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SHANDS at the University of Florida

July/August 2002

Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 18, 2002. 4 drugs or dosage forms were added in the *Formulary* and 6 drugs or dosage forms were deleted. In total, 8 drugs were designated not available.

◆ ADDED

Aspirin + Dipyridamole ER (Aggrenox® by Boehringer Ingelheim)

Corticorelin Ovine Triflutate (Acthrel® by Ferring Pharmaceuticals)

Fluticasone Nasal Inhalation (Flonase® by GlaxoSmithKline)

Sodium Phosphate Oral Liquid (eg, Fleet® Phospho Soda)

◆ DELETED

Beclomethasone Nasal Inhaler (Vancenase® or Beconase®)

Bretylium (generic)*

Corticotropin (Acthar® by Rorer)

Danaparoid (Orgaran® by Organon)

Flunisolide Nasal Inhaler (Nasalide® by Dura)

Potassium Phosphate (Neutraphos® by Ortho McNeil)*

***Nonformulary and not available**

◆ NONFORMULARY, NOT AVAILABLE

Amoxicillin + Clavulanate (Augmentin® ES by GlaxoSmithKline)

continued on next page

PAIN MANAGEMENT

Shaking up meperidine use: Alternatives for post-operative shaking

Meperidine use is discouraged. Oral meperidine and meperidine PCA are not available at Shands at UF. The only appropriate uses of meperidine are for the treatment of drug-induced rigors and for sedation and analgesia in short procedures.

Meperidine is associated with central nervous system toxicities. Despite these adverse effects, meperidine is used for post-anesthetic shivering. This has justified the continued stocking of meperidine in some hospitals. There are other options.

Post-anesthetic shivering is a complication of general anesthesia. Mechanisms are categorized as thermoregulatory or nonthermoregulatory. Thermoregulatory shivering, which is associated with cutaneous vasoconstriction, is a physiological response to peri-operative hypothermia.

Although there are no reports implicating post-anesthetic shivering with major surgical difficulties, it is hypothesized that shivering increases oxygen consumption. This could cause complications in some patients. Shivering is associated with an increased metabolic rate, lactic acidosis, and increased intraocular pressure.

Limiting blood redistribution can prevent thermoregulatory shivering. Nonpharmacological prevention includes pre-operative skin surface or intravenous solution re-warming, raising the operating room temperature, and adequate coverage with surgical drapes.

Nonthermoregulatory shivering is not well described; however, there is a link between its incidence and post-operative pain. Other proposed mechanisms include uninhibited spinal reflexes, decreased sympathetic activity, pyrogen release, adrenal suppression, and respiratory alkalosis. The anti-shivering mechanism of meperidine may be related to actions on kappa opioid receptors.

The pharmacological prevention and treatment of post-anesthetic shivering has been studied in a number of trials. Although meperidine is the most extensively studied, clonidine, other opioids, magnesium, nalbuphine, and tramadol have been researched. The optimal drug, dose, and administration time have not been identified. As a result, the use of pharmacological agents for prevention is not recommended.

There are a number of studies that report superior efficacy of meperidine 25 mg compared to placebo. Meperidine has a faster onset and was more effective when compared to other opioids. Adverse effects may diminish the importance of these findings.

The use of meperidine has been linked to common complications of surgery including nausea and vomiting, sedation, and pruritus. Thus, the use of other drugs with similar efficacy and favorable adverse effect profiles would benefit patients experiencing these complications.

Clonidine, an alpha-2 agonist, has been extensively studied for the treatment of post-anesthetic shivering. Clinical trials report superior efficacy compared with placebo. Furthermore, clonidine given at the onset of shivering provides similar efficacy to

continued on page 3

◆ INSIDE THIS ISSUE

◆ **NONFORMULARY, NOT AVAILABLE**, *continued from front*

Esomeprazole (Nexium® by AstraZeneca)

Famciclovir (Famvir® by GlaxoSmithKline)

Ganciclovir Implant (Vitrasert® by Bausch & Lomb)

Isometheptene + Dichloralphenazone + Acetaminophen (eg, Midrin® by Carnrick)

Potassium phosphate (Neutraphos® K by Ortho McNeil)

Aggrenox® is an antiplatelet agent containing both extended-release dipyridamole and immediate-release aspirin. Aggrenox® is indicated for the secondary prevention of strokes. The labeled dosage of Aggrenox® is 1 capsule twice a day.

The combination of aspirin 50 mg/day and dipyridamole 400 mg/day was shown to be "superior" to aspirin alone in secondary stroke prevention. Immediate-release aspirin and dipyridamole products have been prescribed in an attempt to mimic this regimen using an 81-mg dose of aspirin daily and a 100-mg dose of dipyridamole 4 times daily.

