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Shands at the University of Florida

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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 21, 2008. No drugs were added in or deleted from the *Formulary*. 2 drugs were designated nonformulary and not available, and 2 restrictions were initiated.

◆ ADDED

None

◆ DELETED

None

◆ NONFORMULARY AND NOT AVAILABLE

Ibuprofen Lysine (NeoProfen®)

Lidocaine-Tetracaine Transdermal Patch (Synera®)

◆ CRITERIA-FOR-USE CHANGES

Factor VIIa, Recombinant (NovoSeven® RT)*

**Comprehensive criteria for use approved & must be ordered on a Recombinant Factor VIIa Order Form*

Tretinoin (Vesanoid®)†

†Added in the Chemotherapy Policy

Ibuprofen lysine is an injectable form of ibuprofen with a labeled indication to close a clinically significant patent ductus arteriosus (PDA) in premature infants when usual medical management (eg, fluid restriction, diuretics, and respiratory support) is ineffective. Indomethacin is currently the pharmacologic agent of choice for the treatment of PDA. However, indomethacin use has been associated with transient or permanent renal function impairment, necrotizing enterocolitis (NEC), gastrointestinal (GI) hemorrhage or perforation, and impairment of cerebral blood flow. Ibuprofen lysine is purported to be an effective alternative to indomethacin

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POLICIES AND PROCEDURES

Med reconciliation: There ARE reasons to discontinue some home meds

A policy on *Pharmacy Medication Reconciliation* was passed by the P&T Committee at the October meeting. This policy continues to improve our current medication reconciliation processes, which includes roles for the medical, nursing, and pharmacy staffs and helps meet the Joint Commission's (TJC's) National Patient Safety Goals (NPSGs).

Recently, TJC changed the wording of the medication reconciliation NPSGs to require "documentation" of the medication reconciliation process. Upon admission to Shands at UF, a nurse interviews the patient or the patient's family members to generate a list of all medications the patient takes at home. This list is placed in Smart Chart by the nurse, and is accessible under the "medications" tab in NetAccess. A pharmacist then reviews this list and resolves any discrepancies between the home medication list and the current inpatient medication list. Pharmacists also make any necessary corrections to the list by working with the patient's nurse.

In the newly approved pharmacy process, documentation of these actions will be completed by the pharmacist in the pharmacy information system. The verified and corrected (if necessary) home medication profile will be placed in the patient's chart.

Further changes to the current process include a list of situations in which apparent discrepancies between the home medication profile and the inpatient profile are considered reconciled (see Table). A call to the prescriber is not needed to resolve these apparent discrepancies between the patient's home medications and their admission medications. There are situations when home medication should be stopped. For example, bisphosphonate medications are taken at home, but not continued in the hospital; or warfarin is taken at home, but the patient is admitted as an immediate pre-operative patient.

The medication reconciliation process will be continuously monitored to identify areas for improvement and for possible revisions to the criteria.

TABLE: DISCREPANCIES WITH HOME MEDICATIONS CONSIDERED "RECONCILED"

Bisphosphonates – Stopped during hospitalization for safety reasons
Antidiabetic Meds (oral & injectable) – Replaced with insulin infusion
Antidiabetic Meds (oral & injectable) – Stopped because patient NPO
Blood Pressure Meds – Replaced with IV vasoactive agents in ICU (except diltiazem or verapamil, which may interact with selected meds [eg, tacrolimus]).
Diuretics – Stopped when admitted to an ICU
Warfarin or Antiplatelet Drugs – Stopped for surgery or bleeding diagnosis (eg, GI hemorrhage)
Metformin – Stopped because of contraindication (eg, elevated serum creatinine)
"As Needed" Home Med – Stopped (not necessary)
Vitamins or Dietary Supplements – Stopped (not necessary)
Nonprescription Meds – Stopped (except daily aspirin)
New Antibiotic Started – Patient admitted for infection
Nonformulary Home Med – Changed to formulary alternative
Scheduled Home Pain Med – Changed to alternative pain control regimen (eg, epidural)

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with less effects on cerebral, renal, and mesenteric blood flow. Although the exact mechanism by which ibuprofen lysine causes closure of a PDA is not known, it is believed to be due to the inhibition of prostaglandin synthesis (ie, the same proposed mechanism as indomethacin).

