Volume 24, Number 10

Shands at the University of Florida

November/December 2010

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 19, 2010. 1 product was added in the *Formulary*, and 1 product was deleted. 2 products were designated nonformulary and not available. 1 interchange and 1 restriction were approved.

◆ ADDED

Acetaminophen 80-mg Suppositories
(Generic by Actavis)

◆ DELETED

Urokinase
(Kinlytic®)*

**Nonformulary and Not Available*

◆ NONFORMULARY AND NOT AVAILABLE

Aliskiren-Amlodipine (Tekamlo®)

◆ INTERCHANGES

Phenytoin Oral for **Phenytoin IV**†

†Same dose if meets criteria for interchange

◆ CRITERIA-FOR-USE CHANGES

Nitric Oxide (INOmax®)‡

‡Restricted to Nitric Oxide Order Form for Adults

Acetaminophen 80-mg suppositories were previously deleted from the *Formulary* and designated nonformulary and not available. This was done only because they were no longer available from a manufacturer. Since a new vendor has marketed this dosage form, acetaminophen 80-mg suppositories were re-added in the *Formulary*.

Acetaminophen is used for pain and fever control and is given rectally when patients cannot take medications by mouth. Low dosages used in small children are difficult to give without the 80-mg suppository option.

(continued on next page)

PRESCRIBING

Oral erythromycin for gastroparesis: The more stable choice?

Erythromycin is a macrolide antibiotic that has been available since the 1950s. It is rarely used as an antibiotic today and is primarily used for its "prokinetic" effect on the gastrointestinal (GI) tract. It has been used successfully off-label for the treatment of gastroparesis and other GI hypomotility disorders.

When erythromycin was used as an antibiotic, patients often complained about it causing abdominal pain. Researchers eventually determined that erythromycin stimulates motilin receptors in the GI tract. Motilin receptors stimulate GI contractions and results in increased GI motility.

Erythromycin does have more significant drug interactions than azithromycin.

Both oral and intravenous (IV) erythromycin have been used for its prokinetic effect. The IV form is generally reserved for acute conditions. The oral form is usually given in lower dosages than required for antibiotic effects (ie, 150-250 mg PO 3 to 4 times a day given 30 minutes before a meal). The oral form has been shown to work rapidly and can be substituted when the IV form is unavailable.

There have been some prescribers who use azithromycin instead of erythromycin. There is much less published evidence to support the prokinetic effects of azithromycin compared with erythromycin. Azithromycin suspension also has the disadvantage of being stable for only 10 days after reconstitution. The 10-day stability presents a problem for patients who take the drug longer than 10 days. They need to return to the pharmacy to obtain a fresh bottle 3 times a month. Some have requested that the bottle with the powder for suspension and the measured amount of water be sent home with patients so they could reconstitute the mixture themselves and avoid 2 trips to the pharmacy. It is not clear that this is legal in the State of Florida since a pharmacist is responsible for the final preparation. Erythromycin ethylsuccinate oral suspension (EryPed®) is stable for 35 days after reconstitution, which avoids this issue.

Another concern with the long-term use of azithromycin is the contribution to the development of resistance. Unlike erythromycin, azithromycin is still commonly used for its antibacterial effects and chronic use may contribute to resistance.

Erythromycin does have more significant drug interactions than azithromycin. Erythromycin is an inhibitor of CYP3A liver isoforms, which can lead to increased exposure to some drugs (eg, cyclosporine, carbamazepine, dihydroergotamine, methadone, sildenafil, simvastatin, sirolimus, tacrolimus, triazolam, and vinblastine). Erythromycin also causes QT-prolongation, which can be problematic when used with drugs that also prolong the QT-interval (eg, amiodarone, disopyramide, droperidol, haloperidol, and ziprasidone).

There is better evidence supporting the use of erythromycin rather than azithromycin for prokinetic effects. Erythromycin 35-day stability makes it the obvious choice in the outpatient setting so patients can obtain a 30-day supply at a time.

