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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals, July/August 2009

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In This Issue

Pharmacy & Therapeutics

Update

Drug Information for Health Care Professionals

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Promethazine Extravasation

By: Dawn Kruzan, PharmD candidate

Intravenous (IV) fluid extravasation is defined as a leakage of injectable fluids out of the vein and into the interstitial space. This common problem may be due to a displacement of the IV line or from increased vascular permeability. Tissue may be damaged to varying degrees depending on the solution being injected. Some IV solutions may be irritants (agents that stimulate an inflammatory response) or vesicants (blistering agents that cause burns and destruction of tissue both internally and externally). The most common solutions to extravasate are cationic (eg, potassium ion), osmotically active agents (eg, parenteral nutrition), antibiotics, or cytotoxic drugs. The incidence is greatly increased in children. Common sites of extravasation include the dorsum of the hand in adults and the dorsum of hand or scalp in neonates. Newborns are at a higher risk because of their smaller, more fragile veins and their inability to verbalize pain.[1]

Figure 1. Woman Develops Gangrene after Receiving Phenergan IV. Image provided courtesy of ISMP.

A commonly used medication that can cause harm if extravasated is promethazine (Phenergan®), a vesicant with a pH between 4 and 5.5. It can cause severe tissue damage, regardless of the route of parenteral administration, though IV and inadvertent intra-arterial or subcutaneous administration leads to more significant complications. This damage may include pain, burning, swelling, erythema, severe vessel spasm, thrombophlebitis, nerve damage, paralysis, phlebitis, abscess, venous thrombosis, tissue necrosis and gangrene. Surgical intervention may be required including fasciotomy, skin graft and amputation.[2]

In 2004, a professional musician was awarded $7.4 million after she endured two amputation surgeries following accidental arterial admini-

stration of promethazine. Initially visiting the emergency department suffering from a migraine, she received the dose of promethazine and subsequently developed circulatory problems, followed by progressive gangrene which led to the amputation of her arm.[2]

Because of these potential risks, the product labeling states, "The preferred parenteral route of administration for promethazine injection is by deep intramuscular injection. The proper IV administration of this product is well-tolerated, but use of this route is not without some hazard. Not for subcutaneous administration."[3]

The Institute for Safe Medication Practices (ISMP) recommends the following strategies to prevent or minimize tissue damage when administering IV promethazine.[2,4,5]

- **Limit concentration:** The highest concentration of promethazine that can be given IV is 25 mg/mL. ISMP recommends that hospitals stock only this concentration (not the 50 mg/mL concentration).
- **Limit the dose:** Consider 6.25 to 12.5 mg as the starting dose. These smaller doses have proven to be effective in many patients, while reducing extravasation risks.
- **Dilute the drug:** Further dilution in a running IV or in a mini bag can reduce vesicant effects and enable slow administration, which can allow extravasation to be recognized more quickly. For example, dilute in 10 to 20 mL of 0.9% sodium chloride.
- **Use large patent veins:** Give the medication only through a large-bore vein (preferably via central access) and avoid hand or wrist veins. Check patency of the access site before administration.
- **Inject into the farthest port:** Administer through a running IV line at the port farthest from the patient's vein.
- **Administer slowly**: Consider running over 10 to 15 minutes, but with close monitoring for extravasation effects.
- **Revise orders:** Revise pre-printed orders to ensure orders for promethazine reflect safety measures.
- **Educate patients:** Before administration, tell patients to alert a healthcare professional immediately if they experience burning or pain during or after the injection.
- **Create alerts:** Each time a dose of IV promethazine is accessed and administered, the nurse should be reminded that the drug is a vesicant and should be diluted and administered slowly.
- **Use alternatives:** Consider ondansetron, a serotonin receptor antagonist that may be used for both prophylaxis and as a rescue antiemetic.
- **Remove from formulary:** Some hospitals have banned IV use of promethazine or removed the drug from the formulary.