In the outpatient setting, the frequent dosing of dipyridamole may result in poor patient compliance, potentially reducing the overall benefit of the combination. This does not necessarily apply to the inpatient setting. The addition of this agent in the *Formulary*, however, decreases workload (ie, less frequent dosing, no need to use patient's own meds, decrease workload associated with processing nonformulary orders).

In the inpatient setting, Aggrenox® is 8-times more expensive than aspirin plus dipyridamole and 170-times more expensive than aspirin alone. However, the labor costs associated with the nonformulary process were considered.

Whether to use aspirin or Aggrenox® for secondary stroke prevention is controversial. The absolute reduction in rates of strokes using Aggrenox® compared with aspirin is small and is an area of considerable debate. The potential for improved compliance with twice-daily dosing of Aggrenox® must be weighed against its significantly greater cost.

The American College of Chest Physicians' *Guidelines for the Secondary Prevention of Stroke* states that aspirin, clopidogrel, and Aggrenox® are all acceptable options for initial therapy. In general, however, aspirin alone is first-line therapy.

Aggrenox® was listed in the *Formulary* so those patients admitted on this drug can continue to receive their outpatient therapy during their hospitalization.

Corticorelin ovine triflutate is a diagnostic agent that is used for the differential diagnosis of Cushing's syndrome. It is indicated for differentiating pituitary and ectopic production of adrenocorticotropin hormone (ACTH) in patients with ACTH-dependent Cushing's syndrome.

Corticotropin (Acthar®) is no longer manufactured. The only intravenous products available for diagnostic purposes are corticorelin ovine triflutate and cosyntropin (Cortrosyn®). Therefore, corticorelin ovine triflutate was added in the *Formulary*. The 40-unit/mL strength of corticotropin gel is also no longer marketed and has been deleted from the *Formulary*. The 80-unit/mL vial of corticotropin gel is still marketed. It is used to treat infantile spasms and remains in the *Formulary*.

Fluticasone nasal inhalation was added in the *Formulary*. **Beclomethasone** and **flunisolide nasal inhalers** were deleted. Patients are often admitted to the hospital on nasal corticosteroids that they take intermittently or chronically for seasonal or perennial rhinitis. This contributes to nonformulary drug use. Fluticasone is used commonly in the ambulatory setting.

Nonformulary nasal steroids will be obtained when ordered; however, they are considered low priority. Prescribers will be encouraged to use fluticasone during the patient's admission. For more information on this topic, see *Nasal Steroids in the Hospital* in this issue of the *Bulletin*.

Sodium phosphate oral liquid was added in the *Formulary* when **Neutraphos®** and **Neutraphos® K** were deleted and designated non-formulary and not available. K-Phos Neutral® is now the only oral solid phosphate supplement in the *Formulary*. K-Phos Neutral® is a tablet and Neutraphos® K and Neutraphos® are available as capsules or as packets. The packets are given as a liquid. Sodium phosphate oral liquid was added in the *Formulary* to replace Neutraphos® and Neutraphos® K packets.

The Institute for Safe Medication Practices has warned healthcare professionals of the potential for confusion between K-Phos Neutral® and Neutra Phos® K. Neutraphos K® contains 14.25 mEq of potassium per 8 mmoles of phosphorus, while K- Phos Neutral® only has 1.1 mEq of potassium per 8 mmoles of phosphorus. Confusing these agents could result in a patient receiving excess potassium.

Sodium phosphate oral liquid (eg, Fleet® Phospho Soda) contains 4.1 mmoles/mL of phosphate and 4.8 mmoles/mL of sodium. The high sodium content (ie, 492 mEq in 120 mL) of sodium phosphate oral liquid must be considered, especially if it is used as a bowel prep. Polyethylene glycol-electrolyte solution (eg, Colyte®) is the current bowel prep listed in the *Formulary*. It contains 125 mEq/L of sodium.

Bretylium is a Class III antiarrhythmic agent similar to amiodarone and sotalol. Class III antiarrhythmic drugs are not considered interchangeable, however, because each drug modifies conduction in a unique way.

Bretylium has been used for the treatment of ventricular fibrillation and unstable ventricular tachycardia, although it is not considered a first-line agent. The American Heart Association 2000 guidelines removed bretylium from all Advance Cardiac Life Support algorithms due to its high incidence of adverse effects, availability of safer and effective antiarrhythmic treatment alternatives, and periods of limited supply and availability of bretylium.

The use of bretylium fell out of favor at Shands at UF when a shortage made it unavailable for a prolonged period. During this time, bretylium was pulled from all crash carts and replaced with amiodarone. The Code Blue Committee and the Division of Cardiology support the deletion of bretylium.

Danaparoid was a heparinoid. It was a mixture of low-molecular weight sulfated glycosaminoglycans: heparan (not heparin) sulfate, dermatan sulfate, and chondroitin sulfate. Danaparoid was used as an anticoagulant with a labeled indication for the prophylaxis of DVT after hip replacement surgery.