INSIDE THIS ISSUE

Formulary update, *from page 1*

Urokinase is a thrombolytic enzyme produced by kidney cells. There have been several parenteral urokinase products produced using recombinant DNA technology and tissue cultures of kidney cells. Urokinase has had a history of quality problems. In 1999 it was removed from the market because of a viral contamination of the kidney cell tissue cultures used in production.

Urokinase (Abbokinase®) was remarketed in 2002. Abbott discontinued manufacturing Abbokinase® in 2004. ImaRx purchased Abbokinase® in 2006 and renamed it Kinlytic®, which became available in April 2007. Microbix purchased Kinlytic® in September 2008. Microbix was unable to use the available inventory of Kinlytic®. It is unclear when new product will be available. Therefore, urokinase was deleted from the *Formulary* and designated nonformulary and not available because it cannot be acquired for use.

Alteplase is an alternative to urokinase listed in the *Formulary.*

Tekamlo® is a combination antihypertensive containing the direct renin inhibitor, aliskiren, and the calcium-channel-blocker, amlodipine. There have been many combination antihypertensive agents approved by FDA over the last year or so. Combination products may decrease "pill burden" since many hypertensive patients require multiple medications to control their blood pressure. Tekamlo®'s labeled indication is for add-on or initial therapy for hypertension.

Tekamlo® was designated nonformulary and not available; however, patients may continue to use their supply from home. It is not possible to stock the various combination drugs that are marketed. Shands at UF will not acquire this combination product for inpatient use. If needed, patients may be prescribed the individual ingredients.

Phenytoin is an anticonvulsant that has been on the market for many years. Parenteral phenytoin was removed from the *Formulary* and designated nonformulary and not available several years ago. IV fosphenytoin, which has a much better safety profile and is easier to administer, was used instead. This decision likely prevented phenytoin-related adverse drug events.

Unfortunately, a fosphenytoin shortage required that phenytoin be re-added in the *Formulary.* It is anticipated that this shortage will not end soon. The increased risk of adverse events with IV phenytoin can be partially attributed to clinician unfamiliarity with optimal administration practices for this medication.

The approval of a policy that allows automatic interchange from IV to oral (PO) phenytoin was approved by the P&T Committee to potentially avoid adverse effects of IV phenytoin (ie, cardiac toxicity and extravasation reactions) when oral phenytoin is a viable option.

Intravenous phenytoin sodium injection must be administered at a maximum rate of 50 mg/min for adults and 1 mg/kg/min (up to 50 mg/min) for pediatric patients. If given too quickly, it can cause cardiac arrhythmia and hypotension. For a typical adult loading dose of 1 gram, this dose should be administered over no less than 20 minutes. In addition to concerns about infusion rates, phenytoin injection is a venous and soft tissue irritant. Phenytoin sodium injection has a pH between 11 and 12, and an osmolality of 9740 mOsm/kg. Due to its high pH and osmolality, repeated injections through a peripheral IV site frequently results in phlebitis and the need to find alternate IV sites. Additionally, if IV phenytoin does extravasate, tissue necrosis can occur.

◆

The following are exclusion criteria for automatic IV to PO conversion of phenytoin:

1) **ICU patients,**
2) **patients receiving continuous enteral nutrition,**
3) **patients with a history of seizure activity within the last 72 hours,**
4) **patients on continuous EEG monitoring,**
5) **patients receiving intravenous doses of 400 mg or more (or 10 mg/kg or more for children) will not be automatically converted to PO, and**
6) **loading doses.**

Since oral bioavailability of phenytoin is 90 to 100%, IV dosages of phenytoin sodium can be changed to oral doses of phenytoin sodium in a 1:1 ratio. All patients receiving IV phenytoin sodium **maintenance** doses will be automatically converted by a pharmacist to an equivalent oral dose of phenytoin if the patient is able to take PO medications and is receiving other PO medications. This process is similar to other medications already on the automatic IV to PO conversion list, such as ciprofloxacin, fluconazole, and proton pump inhibitors. The following are exclusion criteria for automatic IV to PO conversion of phenytoin: 1) ICU patients, 2) patients receiving continuous enteral nutrition, 3) patients with a history of seizure activity within the last 72 hours, 4) patients on continuous EEG monitoring, 5) patients receiving intravenous doses of 400 mg or more (or 10 mg/kg or more for children) will not be automatically converted to PO, and 6) loading doses.