There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Partial success has been seen in case reports with elevation of the injection site, corticosteroid therapy, stellate ganglion blockade, and pain control.[6] Other practitioners have used hyaluronidase, nitroglycerin ointment or patch, or dimethyl sulfoxide (DMSO). However, none of these have been studied in promethazine extravasation for which the effects can be catastrophic and often irreversible.[5,7-9]

Here at MUSC, the IV push guidelines specify an administration rate not to exceed 25 mg/min. Promethazine **must** be diluted with 10 to 20 mL of either 0.9% sodium chloride or dextrose 5% in water prior to administration. It should be administered through a large bore vein and the patency of access should be checked before administration. The adult IV push medication administration guidelines can be found on the *MUSC Formulary and Drug Information Resources* Web page under the Nursing and Pharmacy tabs. (www.formularyproductions.com/musc)

Alerts are posted on the promethazine profile in the Acu-Dose-Rx™ cabinets and on the MAR so that the nurse is reminded of the requirements prior to administration.

References available upon request.

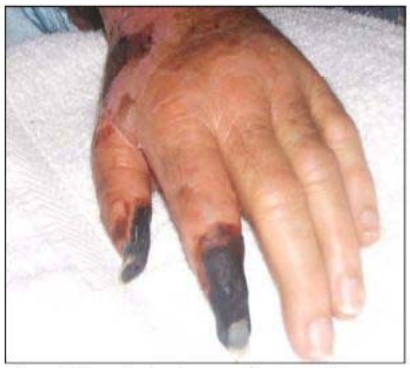

Figure 2. Promethazine Extravasation Causes Gangrene in Man's Fingers. Image provided courtesy of ISMP.

Did You Know…
Automatic Therapeutic Substitution (ATS) at MUSC

With the rising costs of healthcare across the United States, hospital systems are looking for methods to decrease medication costs through better formulary management. The desire to decrease hospital expenditures, though, must never overshadow the universal healthcare goal of maintaining patient safety. One common practice that is able to appease both goals of the healthcare system is therapeutic interchange (TI), also known as automatic therapeutic substitution (ATS).

The American College of Clinical Pharmacy (ACCP) Guidelines for Therapeutic Interchange define TI as the dispensing of a drug that is therapeutically equivalent to, but chemically different from, the drug originally prescribed by a physician or other authorized prescriber. The use of therapeutic substitution has grown recently because of an increase in the number of drugs within the same therapeutic class and the need to decrease healthcare costs while providing high-quality standards of care.

In the ATS process, a pharmacist reviews a physician order and determines if a formulary substitution can be made according to the appropriate protocol. Next, the pharmacist enters the order and documents "automatic therapeutic substitution" in the inpatient pharmacy services computer system (eMeds). The pharmacist then completes the documentation by adding a pre-printed automatic therapeutic substitution sticker to the patient's chart indicating the change of medication. Under computerized provider order entry (CPOE), a therapeutically equivalent formulary alternative appears as a choice when a nonformulary medication that falls under an ATS protocol is entered. If the prescriber does not chose the formulary alternative, the pharmacist will make the conversion based on the protocol.

A mechanism does exist to bypass the ATS protocol if the prescriber deems a specific medication clinically necessary. If the prescriber specifically wants a nonformulary medication, he or she must provide a clinical justification and enter into the comments field or write "DAW" or "dispense as written" on the actual order.

The Pharmacy and Therapeutics Committee (P&T Committee) makes decisions concerning medications potentially appropriate for substitution. Currently, 16 protocols have been approved and implemented by the P&T Committee. Recent changes among the ATS protocols include the addition of a new protocol for venlafaxine (Effexor®) orders and the inclusion of bupropion hydrobromide (Aplenzin®) to the current bupropion protocol. Future protocols may include conversions for angiotensin receptor blocking agents and the newly added carbapenem, doripenem (Doribax®). A list of current protocols can be found in the table below. Specific details regarding each of the ATS protocols can be located on the *MUSC Formulary and Drug Information Resources* Web page (www.formularyproductions.com/musc).

