center cohort study conducted by Cook and colleagues identified 2 independent risk factors for bleeding. The strongest risk factors are mechanical ventilation for more than 48 hours and coagulopathy, defined as a platelet count less than 50,000 mm^3, an International Normalized Ratio (INR) of greater than 1.5, or a partial thromboplastin time of greater than 2 times the control value.[2]

When risk factors no longer exist, SUP should be discontinued in patients without an additional indication for use (eg, gastrointestinal reflux disease [GERD] or history of GI bleed). When a patient transfers or is discharged from an ICU, there is an opportunity to discontinue SUP.

An audit of SUP use in the ICUs at Shands at UF was recently conducted. Thirty adult patients receiving SUP were followed during their hospital admission, beginning upon admission to the surgical intensive care unit (SICU). When mechanical ventilation and coagulopathy were no longer present, SUP was no longer considered necessary. Other reasons to continue SUP included acid suppression therapy prior to admission, or a past medical history of GERD or a GI bleed. Upon transfer from the SICU, 73% of patients were continued inappropriately, 16% continued appropriately, and only 11% discontinued appropriately. A similar evaluation was conducted for 30 patients in the medical intensive care unit (MICU). Upon transfer from the MICU, 36% were continued inappropriately and 64% continued appropriately. SUP was discontinued appropriately in none of the patients. The evaluation also indicated that some patients (ie, 15% from the SICU and 5% from the MICU) were discharged from the hospital on acid suppression therapy with no indication for continued use.

The results of this audit show that some critically ill patients are unnecessarily continued on SUP upon discharge from the ICUs. SUP should be discontinued upon elimination of risk factors. Appropriate use of SUP may translate to a reduction in adverse events and healthcare expenditures.

By Sarah Bush, PharmD

(References listed on page 4)

INSIDE THIS ISSUE

Formulary update, *from page 1*

Ambrisentan was approved by the FDA in June 2007 with a labeled indication for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. It is an alternative to bosentan (Tracleer®), which is listed in the *Formulary* but restricted to patients who have been approved for bosentan's restricted drug distribution program.

Due to the risk of hepatic injury and birth defects, ambrisentan also is only distributed through a restricted drug distribution program (ie, the Letairis Education and Access Program [LEAP]). Prescribers and pharmacists must call 866-663-LEAP (5327) to enroll patients. In order to stock ambrisentan, hospitals must sign an agreement that it will be dispensed only to patients who are already enrolled in the restricted drug distribution program (ie, LEAP).

Compared with bosentan, ambrisentan costs roughly the same (ie, approximately $50,000 per year). Bosentan is given twice a day, while ambrisentan is given once a day.

There is limited information published on the efficacy of ambrisentan; but there is a theoretical pharmacologic advantage for ambrisentan; it is more specific for blocking endothelin A, which is responsible for vasoconstriction and tissue damage in the pulmonary vasculature.

Both bosentan and ambrisentan are pregnancy risk category X because of their teratogenic potential. Both also are associated with liver dysfunction; however, noncomparative incidence data suggest that the rate of hepatotoxicity may be lower with ambrisentan. Also, a small case series, which has been reported as an abstract, suggests that patients intolerant to bosentan (ie, elevated LFTs) may tolerate ambrisentan. These limited benefits for ambrisentan are balanced by the fact that there is considerably more efficacy data on bosentan, and, because bosentan has been used more extensively, there is a greater understanding of its safety profile.

The current American College of Chest Physician guidelines do not specify when or if ambrisentan would be preferred over bosentan. However, the limited data available suggest that ambrisentan may be an alternative in patients who do not tolerate bosentan. Bosentan is currently recommended in patients with early functional class III PAH, especially in patients who are not good candidates for sildenafil (eg, patients with ocular disease or recurrent epistaxis).