Nitric oxide is an inhaled gas that dilates the pulmonary blood vessels. It has a labeled indication for the treatment of hypoxic respiratory failure [in conjunction with ventilatory support and other agents] for term and near-term (greater than 34 weeks) neonates. It has been used extensively for off-labeled uses where patients, including adults, have increased pulmonary arterial pressures.

In November 2008, the P&T Committee required the use of inhaled epoprostenol (Flolan®), a prostaglandin analogue that also dilates the pulmonary vasculature, prior to nitric oxide except in the following situations: 1) pre-ECMO, PPHN, and CDH in the NICU; 2) rapid deterioration (PaO_2/FIO_2 less than or equal to 60); 3) pediatric post-operative cardiac surgery (per the Pediatric Cardiac Surgeons); 4) pulmonary hypertension (primary or secondary) with MPAP of 30 mm Hg or greater in the SICU-NSICU-CICU or 40 mm HG or greater in MICU; 5) patients placed on a ventricular assist device (VAD); and, 6) patients "who do not respond" to inhaled epoprostenol.

The use of nitric oxide in adult patients is now restricted to use with the *Shands at UF Adult ICUs and Operating Room Nitric Oxide Order Form,* which requires the use of inhaled epoprostenol as the first therapeutic consideration [to lower pulmonary arterial pressures] except in the following circumstances: pulmonary hypertension defined as a MPAP 30 mm Hg or greater (MPAP 40 mm Hg or greater in the MICU); MPAP 20 mm Hg or greater in lung transplant, ventricular assistant device initial insertion, no response to inhaled epoprostenol as defined by less than 10% decrease in MPAP or less than 5% increase in SpO_2/SaO_2, or P/F Ratio less than 80 (lung transplant P/F ratio less than 120). A positive response to nitric oxide is defined as an increase in SpO_2 by 5%, an increase in PaO_2 by 10 mm Hg, or a decrease in MPAP by 15%.

The value of this order form will be the assessment of "response" and discontinuing the use of nitric oxide when there is no response. Also, patients will be weaned off nitric oxide as soon as possible. The form should result in less use of nitric oxide.

POLICIES AND PROCEDURES

Do not "Do Not Substitute"

There are 3 main types of drug interchanges that occur in the inpatient setting. The medical staff, via the P&T Committee, approves these interchanges. By policy, the Department of Pharmacy Services is given the authority to interchange a drug to an A-rated generic product (ie, **generic interchange**). In individual cases, the P&T Committee may approve specific instances when a similar but therapeutically equivalent product may be substituted for the ordered drug (ie, **therapeutic interchange**). Therapeutic interchange includes substituting a different salt (ie, pharmaceutical alternatives) for a drug. An example of a pharmaceutical alternative would be substituting hydroxyzine hydrochloride for hydroxyzine pamoate using an equivalent dose. An automatic route change, usually converting the patient from a parenteral (ie, intravenous or IV) to oral (ie, PO) route of administration is the third most common automatic interchange approved by the P&T Committee (ie, **IV to PO interchange)**.

Usually these interchanges are intended to decrease the number of unnecessary choices in the *Formulary* (ie, generic and therapeutic interchange) and promote safety (ie, IV to PO interchange). These interchanges also decrease acquisition and storage costs.

Generic drugs usually cost a fraction of the cost of brand name drugs. Sometimes, when a product becomes available as a generic, brand name manufacturers will match the cost of generics in the inpatient setting to encourage the continued use of the brand name product. However, this pricing policy could end at any time. Sometimes, brand name companies actually increase the costs of brand name drugs when generics become available. This is an attempt to maintain a revenue source in the face of a shrinking market share. Continued use of more expensive brand name drugs would be irresponsible when less expensive alternatives have become available. Evidence has consistently shown that generics are equal to brand name products.

