

Medication Safety Update

CONTRAST AGENTS AND RISK OF NEPHROGENIC SYSTEMIC FIBROSIS

The FDA recently released a warning regarding the potential development of Nephrogenic Systemic Fibrosis (NSF) following the use of gadolinium-based contrast agents (GBCAs) marketed as gadopentetate dimeglumine (Magnevist®), gadobenate dimeglumine (MultiHance®), gadodiamide

(Omniscan®), gadoversetamide (OptiMARK®), and gadoteridol (ProHance®). NSF is a highly debilitating and potentially fatal disease that is associated with renal insufficiency. Therefore, manufacturers of these products are required to add new boxed warnings to reflect this development. In light of

these changes, The Medical Center has adopted new policies and procedures regarding the use of GBCAs that are included as an insert in this issue of the *Pharmacy Bulletin*.

Nephrogenic Systemic Fibrosis was recently identified in 1997 in patients with acute or

continued on page 4

*Diluted
promethazine
administered slowly
allows for quick
discontinuation if
extravasation
occurs*

Therapy Update

PROMETHAZINE (PHENERGAN) IV SAFETY ISSUES

Intravenous promethazine is a chemical irritant which is highly caustic to blood vessels and surrounding tissue that may lead to an injection site reaction. Manifestations of this reaction include thrombophlebitis, tissue necrosis, nerve damage, muscle paralysis

and gangrene. These reactions usually occur due to medication extravasation or inadvertent intra-arterial injection. These complications are often severe enough to lead to surgical intervention including fasciotomy, skin graft, and even amputations. Patients should be

monitored for signs and symptoms of local injury such as severe skin irritation including burning, pain, erythema, swelling, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and

continued on page 2

FDA Fast Facts

GUAIFENESIN PRODUCTS

The FDA has revealed its intent to take action against companies that market unapproved timed-release dosage forms of guaifenesin products. Mucinex®, Mucinex-D®, Mucinex-DM®, and Humibid® are the only FDA approved timed-release guaifenesin products. Companies marketing unapproved products are expected to stop manufacturing them within 90 days and must cease shipping them within 180 days. This action does not affect products containing guaifenesin in immediate release forms.

PREGABALIN (LYRICA®)

The FDA approved pregabalin as the first drug for use in fibromyalgia, a disorder characterized by pain, fatigue, and sleep problems. Studies have shown that such patients have decreased pain after taking pregabalin, but the mechanism by which it produces such an effect is unknown. Pregabalin is already approved for treating partial seizures, postherpetic neuralgia, and diabetic neuropathy.

DEFERASIROX SAFETY

Novartis has changed the Warnings and Adverse Reactions sections of product labeling due to cases of acute renal failure, some with a fatal outcome, following post marketing use of deferasirox (Exjade®).

Deferasirox is a medication that is used for patients with iron overload. There were post marketing reports of agranulocytosis, neutropenia and thrombocytopenia, leukocytoclastic vasculitis, urticaria, and hypersensitivity reactions.

INSIDE THIS ISSUE

ADRs	Page 1
FDA Fast Facts	Page 1
Promethazine	Page 1,2
Contrast Agents	Page 1,4
Formulary Changes	Page 2,3
Atomoxetine	Page 3
Protocol for Radiology	Insert

Therapy Update

PROMETHAZINE, CONTINUED FROM PAGE 1

gangrene. While the rate of infusion may not be directly associated with the tissue damage that results from extravasation, a dilute drug administered slowly allows for quick discontinuation of the drug if extravasation does occur.

For these reasons, promethazine should be given intramuscularly (IM), rectally or orally if the patient is able to tolerate these routes of administration. If intravenous (IV) promethazine is necessary, the starting dose should be limited to 6.25 mg to 12.5 mg instead of the current standard of 25 mg. After initiation, promethazine doses should be adjusted to the lowest effective dose. Therapy should be switched to the oral formulation as soon as possible to prevent the potential occurrence of these severe adverse reactions.

Ondansetron is an alternative that may be used for both prophylaxis and as a rescue antiemetic. It is available as an IV infusion, oral tablet, and also as an orally disintegrating tablet which does not require water for swallowing. An appropriate starting dose for ondansetron is 4 mg IV every 8 hours. No dosage adjustment is needed for patients with renal impairment, however the dose should not exceed 8 mg/day IV or orally in patients with severely impaired hepatic function. Ondansetron is well tolerated in both adults and children, with headache being the most reported adverse event. Other rare adverse events include extrapyramidal reactions, transient elevations in hepatic enzymes, angina with ECG alterations, anaphylactic reactions, and transient blindness.

If promethazine is to be administered IV, safety can be improved by diluting IV promethazine with 10 mL of normal saline and pushing slowly over 5 minutes. It should be injected through a running IV line at the port furthest from the patient's vein, and only through large-bore veins or a central line. Nurses should ask the patient to report any burning or pain during and after administration, and stop the infusion immediately if the patient reports discomfort.

These guidelines should help to prevent adverse sequelae associated with promethazine use.