Because it was expensive and offered no advantage over other drugs that can be used for DVT prophylaxis, the use of danaparoid was limited to patients who required anticoagulation and who had immune-mediated heparin-induced thrombocytopenia (HITT).

Using danaparoid as an anticoagulant was difficult. The diagnosis of HITT requires specialized laboratory testing. Monitoring the therapeutic activity of drugs like danaparoid with anti-factor Xa levels requires laboratory tests that are not commercially

available. Therefore, danaparoid's use was limited to patients who were approved by Hematology.

Organon discontinued manufacturing danaparoid sodium in April due to problems obtaining the raw material. There are other agents listed in the *Formulary* for these indications including argatroban, bivalirudin, and lepirudin.

Augmentin® ES (Extra Strength) was recently approved by the FDA with a labeled indication for the treatment of recurrent or persistent acute otitis media due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* in children who have been exposed to antibiotics for acute otitis media within the preceding 3 months, who attend day care, or who are ≤ 2 years of age. These patients have a greater risk of acute otitis media with non-susceptible *Streptococcus pneumoniae.*

Augmentin® ES has a 14:1 ratio of amoxicillin to clavulanate. Clavulanic acid is a beta-lactamase inhibitor that extends amoxicillin's spectrum of activity to bacteria that produce beta-lactamase. The original Augmentin® has a 7:1 ratio of amoxicillin to clavulanate. Augmentin® has a wide variety of uses including skin and skin structure infections, pneumonia, acute otitis media (AOM), and other common infections. The increased amoxicillin dose in Augmentin® ES matches the American Academy of Pediatrics' recommended dosage of amoxicillin (ie, 90 to 100 mg/kg) for resistant acute otitis media.

Although there is a role for both agents, it is unsafe to have 2 different concentrations of a drug with a similar name listed in the *Formulary*. The Anti-Infective Subcommittee's recommended that Augmentin® be listed in the *Formulary* and that Augmentin® ES be designated nonformulary and not available. Orders for Augmentin® ES will be automatically interchanged to regular Augmentin® with an additional dose of amoxicillin. Augmentin® provides 45 mg/kg/day and amoxicillin provides and additional 45 mg/kg/day of amoxicillin. Like all P&T Com-mittee authorized therapeutic interchanges, this change will be documented in the Orders and Progress Notes sections of the chart.

Esomeprazole is the newest proton-pump inhibitor on the market. Proton-pump inhibitors have previously been designated therapeutically equivalent by the P&T Committee. This was done before esomeprazole (Nexium®) was marketed.

Research suggests that 40 mg of esomeprazole is marginally better than lansoprazole 30 mg. Therefore, 30 mg of lansoprazole is the closest equivalent dose for a 20-mg dose of esomeprazole. 40 mg of omeprazole is a reasonable equivalent dose for 20 mg of esomeprazole. Therefore, esomeprazole was designated nonformulary and not available and will be automatically interchanged. Currently, a 20-mg dose of esomeprazole will be changed to 40 mg of pantoprazole tablets or 30 mg of lansoprazole suspension.

Famciclovir is a prodrug of penciclovir, which is an antiviral structurally similar to acyclovir. Famciclovir is a frequently requested nonformulary drug that was designated nonformulary and not available.

The spectrum of activity of famciclovir is identical to acyclovir. However, famciclovir has a longer half-life and can be given fewer times per day compared with acyclovir. Famciclovir is only available as a tablet and has a labeled indication for the treatment of acute herpes zoster infections, treatment or suppression of recurrent genital herpes in immunocompetent patients, and treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

Acyclovir and valacyclovir are listed in the *Formulary*. Acyclovir is available in multiple dosage forms. Valacyclovir is a prodrug of acyclovir. It has a longer half-life than acyclovir and can be given fewer times per day. Valacyclovir is 3- to 7-times more expensive than acyclovir and should be limited to the prevention of herpes infections in bone marrow transplant patients with mucositis. It is being given in a dosage of 500 mg daily for this indication. Famciclovir costs approximately twice as much as valacyclovir and 10 times as much as acyclovir.

An automatic therapeutic interchange was not approved. If famciclovir is prescribed, the prescriber will be contacted and acyclovir or valacyclovir will be recommended.

Vitrasert® is an implantable device that delivers ganciclovir intraocularly in patients with cytomegalovirus (CMV) retinitis. It is designed for outpatient insertion in the Ophthalmology Clinic. Reimbursement schemes will not cover inpatient dispensing. Therefore, it was designated nonformulary and not available for inpatient use.