Therapeutic interchange substitutes a similar drug in the same category to avoid stocking multiple drugs in the same category. A complete list[a] of the current drugs that are therapeutically interchanged at Shands at UF is available on the Portal.

A list[b] of current IV to PO conversions at Shands at UF is also available on the Portal. There are minimum criteria that a patient must meet before the interchange will be considered. However, the most important criterion is that patients are receiving other drugs by the oral route. Some drugs (eg, phenytoin) may have additional criteria.

Some prescribers may be familiar with the ability to prevent generic interchange in the outpatient setting. Florida law prevents a pharmacist from substituting a generic for a brand name drug if the prescriber writes "Medically Necessary" on the face of the prescription. It is important to note that this law applies ONLY to prescriptions. Inpatient orders are NOT prescriptions, thus writing "Medically Necessary" or other terms like "Do Not Substitute" with the order will not prevent an interchange from occurring.

If a physician has a concern with an interchange for a specific patient because of unusual circumstances (eg, the patient is allergic to an "inert" ingredient in a generic or specific brand named product), they should consult with the pharmacist in their area. The best solution, however, is to write an order that will allow their patient to use their own supply of drug from home.

If a physician has a problem with a substitution policy at Shands at UF, they should petition the P&T Committee to reconsider the existing policy. In addition to a letter requesting this re-evaluation (sent to Secretary, P&T Committee PO Box 100316), evidence should be submitted that refutes the current policy along with a Disclosure Form. The requester will be invited to the P&T Committee meeting when this issue will be discussed. An independent review of the available evidence will be presented to the P&T Committee along with the evidence provided by the requester.

The P&T Committee-approved interchange polices are critical for cost-containment. They enable us to be good stewards of our limited resources. However, no interchange would be done if there is evidence that this would result in patient harm. The complete policies on interchanges are available on the Portal.[c,d]

LINKS

[a]https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange/TIs/IVtoPO/IV-to-PO.pdf

[b]https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Pharmacy/UF/Formulary/TherapeuticInterchange

[c]https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Policies/SUF/DEPT/Pharmacy/SatelliteOperations/06-05-42.pdf

[d]https://my.portal.shands.ufl.edu/portal/page/portal/DEPT_CONTENT/Policies/SUF/DEPT/Pharmacy/SatelliteOperations/06-05-39.pdf

POLICIES AND PROCEDURES

Desvenlafaxine-Venlafaxine interchange (correction)

In the October 2010 issue of the *Bulletin*, the interchange from desvenlafaxine (Pristiq®) to venlafaxine was announced. The following interchanges will occur when a patient cannot provide their own supply of desvenlafaxine:

ORDERED [DAILY DOSE]	INTERCHANGED [DAILY DOSE]
Desvenlafaxine 50 mg	Venlafaxine XR 75 mg
Desvenlafaxine 100 mg	Venlafaxine XR 75 mg
Desvenlafaxine 150 mg	Venlafaxine XR 150 mg
Desvenlafaxine ≥ 200 mg	Venlafaxine **XR** 225 mg

In last month's issue of the *Bulletin*, the **"XR"** was inadvertently left off the Venlafaxine XR 225 interchange.

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 24, No. 10 Nov./Dec. 2010
This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

EDITOR, DRUGS & THERAPY BULLETIN
Randy C. Hatton, PharmD

DIRECTOR, PHARMACY SERVICES
Alan Knudsen, MS, RPh

CHAIRMAN, PHARMACY & THERAPEUTICS COMMITTEE
Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION
Shands HealthCare's Publication Svcs.

FOR MORE INFORMATION, VISIT US ONLINE
http://shands.org/professionals/druginfo/bulletin.asp

SHANDS
Shands at the University of Florida
DRUG INFORMATION SERVICE
PO Box 100316
Gainesville, FL 32610-0316

NON-PROFIT ORG.
U.S. POSTAGE
PAID
GAINESVILLE, FL
PERMIT NO. 94

2010 Annual index