The results of 2 meta-analyses and recent studies demonstrate that ibuprofen has similar efficacy to indomethacin in the closure of PDA. While ibuprofen reduces the risk of oliguria, it may increase the risk for chronic lung disease. No significant differences were found in the incidence rates of mortality, reopening of the ductus arteriosus, need for surgical closure, intraventricular hemorrhage (IVH), NEC, or intestinal perforation. There were also no differences in the duration of ventilator support, time to full enteral feeds, or duration of hospitalization. No long-term data were reported on neurodevelopmental outcomes.

The most frequently reported adverse effects of ibuprofen lysine include sepsis, anemia, IVH, apnea, GI disorders, and renal impairment. Compared to indomethacin, ibuprofen has a significantly lower incidence of decreased urine output and increased creatinine. GI perforation and NEC have recently been added to the *Adverse Reactions* section of the product labeling due to post-marketing experiences. Contraindications of ibuprofen lysine include untreated infection; congenital heart disease; active bleeding (eg, IVH or GI bleed); thrombocytopenia; coagulation defects; suspected NEC; and significant renal function impairment. Five cases of pulmonary hypertension have been reported after the use of ibuprofen for either the prevention or treatment of PDA. Because ibuprofen lysine may decrease renal blood flow, it may interact with other medications that undergo renal elimination and may have an additive effect with nephrotoxic drugs. Concomitant use of corticosteroids may increase the risk of intestinal perforation.

Although ibuprofen lysine has a lower acquisition cost than indomethacin, due to the stabilities and dosing regimens of ibuprofen and indomethacin, treating a PDA with ibuprofen lysine is nearly 3 times more expensive than indomethacin therapy since 3 ibuprofen vials would have to be used as opposed to delivering all 3 doses from 1 indomethacin vial.

Although ibuprofen reduces the risk of oliguria, it is not more efficacious than indomethacin for the treatment of PDAs. Ibuprofen may increase the risk of chronic lung disease and pulmonary hypertension. Since ibuprofen offers no net benefit over indomethacin for the treatment of PDA, the P&T Committee designated ibuprofen lysine nonformulary and not available.

Synera® transdermal patches are a mixture of lidocaine and tetracaine that provide local dermal analgesia when applied to intact skin by the release of its active components into the skin. Lidocaine plus tetracaine is a "eutectic mixture," which forms a liquid when 2 solids are combined that lower the melting point of the combination. Synera® has a labeled indication for use in children 3 years of age and older as well as adults. It is indicated for application to intact skin for 20 to 30 minutes before superficial venous access and superficial dermatological procedures such as excision, electrodessication, and shave biopsy of skin lesions.

Synera® topical patches uses a novel delivery system consisting of a thin, uniform layer of a local anesthetic formulation with an integrated, oxygen-activated heating component that is intended to enhance the delivery of the local anesthetic. The patch begins to heat once the patch is removed from the pouch and is exposed to oxygen in the air. Of note, the integrated heating component contains iron powder; therefore, the patch must be removed before a patient undergoes magnetic resonance imaging (MRI). Iron-containing products may be a source of magnetic susceptibility artifact.

Synera® patches are similar to other topical anesthetic agents listed in the *Formulary* (eg, LMX® [lidocaine 4%] topical cream). The promoted advantages for Synera® over the currently available products are its ease of use (ie, peel-and-stick method versus occlusive dressing bandage), Band-aid®-like packaging, as well as an enhanced delivery of transdermal medication via heat activation. It supposedly has a quicker onset of action with a 20-minute onset as compared to a 30-minute onset of action for LMX® Cream (although these agents have not been compared head-to-head and this is not a proven advantage).

