

Drugs & Therapy

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FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 15, 2011. 1 product was added in the Formulary, and 6 were deleted and designated nonformulary and not available. 2 interchanges and 3 criteria for use were approved.

◆ ADDED

RimabotulinumtoxinB (Myobloc®)*

*Restricted: treatment failures with toxin type A at FSC

◆ DELETED

Camphorated Opium Tincture (Paregoric®)†

Drotrecogin Alfa (Xigris®)†

Fluocinolone Topical Solution (Generic)†

Mebendazole Tablets (Vermox®)†

Nelfinavir Powder (Viracept®)†

Quinupristin/Dalfopristin (Synercid®)†

†Nonformulary and not available

◆ INTERCHANGES

Sitagliptin & Simvastatin (component parts) for Juvisync®

Sotalol (Generic) for Betapace AF®

◆ CRITERIA-FOR-USE CHANGES

Acetylcysteine Injection (Acetadote®)‡

‡Restricted to high dye volume, impaired renal function, and inability to take enteral medication.

Coagulation Factor VIIa (NovoSeven® RT)*

Opium Tincture, Deodorized (Morphine Anhydrous Solution)*

*Restricted (see text)

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PRESCRIBING

Three Routes of Acetaminophen: Three Ways to Achieve the Same Result

Acetaminophen is an antipyretic and analgesic with minimal anti-inflammatory properties that was first synthesized in 1878 and used clinically in 1887.^{1,2} It was later approved by the FDA in 1950.² Today, acetaminophen is a common nonprescription drug and is used frequently in both inpatient and outpatient settings for mild to moderate pain and fever.¹ Acetaminophen's mechanism of action is unknown but it is believed to be through inhibition of prostaglandin synthesis.²

The rectal and oral routes of administration have been the only way to deliver acetaminophen in the US, until recently. In 2010, an intravenous (IV) formulation was approved by the FDA, which is marketed as Ofirmev®. The dosing is similar between each of the different acetaminophen routes, and it is important to remember to not exceed 4 grams per day in patients greater than 50 kg and 75 mg/kg/day in patients less than 50 kg due to concerns of hepatotoxicity.² Acetaminophen has a similar duration of action of 4 to 6 hours among all routes.²

Among the different ways to give acetaminophen, the oral route is most common. The immediate-release oral tablet reaches its peak concentration within an hour for adults and 30 minutes in children.² This route is ideal in most circumstances as it is non-invasive, easy to administer, safe, and has a relatively quick onset of action.

Sometimes though, the oral route is not ideal and other routes are needed to administer acetaminophen. There are many methods to administer a drug to achieve systemic absorption, which include rectally, intramuscularly, subcutaneously, intravenously, via intraosseous, as well as other less common routes.

There are many reasons to choose different routes; for example, the oral route is often chosen when there is adequate absorption through the gastrointestinal tract and the patient can tolerate it. When medications are not able to be taken orally due to unconsciousness, nausea and vomiting, or being in the peri-operative setting, the clinician must start becoming creative. A clinician may

choose to give the medication rectally or IV depending on the availability and patient's needs.

Looking closer at rectal acetaminophen, the dose is the same as the oral route.² In the literature, it has been described as having a lower bioavailability and variable plasma concentrations.³ However, this has not been shown to have an impact on the reduction of pain and fever.

The IV route must be given as an infusion over 15 minutes.⁴ It reaches its peak concentration 30 minutes after the beginning of the infusion.⁴ IV acetaminophen reaches a 70% higher peak than oral acetaminophen but overall exposure to acetaminophen is equivalent.⁴ The patient must have IV access to use, and it takes longer to administer as it has to be infused.

In the inpatient setting, acetaminophen is often used post-operatively as an adjunct to opioids. In the post-operative setting, oral acetaminophen may not be a viable option, which leaves only rectal and IV acetaminophen as an adjunctive agent for pain control. There is a perception that IV acetaminophen works better than rectal acetaminophen but this has not been proven.