Table 1. MUSC Automatic Therapeutic Substitution Protocols

- Albuterol/ipratropium nebulization solution (DuoNeb®)
- Angiotensin converting enzyme (ACE) inhibitors
- Bupropion (Wellbutrin® IR; Wellbutrin® XR; Aplenzin®)
- Escitalopram (Lexapro®)
- Ferrous sulfate products
- Fluoroquinolone antibiotics
- Fluticasone (Flovent® HFA) to Beclomethasone (QVAR®)*
- H_2-antagonists
- Insulin products (selected)
- Intranasal steroids
- Levalbuterol (Xopenex®)
- Nonsedating antihistamines
- Paliperidone (Invega®)
- Polyethylene glycol (MiraLax®)
- Proton pump inhibitors (PPIs)
- Venlafaxine immediate release (Effexor®) and extended release (Effexor® XR)

* Only for patients that require treatment while on mechanical ventilation, have a tracheotomy tube, or require a large volume spacer

FORMULARY UPDATE FOR JUNE & JULY 2009

In June and July 2009, the Pharmacy and Therapeutics Committee approved the actions listed below. The changes are considered formulary effective unless otherwise stated .

Additions:

Doripenem (Doribax®)

It was recommended that *doripenem* be added to the formulary and *meropenem* be **RESTRICTED** to the following services/indications: pediatrics, infectious diseases, hematology/oncology, and in those patients with suspected or documented meningitis. Guidelines for doripenem dosing, as well as an automatic therapeutic substitution program will be developed and implemented in the near future. The projected effective date is **October 1, 2009**.

500-mg vials

Sodium Phosphate (monobasic monohydrate/ dibasic anhydrous) [OsmoPrep®]

OsmoPrep® is a prescription product indicated for colonoscopy preparation that has been proven to be non-inferior to PEG electrolyte solutions (ie, Colyte®, GoLYTELY®) and is preferred by patients. Until smaller-volume, oral NaP solutions become available, OsmoPrep® will be temporarily added to the formulary.

Tablets (Sodium phosphate monobasic monohydrate 1.102 g, sodium phosphate dibasic anhydrous 0.398 g)

Benzocaine OSP 20% (Dermoplast®)

Dermoplast® is indicated for the temporary relief of pain and itching due to minor skin irritations. It is also commonly used for the relief of pain from episiotomy. It is significantly cheaper than Epifoam®, and the addition of hydrocortisone offers no further pain relief. Therefore, Dermoplast® was added for pain relief from episiotomy, and Epifoam® will be removed.

60-mL spray can

Esomeprazole (Nexium®)

Esomeprazole is indicated for the treatment of acid-related disorders in adults and pediatric patients (>1 year). Esomeprazole will be added to the formulary as the proton pump inhibitor of choice for all patient populations (ie, adult, pediatric, neonate), and pantoprazole, omeprazole, and lansoprazole will be deleted. The intravenous formulation will be restricted per clinical guidelines and the order form. The automatic therapeutic substitution protocol will be updated to reflect this change. The projected effective date is **October 1, 2009**.

20- and 40-mg delayed-release capsules, 10-, 20-, 40-mg delayedrelease powder for suspension, 20-, 40-mg injection

Hydroxyethyl starch 130/0.4 in NS (Voluven®)

Hydroxyethyl starch 130/0.4 in NS (Voluven®) is a volume expander for the prevention/ treatment of hypovolemia. The newer generations of starches (ie, Voluven®) have several potential advantages over hetastarches: less plasma accumulation, faster clearance from the body, similar infusion rates/volumes despite increased clearance, less effect on coagulation parameters, and the potential for less use of replacement blood products.

500-mL IV solution

Addition of Restriction:

Insulin U-500

Due to the potential for medication errors, insulin U-500 will be restricted to the Diabetic Management Service.

Changes in Restrictions:

Meropenem (Merrem®)

Meropenem will now be restricted to the following services and/or indications: pediatrics, infectious diseases, hematology/oncology, and in those patients with suspected or documented meningitis. The projected effective date is **October 1, 2009**.

Ketamine

A pre-printed order form was approved with dosing guidelines for the use of ketamine continuous infusions outside of the ICU setting. It will primarily be used in major gastrointestinal/thoracic postoperative patients with high opioid requirements. The ketamine restriction will be updated to the following:

- Attending physicians from the anesthesiology or oral/maxillofacial surgery services ***OR***
- Patient location: emergency department, ICU ***OR***
- Outside of ICU setting: Regional Anesthesia Pain Service (RASP) for use in gastroin-

FORMULARY UPDATE FOR JUNE & JULY 2009

testinal/thoracic postoperative patients with high opioid requirements. *Order form will be required.*

The projected effective date is **October 1, 2009**.