There are limited efficacy data for Synera®. The only published comparison study did not favor the use of Synera® over lidocaine infiltration in pregnant women prior to epidural insertion. Thus, there are currently no data to support superiority for Synera® over other available topical anesthetic products.

The most common adverse reactions are local reactions including erythema, blanching, and edema. These reactions were mild and resolved spontaneously after treatment. Keeping a patch on longer than recommended or applying multiple patches simultaneously or sequentially could result in systemic absorption sufficient to result in serious adverse events that are typical of drugs in this class and should be avoided.

Synera® patches are approximately 2.5 times more expensive than LMX® Cream. The theoretical advantage of the 10-minute faster onset (which is unproven) and ease of use do not justify the difference in cost. Therefore, the P&T Committee designated Synera® patches nonformulary and not available.

Recombinant factor VIIa (rFVIIa) promotes local hemostasis through the extrinsic pathway of the coagulation cascade. Factor VIIa complexes with tissue factor leading to activation of the coagulation cascade and the generation of thrombin, ultimately leading to a stable fibrin clot. rFVIIa has labeled indications for the treatment and prevention of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia; treatment of bleeding episodes in congenital FVII deficiency; and, prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency. rFVIIa has also been used off-label extensively because of its effectiveness in stopping bleeding. Unfortunately, it is very expensive and many off-labeled uses are not reimbursed.

Therefore, an ad hoc committee was formed to review the off-labeled use of rFVIIa and make recommendations for its appropriate use in adults. The Factor VIIa Utilization Committee used benchmarking data and an evaluation of the literature to create a protocol for appropriate off-label use of rFVIIa. Further, they identified ICD-9 codes for reimbursement in specific non-hemophilic uses. An order form was developed to facilitate the monitoring of rFVIIa compared with the criteria for use and promote the use of the appropriate ICD-9 codes. rFVIIa must now be ordered using this form in adults.

rFVIIa should not be used for futile care, in pregnant patients (unless the patient has a factor VII deficiency and in consultation with Hematology), for prophylaxis (except for the labeled indications), or for disseminated intravascular coagulation (DIC). It is not effective in patients with acidosis, in patients who are hypothermic (< 35° C), in patients with a platelet count < 50,000 cells/mm^3, or when fibrinogen levels are < 100 mg/dL.

rFVIIa can be used under specific circumstances for trauma, cardiac surgery, and peri- or post-operative

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bleeding in the Operating Room (OR) or Critical Care Unit (ICU) setting. Recombinant factor VIIa may be used for severe multiple trauma patients with ongoing bleeding and medical coagulopathy despite surgical intervention and continued infusions of plasma (>4 units fresh frozen plasma [FFP]) and/or ≥ 10 units of packed red blood cells (PRBC) in 6 hours, in conjunction with the massive transfusion protocol. It may also be used for uncontrolled hemorrhage associated with inability to achieve adequate hemostasis for chest closure, and after post-transfusion platelet count and coagulation factors are acceptably corrected and qualitative clot in the surgical field remains inadequate with no obvious surgical cause. rFVIIa use to control peri- or post-operative bleeding in the OR or ICU setting may be used for rescue therapy for life-threatening ongoing bleeding despite other measures to correct coagulation profile, platelet administration if platelet count > 50,000, and cryoprecipitate to replace fibrinogen if < 100; and no obvious surgical cause.

The initial recommended dose of rFVIIa is 45 mcg/kg for surgical use, including cardiac surgery. A fixed dose of 5 mg is used for trauma. All doses greater than 1 mg will be rounded to the nearest vial size (ie, nearest milligram).

A complete blood count (CBC), fibrinogen, and blood gas (for pH) should be measured before the administration of factor VII. A prothrombin time/international normalized ration (PT/INR), activated partial prothrombin time (aPTT), and thromboelastogram (TEG) may be considered in select cases. The degree of bleeding should be reassessed 20 to 30 minutes after the initial dose of rFVIIa for either resolution of bleeding or, if excessive bleeding continues, redosing or surgical exploration.