There has been one randomized controlled trial in children comparing rectal and intravenous administrations.⁵ A 1-time, post-operative rectal dose of 40 mg/kg was compared to IV acetaminophen 15 mg/kg after adenotonsillectomy. It was found that there was no difference in efficacy for the first 6 hours but the rectal administration remained effective longer.⁵ Unfortunately, this study had many limitations. It studied a 3-4 times higher dose of rectal acetaminophen than is currently recommended and it only included children.⁵ This rectal loading dose has been seen to more con-

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◆ INSIDE THIS ISSUE

◆ Drug-Induced Diabetes

Formulary Update, from page 1

Botulinum toxins are used for a variety of uses where the “toxin” paralyzes muscle. This class of medications was reviewed for use at the Florida Surgical Center as part of the movement disorder program.

Since onabotulinumtoxinA (Botox®) has been on the market the longest, it has the most labeled and off labeled uses; however, theoretically, any botulinum toxin could be used for these uses as long as the appropriate dose is used. Botox has been the *Formulary* agent, while abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®), and rimabotulinumtoxinB (Myobloc®) were nonformulary and not available.

These products have different potencies, and the units for these agents are NOT equivalent. The generic names are supposed to prevent medication errors, although brand names are usually used.

Data are available comparing the botulinum toxins to placebo for the treatment of movement disorders, but there are limited data comparing the toxins to each other for efficacy and safety. The data that do exist demonstrate that the type A toxins are similar in efficacy and safety, showing similar duration of effect and adverse effect profiles.

Despite being the most expensive agent on a per-dose or per-patient basis, Botox® has the most experience behind its use, appears to have comparable or increased duration of action to other products, and has the least incidence of common adverse effects such as dysphagia.

Based on more experience using Botox® and limited data for other type A products, it will remain the preferred botulinum toxin agent when treating conditions where botulinum toxins are indicated. Myobloc® will be added in the *Formulary* for use at the Florida Surgical Center [only] with criteria for use of documented treatment failure with botulinum toxin type A, while Dysport® and Xeomin® will remain nonformulary and not available.

Camphorated opium tincture is an oral alcoholic solution containing morphine (as opium) used for the treatment of non-infectious diarrhea. It will no longer be available, as it is an unapproved drug and FDA forced this product off the market. It was deleted from the *Formulary* and designated nonformulary and not available.

Opium tincture is a potent form of oral opium (ie, anhydrous morphine) that is only used to treat patients with resistant chronic diarrhea. Many institutions have made opium tincture nonformulary and not available in order to prevent medication errors and confusion with camphorated opium tincture (Paregoric®). However, a few patients may benefit from opium tincture at Shands at UF.

The P&T Committee decided that it would be safer if opium tincture is in the *Formulary* with appropriate restrictions on its use to prevent medication errors. Therefore, opium tincture is only dispensed after the approval of a pharmacy administrator. The pharmacy administrator on-call, working collaboratively with pharmacists, verifies the intended product with the prescriber. Several questions have been asked, including if the patient had tried and failed Paregoric®.

There is concern that deletion of camphorated opium tincture from the *Formulary* will increase the use of tincture of opium, which could lead to errors. Further, the criterion of failure of camphorated opium tincture can no longer be used as a restriction criterion. The P&T Committee approved new criteria for use restricting tincture of opium to patients continuing home therapy or who have failed maximum doses of loperamide or Lomotil® and requiring prescribers to answer a series of questions in EPIC to encourage safe use.

Drotrecogin alfa is a recombinant human activated protein C product initially approved in 2001 to reduce mortality in patients with severe sepsis. On October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris®. In the recently completed PROWESS-SHOCK trial, drotrecogin alfa did not show a survival benefit in 28-day all-cause mortality. It was deleted from the *Formulary* and designated nonformulary and not available.

Fluocinolone is a low to medium potency topical, synthetic corticosteroid used in the treatment of mild to moderate inflammatory manifestations of corticosteroid-responsive dermatitis. The topical solution of fluocinolone is no longer being manufactured, thus it was deleted from the *Formulary* and designated nonformulary and not available. Available topical formulations include fluocinolone ointment and cream, which will be recommended in place of the topical solution.