Exclusions:

6% hetastarch in LR (Hextend®)

Hextend® does not offer a significant advantage over the current hetastarch product.

Automatic Therapeutic Substitution (ATS) Protocol Addition:

Venlafaxine extended release tablets

Venlafaxine immediate release tablets are no longer used clinically and venlafaxine extended release (generic) tablets are not therapeutically equivalent (not AB-rated) to brand Effexor® XR; therefore, they cannot be automatically substituted without a prescriber's order. An automatic substitution protocol has been developed for the conversion of orders for venlafaxine immediate release and Effexor® XR tablets.

Change in ATS Protocol:

Bupropion hydrobromide (Aplenzin®)

The ATS protocol for bupropion was revised to include conversions for bupropion hydrobromide (Aplenzin®) orders. These orders will be switched to bupropion hydrochloride sustained release (SR) based on the dose, unless the physician indicates "dispense as written" and includes a clinical justification on the order.

Line Extensions:

- Diphenhydramine (Benadryl®) 25-mg tablets
- Gadobenate dimeglumine (Multihance®) 10-, 15-, and 20-mL vials
- Diphenhydramine (Benadryl®) elixir 12.5-mg/5-mL unit-dose cups
- Venlafaxine extended release 225-mg tablets
- Esmolol (Brevibloc®) 2-g/100 mL premix IV solution **(October 1, 2009)**
- Haloperidol (Haldol®) 2-mg/mL (5 mL) unit-dose cups
- Wheat dextrin powder (Benefiber®) 3-g/3.5-g unit-dose stick packs

Deletions:

- Pramoxine/hydrocortisone 1% (Epifoam®)
- Gadobenate dimeglumine (Multihance®) 50- and 100-mL vials
- Albuterol (Ventolin®) 200-dose inhaler
- Carmustine (Gliadel®) 7.7-mg wafer
- Esmolol injection 10-mg/mL vial and 1-g/100-mL premixed IV solution **(October 1, 2009)**
- Hydroxyzine pamoate (Vistaril®) suspension
- Theophylline sustained release (Slo-Bid®) 125-, 200-, and 300-mg capsules
- Pantoprazole (Protonix®) 20- and 40-mg tablets; 40-mg injection; 2-mg/mL extemporaneous suspension **(October 1, 2009)**
- Lansoprazole (Prevacid®) 15- and 30-mg capsules; 3-mg/mL extemporaneous suspension **(October 1, 2009)**
- Omeprazole (Prilosec®) 2-mg/mL extemporaneous suspension **(October 1, 2009)**

Intralipid Guidelines for Treatment of Anesthetic-induced Cardiotoxicity

The P&T Committee approved the guidelines for use of intralipid 20% to reverse anesthetic-induced cardiotoxicity. The guidelines have been posted in the various operating room areas where the 500-mL bottles of intralipid 20% are stored. Guidelines can also be found online* on the *Formulary and Drug Information Resources* Web page and on the Clinician Order Forms page under the OR section.

Policy C82: Formulary System

The Pharmacy Services policies regarding drug recall and shortage procedures will be formally added to the C-82 policy. Additionally, the criteria for medications restricted to clinic use was clarified to indicate that a patient must be discharged from the hospital and registered in an outpatient clinic before a restricted medication will be dispensed. Please refer to the *Formulary and Drug Information Resources* Web page for specific criteria.

Teatment/reversal of Anticoagulant-associated Intracranial Hemorrhage

Guidelines and a pre-printed order form regarding the treatment of anticoagulant-associated intracranial hemorrhage using IV vitamin K, factor IX complex (Profilnine®), or fresh-frozen plasma (FFP) were developed. These will be available through the clinician order forms site after approval by the Forms Committee.

Intralipid Guidelines: http://www.musc.edu/pharmacyservices/medusepol/IntralipidGuidelinesCardioAnesth.pdf
Formulary and Drug Information Resources Web page: www.formularyproductions.com/musc