Midrin® is a combination of isometheptene, dichloralphenazone, and acetaminophen that is used to treat migraine and tension-type headaches. This combination product was marketed before 1938. Recently, Midrin® was re-classified as a Schedule IV controlled substance. Thus, patients could no longer take their own supply from home when they were admitted to the hospital. Midrin® had to be listed in the *Formulary* or designated nonformulary and not available.

Midrin® is classified by the FDA as being "possibly effective" in the treatment of migraines. Isometheptene is a sympathomimetic that possesses alpha- and beta-adrenergic effects. Dichloralphenazone is a complex of chloral hydrate and phenazone (antipyrine) and is a mild sedative. Acetaminophen 325 mg is included in each dose for additional pain relief.

Even though this product has been on the market for over 60 years, there are limited data to support its effectiveness. The number of migraineurs who would need Midrin® in the inpatient setting is too small to justify maintenance of a supply. Also, parenteral or oral opiates can be used instead of Midrin® for these patients. Therefore, Midrin® was designated nonformulary and not available.

Pain management, *from page 1*

meperidine. The anti-shivering mechanism of clonidine is not fully understood; however, it is proposed this agent may act centrally to inhibit the shivering center of the anterior hypothalamic region of the brain.

Various dosing schemes and administration times have been studied for clonidine. A 150-mcg injection at the onset of shivering has been most commonly studied. Hemodynamic effects related to clonidine use are a concern; however, the trials do not report post-operative hemodynamic changes with clonidine use. Thus, clonidine is a viable alternative for the treatment of post-anesthetic shivering.

Magnesium sulfate has been studied at 30-mg/kg and 1-gram doses. When administered at shivering onset, both regimens demonstrate good efficacy. Currently, there are no clinical trials comparing magnesium to meperidine.

Nalbuphine, a mixed narcotic agonist-antagonist, has also been shown to be an effective anti-shivering agent. A trial comparing nalbuphine 0.08-mg/kg and meperidine 0.04 mg/kg reported similar response rates.

Post-anesthetic shivering causes patient discomfort with unknown physiological implications. Although meperidine is often used for this indication, adverse effects may limit its use. Clonidine and other agents are viable alternatives to meperidine for the treatment of post-operative shivering.

by Shalonda Barnes, PharmD

References available upon request to the editor.

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NONFORMULARY DRUGS

Nasal steroids in the hospital

Intranasal corticosteroids (ie, nasal steroids) are generally considered therapeutically equivalent. There are currently 6 nasal steroids on the US market. In general, patients admitted to the hospital who need to continue their outpatient nasal steroid can be converted to an equivalent dosage of fluticasone, which is now the nasal steroid listed in the *Formulary*.

However, this will not be an automatic interchange. Excipients can cause sneezing, nasal burning, or nasal irritation. This may be reduced by using another product or by avoiding products without chlorofluorocarbons (CFCs) or propylene glycol. Some agents (eg, fluticasone, budesonide, and mometasone) have less systemic absorption when they drip down the patient's throat. Whether the low systemic amounts of nasal steroids that are absorbed are clinically significant is not clear; however, the P&T Committee chose fluticasone to minimize this issue.

If fluticasone nasal inhalation is unacceptable, another agent can be obtained through the nonformulary process. However, this may take up to 96 hours. Although a delay in the use of a nasal steroid in the hospital should not be a clinical problem, the use of fluticasone is strongly recommended.

Comparable dosages of intranasal steroids are listed below. The following dosages are approximately equivalent to 200 mcg per day of fluticasone for seasonal allergic rhinitis: beclomethasone 336 to 400 mcg/day, budesonide 336 to 400 mcg/day, flunisolide 200 mcg/day, mometasone 200 mcg/day, and triamcinolone 220 mcg/day.

These same dosages can be used for perennial rhinitis, but a dosage of 200 mcg/day of beclomethasone is usually used. Patients can be switched back to their original nasal steroid when they are discharged.

Nasal steroids have low systemic biovailabilities, because they are administered topically. Thus, they exhibit fewer side effects than systemically administered steroids. In general, all intranasal steroids are well tolerated in both adults and children. Generally, the adverse effects reported with nasal steroids have been mild to moderate. The most common adverse effects are epistaxis, nasal burning, nasal dryness, sore throat, and headache.

References available upon request to the editor.

THE FOLLOWING NASAL STEROIDS ARE AVAILABLE IN THE US:

Beclomethasone dipropionate (Beconase®, Vancenase®)	42 mcg/spray [DS = double strength = 84 mcg/spray]
Mometasone furoate (Nasonex®)	50 mcg/spray
Fluticasone propionate (Flonase®)	50 mcg/spray
Budesonide (Rhinocort®, Rhinocort® Aqua™)	32 mcg/spray
Triamcinolone acetonide (Nasacort®)	55 mcg/spray
Flunisolide (Nasalide®, Nasarel™)	25 mcg/spray