Mebendazole is an oral, broad-spectrum antihelminthic agent used in the treatment of various pathogenic intestinal parasites such as pinworms and hookworms. Mebendazole tablets will no longer be available on the market due to manufacturer discontinuation. Currently Shands at UF has approximately 40 (100-mg) tablets in stock with expiration dates in calendar year 2013. Mebendazole will be deleted from the *Formulary* once the current product has expired or has been consumed. At the time of formulary removal, the Anti-Infective Subcommittee will evaluate albendazole and ivermectin as possible replacements.

Nelfinavir is an oral antiretroviral protease inhibitor indicated for the treatment of human immunodeficiency virus infection in combination with other agents. Nelfinavir powder for oral suspension is no longer being manufactured, thus it was deleted from the *Formulary* and designated nonformulary and not available. Tablets are the remaining product formulation.

Synercid® (quinupristin and dalfopristin) is a combination of streptogramin antibiotics

that are used in treating gram-positive infection. Synercid® has been in the *Formulary* since 2005. Since that time, the agent has been prescribed for 3 patients, with the last patient in 2009. Due to the presence of multiple antibiotics with activity against MRSA and E. faecium and a lack of product use, Synercid® was deleted from the *Formulary* and designated nonformulary and not available.

Juvisync® is a fixed-dose combination medication containing sitagliptin (a DPP-4 inhibitor) and simvastatin (an HMG-CoA reductase inhibitor). It is the first product to combine a type 2 diabetes drug with a cholesterol-lowering drug. Sitagliptin and simvastatin are both listed in the *Formulary*, so an interchange was approved to convert patients taking Juvisync® to its component medications.

Sotalol is a non-selective beta-adrenergic blocking agent with Class III antiarrhythmic properties used to treat ventricular and supraventricular arrhythmias. Betapace® and Betapace® AF are both formulations of sotalol. Both drugs have the same mechanism of action and pharmacokinetics but have different indications. Betapace® AF was studied in atrial fibrillation and atrial flutter and has a labeled indication for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or flutter. Betapace® is indicated for the treatment of documented life-threatening ventricular arrhythmias.

The only product difference is the inactive ingredient FD&C color blue in Betapace® AF. They are not equivalent in the Orange Book because they are not FDA-approved for the same indications. Because the chemical entities are identical, an interchange from Betapace® AF to generic sotalol was approved.

Injectable acetylcysteine (IV NAC) is routinely given to prevent the development of radiographic contrast dye-induced nephropathy (RCIN) despite mixed results from clinical trials. RCIN is a potentially serious adverse drug reaction that occurs in up to 50% of high-risk patients requiring contrast for coronary angiography and computed tomography.

Eleven randomized controlled trials specifically comparing IV NAC to hydration for prevention of RCIN were reviewed. Three of the 11 IV NAC studies provided evidence that it may offer protection against RCIN. However, the evidence is limited supporting the use of IV NAC. IV NAC may be most beneficial when administered to patients at high risk for RCIN that receive high volumes of contrast dye. Oral n-acetylcysteine (NAC) should be given in most cases, if NAC use is deemed reasonable.

Oral NAC is well absorbed, but undergoes extensive first-pass metabolism. Overall bioavailability is low and highly variable between patients and various products. NAC is metabolized to glutathione, an antioxidant itself. The role of glutathione in preventing RCIN after NAC

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Formulary Update, from page 2

administration is unclear. IV NAC can be rapidly administered in emergent situations when there is insufficient time to execute an oral prophylactic regimen. However, there are no studies comparing IV and oral NAC and there is a significant cost difference.

Currently over \$430,000 per year is spent on IV NAC. The cost of IV NAC for any given dose is approximately 10 times the cost of oral NAC. Based on the lack of data supporting routine use of NAC, no comparative studies evaluating IV versus oral administration, and the considerable cost difference, the use of IV NAC beyond the first dose will be restricted to patients at high risk of developing RCIN (greater than or equal to 200 mL dye volume and impaired renal function [eGFR less than 30 mL/min or have both an eGFR less than 50 mL/min and either diabetes or congestive heart failure]). Patients able to take medications enterally will be switched to oral NAC.