Anidulafungin was added in the *Formulary* as the sole representative of the echinocandin antifungal agents. **Caspofungin** was deleted from the *Formulary* and designated nonformulary and not available. Micafungin (Mycamine®) remains nonformulary and not available.

The echinocandins were originally reviewed in November 2006. At that time, caspofungin, micafungin, and anidulafungin were deemed equivalent. Caspofungin was selected as the formulary agent, and micafungin and anidulafungin were designated nonformulary and not available.

The echinocandins were re-evaluated because increased competition among these products has resulted in cost reductions. Little new evidence has been published in the last year. There is a study showing equivalency of micafungin at doses of 100 mg and 150 mg once daily with standard doses of caspofungin for the management of candidemia and invasive candidiasis. In addition, results from a study comparing anidulafungin to fluconazole in the management of invasive candidiasis were published, and anidulafungin was found to be noninferior to fluconazole.

Anidulafungin was selected for the *Formulary* because it results in the most potential cost savings.

Aprotinin is a proteolytic enzyme from bovine lung that has a labeled indication for the prevention of blood loss and transfusion in patients undergoing surgery requiring cardiopulmonary bypass. It was deleted from the *Formulary* and designated nonformulary and not available after marketing was suspended based on recent safety concerns.

The FDA recently released safety information from the study, ***B****lood Conservation Using* ***A****ntifibrinolytics: a* ***R****andomized* ***T****rial in a Cardiac Surgery Population* or BART. This study was done to determine if aprotinin is superior to aminocaproic acid and tranexamic acid in terms of decreasing massive postoperative bleeding, minimizing exposure to blood products, and decreasing both fatal/life-threatening or serious post-operative complications. It was a 25-center study in Canada. If aprotinin was found to decrease allogenic exposure and decrease clinical complications, then its use would be endorsed. If aprotinin only decreased exposure to allogenic blood products, then an economic evaluation was planned. If the therapies were found to be equally effective, the researchers felt that the preferential use of aminocaproic acid would be justified.

The data safety monitoring board for the BART suspended the study when the 30-day mortality in the aprotinin group nearly reached a statistically significant higher rate compared with either of the other treatment arms. This trend of higher mortality with aprotinin was observed throughout the study. Although less blood was used in the aprotinin arm compared with either of the other treatments, more deaths due to hemorrhage were observed in the aprotinin arm. The data safety monitoring board concluded that continued enrollment of patients was unlikely to change these findings.

The FDA is currently evaluating these results and determining what additional actions are needed (eg, further modification of the product labeling or permanently pulling the drug from the market). These data from a randomized controlled trial are consistent with an observational study published approximately a year ago that also found a higher rate of mortality with aprotinin. The Director of the Office of New Drugs was quoted as saying, "FDA cannot identify a specific patient population where we believe the benefits of using Trasylol® [aprotinin] outweigh the risks."

The FDA's decision not to recall aprotinin was intended to prevent a shortage of alternatives (ie, aminocaproic acid and tranexamic acid). Shands at UF has been able to get an ample supply of aminocaproic acid and tranexamic acid to be used as an alternative. Based on the new warnings and the availability of alternatives agents, the P&T Committee determined that the continued use of aprotinin is not warranted at this time.

Itraconazole IV is an intravenous triazole antifungal agent that has been used for the treatment of susceptible fungal infections. Ortho Biotech is discontinuing the sale and distribution of Sporanox® injection, but itraconazole capsules and oral solution will continue to be available. Currently there are other antifungal options for the treatment of these infections. Itraconazole was deleted from the *Formulary* and designated nonformulary and not available.

Ranitidine effervescent tablets were deleted from the *Formulary* and designated nonformulary and not available. GlaxoSmithKline no longer makes these effervescent tablets, which were rarely used.

The only alternative to ranitidine effervescent tablets is ranitidine syrup 15 mg/mL, which uses sorbitol as a vehicle and sweetener. In larger doses, the amount of sorbitol in ranitidine syrup has been associated with an increased incidence of diarrhea. The sweet taste of this syrup has not

(continued on next page)

Formulary update, *from page 2*

been tolerated by some adult patients.