The criteria for use are voluntary at this time; however, all rFVIIa use going forward will be compared to these criteria to determine whether additional actions are needed. Emergent use will be reviewed retrospectively; for non-emergent use, the Hematology Service is available for consultation.

Tretinoin must now be ordered on a *Chemotherapy Order Form*. Tretinoin, also known as all-trans retinoic acid (ATRA), is a retinoid currently listed in the *Formulary* with a labeled indication for the induction of remission in patients with acute promyelocytic leukemia (APL).

The most frequent adverse effects associated with tretinoin are typical of the retinoids (eg, headache, skin abnormalities [dry skin, pruritus, chelitis, and xerostomia], bone pain, and arthralgias). Respiratory toxicities are common. Tretinoin is also a potent teratogen and should be avoided in pregnant patients, although its use has been reported in the second and third trimesters.

MEDICATION MANAGEMENT

Pharmacist order review: Exceptions and misconceptions

Pharmacists are the healthcare professionals usually responsible for the preparation and dispensing of medications. Pharmacists promote good patient care and prevent serious medication errors. However, what happens when pharmacists do not review medications orders? Is it acceptable to circumvent the pharmacist?

The Joint Commission (TJC) has Medication Management standards (MM.05.01.01) for the selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, and monitoring of medications. These standards are intended to increase safety and improve patient care and mandate that pharmacists *review the appropriateness of all medication orders for medications dispensed in the organization.*[1] Orders are assessed for correctness of the medication, dose, frequency, route of administration, the absence of therapeutic duplication, and the validity of potential allergies or sensitivities. In addition, potential drug and food interactions, contraindications, laboratory values that may potentially be impacted, and other relevant medication-related issues or concerns must be considered. Usually pharmacists are in the best position to oversee this process. If there are concerns, the pharmacist clarifies the order with the prescriber.[1]

The TJC standards list **4 exceptions to these "pharmacist" responsibilities**. Pharmacists' **duties may be waived if a delay will cause harm to the patient, a licensed independent practitioner (LIP) is available at bedside**, for **a controlled emergency department medication list**, and for **a listing of radiology department needs as deemed appropriate**.

Numerous medications are available without pharmacist review ("override medications") in automatic dispensing cabinets (ie, Omnicell cabinets) for the situations specified in TJC standards. A pharmacist does not have to review a medication order if a delay would harm the patient in an urgent situation, like epinephrine for anaphylaxis.[1] Thus, epinephrine is an "override medication." Override medications also may be obtained without a pharmacist's review if a LIP is physically at the patient's bedside during administration of the medication. A LIP must control the ordering, preparation, and administration of a medication during critical times. For instance, if a practitioner ordered a dose of intravenous beta-blocker for a patient experiencing tachycardia, he or she is responsible for assessing, preparing, and administering the medication. The LIP must be present physically at the beside…not simply in the vicinity. The practitioner assumes the role of the pharmacist in these situations.

TJC has addressed questions about managing the administration of radiopaque contrast agents. Oral and rectal contrast agents may be administered without prior pharmacist review under protocols developed and approved jointly by both medical staff and the Department of Pharmacy Services. However, a LIP may obtain a contrast agent without pharmacist review when a delay could cause patient harm or if the radiologist is at the bedside. A pharmacist may be available on-call, if necessary.[2] A sampling of contrast use without prior pharmacy review must be done to assure compliance with this standard and to determine if there are opportunities for improvement.

The P&T Committee is currently reassessing which medications should be listed in the list of "override medications." TJC standards will determine which medications cannot be overridden (eg, medications with slow onsets of action like transdermal and sustained-release products).

Medication management standards decrease medication errors and improve patient safety. The Pharmacy Department has the responsibility to evaluate orders for medications; however, there are limited exceptions. Shands at UF is continually improving this process.

by Abigail A. Dee, PharmD

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