Coagulation factor VIIa (Factor VII) is a recombinant coagulant similar to human factor VII. Factor VII has labeled indications for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia, prevention of bleeding in surgical interventions or invasive procedures in this same patient

population, treatment of bleeding episodes in patients with congenital factor VII deficiency, and the prevention of bleeding in surgical interventions or invasive procedures in patients with congenital factor VII deficiency. Factor VII is used extensively (greater than 90%) for off-labeled uses according to published reports.

Hospital administration directed the P&T Committee to review Factor VII and to limit its use. In this fiscal year, it is projected that \$2 million will be spent on NovoSeven®.

An Ad Hoc Advisory Committee, comprised of representatives from cardiothoracic surgery, hematology, and the P&T Committee, was formed to make recommendations about the use of Factor VII in cardiothoracic surgery. The committee evaluated the evidence to support the off-label use of Factor VII as well as a comparison of its use at institutions similar to Shands at UF.

Factor VII is now restricted to situations deemed appropriate by the advisory group. The advisory group felt there was insufficient evidence to support routine or prophylactic use of Factor VII with CT surgery. Evidence was sufficient to support limited use during surgery for refractory bleeding when the risk of continued bleeding outweighed the risk of thrombosis. Prior to use of Factor VII, the patient's acid-base status, coagulation parameters, and core temperature must be documented

to be normal. The attending surgeon and anesthesiologist must concur that bleeding is "refractory" and that the risks of persistent bleeding exceed the increased risk for stroke, and this rationale be documented in the medical record. The dose of Factor VII would be limited to an initial 45 mcg/kg dose, which could be repeated within 24 hours if the above criteria continue and appropriate rationale is documented.

The advisory group felt there was sufficient evidence to support limited use of Factor VII in CT surgery patients for refractory bleeding in the ICU setting. Criteria for use would include chest tube output of 3 mL/kg/hr or greater for 2 consecutive hours, reversal of coagulopathy, correction of core body temperature, and adequate heparin reversal. The same documentation criteria as above would apply.

The P&T Committee determined that any use outside of the OR or ICU (CT ICU for adults or PICU for children) be limited to patients either documented to have hemophilia or who have anticoagulant overdose for whom a hematology attending recommends use after completing a full in-patient consultation. Each use of Factor VII will be reviewed to ensure compliance with the established criteria.

By Ryan Rodriguez, PharmD

Prescribing, from page 1

sistently reach the proposed plasma concentrations of 10-20 mcg/mL.⁵ This study suggests that rectal acetaminophen may have a longer analgesic effect either due to the route or higher dose.⁵ More comparative studies are needed before drawing any conclusions about which route is better for adjunct analgesia in the immediate post-operative setting or when oral acetaminophen cannot be used.

Acetaminophen has the same effect regardless of the route administered. There are no data to show that the IV route is superior to oral or rectal administration. The oral route is usually the preferred route.

By Elaine K. Speed, PharmD

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ADVERSE DRUG REACTIONS

Cardiovascular Drug-Induced DM

Could a drug prescribed for cardiovascular (CV) risk reduction actually increase long-term CV risk? Recent publications have reported a link between statin therapy and new-onset type II diabetes mellitus (T2DM), a leading cause of CV morbidity and mortality. The notion of "statin-induced diabetes" is particularly concerning given the high frequency of statin use.

Pharmacologically feasible mechanisms for this adverse effect have been proposed, yet many questions remain. How often does statin-induced T2DM occur, and who is at greatest risk?

What are the long-term consequences of statin-induced T2DM? Does the risk ever outweigh the benefits? When do the risks manifest compared with the benefits? Answers to these questions may help guide clinicians towards optimizing statin prescribing.