Ramelteon is a unique hypnotic that does not work at GABA receptors; it is not a controlled substance because it has limited abuse potential. It is the first in a new class of agents known as melatonin receptor agonists. Ramelteon selectively targets the MT_1 and MT_2 melatonin receptors, which are believed to be involved in the promotion of sleep and the maintenance of the normal circadian rhythm. Ramelteon has a 3- to 16-times higher affinity for the receptors than melatonin.

Ramelteon is rapidly absorbed, but has poor bioavailability (1.8%) due to high hepatic first-pass metabolism. The half-life is short and ranges from 1-2.6 hrs. Metabolism is primarily oxidation via CYP1A2 isoenzymes. Serum concentrations of ramelteon and the major active metabolite are essentially undetectable at 24 hours.

Rozerem® only has an FDA-labeled indication for the treatment of insomnia characterized by difficulty with sleep onset. The recommended dosage is 8 mg taken within 30 minutes of going to bed. Dosage adjustments are not needed in patients with renal impairment and caution is advised in patients with hepatic impairment.

Published clinical trials have shown a small (ie, approximately 10-15 minutes) but statistically significant decrease in sleep latency when compared to placebo. Effects on total sleep time and sleep efficiency are even less pronounced and are not consistently observed in all trials. Currently there are no clinical trials comparing ramelteon with other hypnotic agents.

During clinical trials, 6% of patients exposed to ramelteon discontinued treatment, with the most common adverse effects being headache, dizziness, and fatigue. In addition, long-term use has been associated with increased prolactin levels in women. Drug interactions are a concern with ramelteon, especially for strong inhibitors of CYP1A2. Co-administration with fluvoxamine results in a 190-fold increase in AUC and 70-fold increase in Cmax of ramelteon. The clinical significance of increased levels has not been determined.

Although ramelteon may appear to have several advantages over other hypnotic agents, data from clinical trials show that it has minimal efficacy. Since ramelteon is not a controlled substance, patients will be allowed to use their own supply from home; however, it will not be obtained for nonformulary use.

Altretamine, also known as hexamethylmelamine, is a synthetic antineoplastic agent effective in the treatment of some ovarian tumors resistant to alkylating agents. Its mechanism of action is not related to any other available antineoplastic. This capsule is not listed in the *Formulary*.

Altretamine must be metabolized to be active. Altretamine is associated with dose-related myelosuppression (ie, leukopenia and thrombocytopenia), which occurs 3-4 weeks after beginning altretamine therapy.

Since altretamine is a cytotoxic chemotherapy agent associated with dose-dependent myelosuppression, it was added in the list of medications that must be ordered via a Chemotherapy Order Form.

Ceftriaxone is an injectable third-generation cephalosporin with activity against gram-positive and gram-negative bacteria. Its penetration into the central nervous system has made it a valuable agent in the treatment of meningitis. Its long half-life has allowed for once-daily dosing.

The criteria for ceftriaxone use were reviewed based on recent changes to the product's labeling. These changes include a contraindication for the co-administration of ceftriaxone and calcium-containing intravenous solutions, including parenteral nutrient preparations, in neonates age 28 days or younger. Ceftriaxone was already contraindicated in hyperbilirubinemic newborn infants.

Cefotaxime is an alternative third generation cephalosporin that was added in the *Formulary* specifically for use in neonates (ie, because of the biliary sludging associated with ceftriaxone use).

New warnings were added in the labeling stating that ceftriaxone should not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines and that calcium-containing solutions or products must not be administered within 48 hours of the last administration of ceftriaxone. These warning are based on 5 neonatal deaths reported between 1992 and 2002 by post-marketing surveillance where there was an association between ceftriaxone and calcium-containing products and crystalline material found in the kidney and lungs upon autopsy.

The P&T Committee found no conclusive evidence to support a significant safety risk of ceftriaxone in non-neonate patients. Ceftriaxone use in children 28 days old or younger will be prohibited based on the contraindication language in the labeling.

Menactra® is 1 of 2 meningococcal vaccines currently listed in the *Formulary*. It was initially reviewed and added in the *Formulary* in January 2007. It is the first and only quadrivalent conjugate vaccine licensed in the US for the prevention of meningococcal disease and offers protection against 4 of the 5 most common serogroups that cause meningococcal infection.

At the time of its initial review, Menactra® only had a labeled indication for patients aged 11–55 years of age. However, the manufacturer has recently been granted approval to expand the indication to include patients 2–10 years of age based on recent studies. These studies demonstrated that seroconversion rates were similar between Menactra® and Menomune®. Therefore, both Menactra® and Menomune® are available for patients 2–10 years of age. Menactra® will still be available to those patients aged 11–55 and Menomune® for those patients older than 55 years that are identified as candidates for meningococcal vaccination.

To Report an Adverse Drug Reaction

Call the ADR Hotline: 5-ADRS (5-2377)

PROVIDE:

- Patient's name
- Patient's location
- Suspected drug(s)
- Type of reaction
- Whether the reaction was — probable, possible, or definite
- Your name and pager # or extension

And we'll do the rest!

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☎ ADR HOTLINE: 5-ADRS

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NEWS

P&T Committee Actions 2007

Another year of Pharmacy and Therapeutics (P&T) Committee activity was just completed. During this time, the Committee met 10 times. The goals of the Committee are to use evidence-based medicine principles to establish drug use policies and to establish a formulary. In addition, medication safety is promoted.

The P&T Committee is a medical staff committee that is the formal line of communications between the medical staff and Shands at UF as it relates to all drug-related matters. Currently, 16 medical staff members help decide which drugs are readily available for use, what limitations should be put on those drugs that are available, and what can be done to improve medication safety. Members of the P&T Committee are appointed by the Chief of Staff.

The *Formulary* is a list of drugs that are readily available for use. Drugs listed in the *Formulary* can be found on the Shands intranet at http://tinyurl.com/yw28td. This database of drugs listed in the *Formulary* requires a portal username and password, if you are not already logged into the portal.

Last year, 21 new products were added in the *Formulary*. Only 7 new drugs were requested; the rest of the additions were proactive actions taken by the P&T Committee. 31 drugs were deleted from the *Formulary*.

34 drugs were reviewed by the P&T Committee and designated nonformulary and not available. These medications cannot be obtained through a nonformulary request. 16 of the products designated "not available" were removed from the market.

Several drug use policies were approved. For example, a policy was approved that prohibits a drug manufacturer's sales representative from promoting the off-label use of drugs at Shands at UF. Also, policies were passed to continue to standardize IV concentrations and establish ready-to-use doses (eg, for electrolytes like calcium, magnesium, phosphate, and potassium) and to discontinue orders for drugs with automatic stop orders or unapproved restricted drugs. Therapeutic interchange changes, IV-to-oral conversions, physician approved protocols, and restriction changes were also approved.

The *Drugs & Therapy Bulletin* (now beginning its 22nd year of publication) remains the primary method for communicating P&T Committee actions. Please take the time to read the changes that occur each month. Back issues of the *Bulletin* are available on the Internet at http://www.shands.org/professionals/drugInfo/bulletin.asp.

If you have questions or comments about the activities of the P&T Committee, please contact us. Dr. Ricardo Gonzalez-Rothi chairs the P&T Committee. This is his 8th year leading this medical staff committee. Dr. Gonzalez-Rothi can be reached by e-mail at ricardo.gonzalez-rothi@medicine.ufl.edu. Correspondence regarding P&T procedures can be sent by regular mail to Secretary, P&T Committee, PO Box 100316, or by e-mail to hatton@ufl.edu.

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