Statins have been hailed for their pleiotropic actions beyond lipid-lowering (eg, improvement of endothelial function, stabilization of atherosclerotic plaques, and antioxidant properties). Unfortunately, there is mounting evidence indicating that statins may also have off-target effects on glucose metabolism. Statins may suppress glucose-induced calcium elevations in pancreatic beta cells, thereby inhibiting calcium-dependent insulin secretion. Other theories involve down regulation of glucose transporters and statin-medi-

ated suppression of the adipose-derived hormone adiponectin, which augments and mimics the actions of insulin.¹ Also, there is a theory that low density lipoprotein (LDL) is required for the pancreas to make insulin, and if LDL is lowered too much, it is not as efficient at secreting insulin.

The incidence of statin-induced T2DM has varied in clinical trials. The JUPITER trial in 2008 (Justification of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) suggested a relationship between statin therapy and the development of diabetes. In JUPITER, 20 mg of rosuvastatin daily increased the relative risk of new-onset T2DM by 25%. A recent meta-analysis of 13 randomized trials comparing statins to placebo or standard care found that the relative risk of new-onset T2DM was increased by 9% in patients taking statins.² It is important to also consider such findings in terms of absolute risk. The 25% relative risk increase reported in JUPITER amounts to an absolute risk increase of 0.4% (3.0% and 2.6% of patients assigned to rosuvastatin and placebo developed T2DM, respectively). The previously mentioned meta-analysis found 4.9% of patients on statins developed diabetes versus 4.5% of control patients. This 0.4% absolute risk increase seems modest compared to the 9% relative risk increase.

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Adverse Drug Reactions, from page 3

Pre-existing risk factors for T2DM, the specific statin and statin dose, and gender may influence risk for statin-induced T2DM. A meta-analysis of 3 atorvastatin trials suggests that statin therapy increases the risk of new-onset T2DM compared to placebo only when patients have 3 or 4 existing risk factors for diabetes (eg, impaired fasting glucose and other components of metabolic syndrome).³ The risk of statin-induced T2DM may be further dependent upon the specific statin. Atorvastatin, rosuvastatin, and simvastatin appear to increase the incidence of T2DM, while pravastatin may actually enhance insulin sensitivity and offer some protection from T2DM.¹ A meta-analysis comparing high-dose and low-dose statin therapy suggests the risk of T2DM increases in a dose-related manner.⁴ Finally, in a JUPITER subgroup analysis, rosuvastatin increased the risk of new-onset T2DM primarily in women. However, disparity in baseline risk for diabetes may explain the difference observed between these subgroups.⁵

The benefits of statin therapy convincingly outweigh the risks in several randomized controlled trials. Unfortunately, clinical trials can offer only a glimpse of what long-term effects may accompany any drug. Can a follow-up period of roughly 5 years, as in most statin trials, reveal the complete risk profile associated with a drug that may

be taken for decades? Randomized controlled CV trials have not been designed to specifically investigate drug-induced T2DM and most lack adequate power or follow-up duration to detect any associated CV risk. The influence of long-term statin therapy on the development of T2DM and related sequelae remains unknown at this time.

It is sensible to identify patients at risk for this adverse effect. Such patients should be closely monitored for signs and symptoms of worsening glucose control early during statin therapy. Decreases in insulin sensitivity have been observed within the first 2 months of statin treatment. Although statin-induced diabetes occurs in a dose-related fashion, high-dose statin therapy may often provide net benefit. Yet, the optimal statin dose is patient specific; the lowest dose that achieves evidence-based lipid goals should be prescribed. Statins should only be prescribed for populations in which a benefit has been proven.

Analyses describing the association of new-onset T2DM and statin therapy should be considered carefully, while bearing in mind the substantial CV benefit statins impart. Statins have been shown to reduce myocardial infarctions, strokes, peripheral vascular disease, need for revascularization procedures, and overall mortality. The absolute risk of statin-induced T2DM is low and outweighed by the CV benefit

gained when statins are prescribed appropriately. Nonetheless, our current understanding is hampered by the relatively short duration of clinical trials. The phenomenon of drug-induced T2DM serves as a reminder that the pharmacologic management of disease demands continual assessment of risks and benefits.

By Joseph Pardo, PharmD Student

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