Lindsay Matzenger, PharmD
Clinical Pharmacist

Medication Safety Update

NALOXONE MEDICATION USAGE EVALUATION

Results of a recent Medication Use Evaluation involving the use of naloxone were reviewed by the Pharmacy and Therapeutics Committee. Naloxone is FDA approved for use in complete or partial reversal of opioid depression and in opiate agonist overdose. Naloxone should be given at doses of 0.4—2 mg IV, IM, or SC,

up to a total dose of 10 mg and may be repeated every 2—3 minutes, as needed for reversal of opioid depression. Monitoring should include heart rate, respiratory rate, and blood pressure. At present, there are inadequate data to support the use of naloxone for non-FDA approved indications. Other non-FDA approved uses

include reversal of the effects of ethanol and benzodiazepines, reversal of hypotension associated with spinal injury, improvement of neurologic recovery after ischemic stroke, treatment of hypercapnic COPD, and pruritus. As of yet, data do not support the use of naloxone for these non-FDA approved indications.

Policy Update

FORMULARY CHANGES

Gadopentetate dimeglumine (Magnevist®) is a gadolinium based MRI contrast that has been added to the formulary for patients with stage 3,4, or 5 chronic kidney disease after a radiologist's approval. Gadodiamide (Omniscan®) will remain on the formulary for the majority of patients. See accompanying article describing gadolinium based MRI policy change.

Esomeprazole (Nexium®) is a proton pump inhibitor that has been added to the formulary for patients with nasogastric (NG) tubes. Esomeprazole is FDA approved for administration via NG tube due in part to its smaller pellet size compared to lansoprazole and omeprazole capsules. Esomeprazole capsules can be opened and the intact granules emptied into a 60 mL syringe, mixed with 50 mL of water, and shaken

vigorously for 15 seconds after replacing the plunger. The syringe should be held with the tip up and checked for granules remaining in the tip. After attaching the syringe to NG tube and administering the granules, the NG tube should be flushed with additional water. The pellets should not be administered if they have dissolved or disintegrated. The suspension must be used immediately after preparation.

Tenecteplase (TNKase®) has been added to the formulary and will replace reteplase

on the acute myocardial infarction (AMI) order set (included in Pharmacy Bulletin). Tenecteplase is a thrombolytic agent that is easier to administer than reteplase requiring only one bolus dose over 5 seconds as compared to two doses of reteplase. The dose of tenecteplase is based on the patient's weight (See Table 1). Alteplase will continue to be used for stroke, pulmonary embolism, and catheter occlusion (as Cathflo®). Reteplase has now been removed from the formulary.

TABLE 1: TENECTEPLASE WEIGHT-BASED DOSING

Patient weight (kg)	Tenecteplase (mg)
Less than 60	30
60 or more but less than 70	35
70 or more but less than 80	40
80 or more but less than 90	45
90 or more	50

continued on page 3

Medication Safety Corner

HEPATOTOXICITY WITH ATOMOXETINE (STRATTERA®)

Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor that produces therapeutic effects in patients with Attention-Deficit/Hyperactivity Disorder (ADHD). The exact mechanism of action for atomoxetine remains unknown.

Atomoxetine's adverse drug reaction (ADR) profile in adults and pediatrics includes nausea/vomiting (10 - 30%), anorexia or decrease in appetite (2% - 14%), and dizziness (6%). Other adverse reactions reported in pediatrics include dyspepsia (4 - 8%), fatigue (up to 9%), and emotional lability (2 - 5%). In adults, additional common ADRs were constipation (10%), xerostomia (21%), insomnia (16%), libido decrease (6%), ejaculation dysfunction (5%), impotence (erectile dysfunction) (3%), urinary retention or hesitancy (8%), and dysmenorrhea (7%).^{1,2} Previous studies in 6000 patients did not reveal any signs or symptoms of liver injury associated with atomoxetine.³

Post-marketing reports have included rare cases of serious liver disease.¹ On December 17, 2004, the FDA issued a warning about severe liver injury after two reports in patients who had been treated for several months with atomoxetine. The FDA statement included a request that the manufacturer (Eli Lilly) add a bolded warning about severe liver injury to the product's labeling. Following the warning, the company also updated the patient package insert with information about the signs and symptoms of liver problems, which include pruritus, jaundice, dark urine, upper right-sided abdominal tenderness, or unexplained "flu-like" symptoms.⁴

A primary literature search revealed that there have been 3 case reports of hepatotoxicity associated with atomoxetine administration since the FDA-issued warning in 2004. Two case reports of children indicated that acute hepatitis occurred after starting therapy with

atomoxetine and improved after withdrawal of the medication. The causality assessment was reported using the Rousel Uclaf Causality Assessment Method with the first case being probable and the second case having a score of 2 (causally not related to atomoxetine).⁵ A third case report described an 8 year old child who experienced severe acute hepatitis. The association of the hepatitis and atomoxetine was evaluated with the International Organization of Medical Science Diagnostic Scale and the Naranjo scale and reported as "probable".⁶

Although hepatotoxicity has not been reported as a percentage in previous clinical trials, post-marketing case reports and an FDA warning indicate that hepatotoxicity is a rare but serious adverse event associated with atomoxetine.

Ashley Mehaffie, Pharm D
Clinical Pharmacist

FORMULARY CHANGES, continued from page 2

Lidocaine (Lidoderm®) patches have been added to the formulary for use in refractory neuropathic pain. Lidocaine (Lidoderm®) patches should be applied topically to painful areas for up to 12 hours in a 24 hour period.

Tdap (ADACEL™), a vaccine for tetanus, diphtheria, and pertussis, has been added to the formulary for adults age 11-64, including health care workers, who have direct contact with infants <12 months of age. The Infection Control Committee has recommended that Employee Health provide employees that are in contact with infants <12 months of age with Tdap beginning July 2007.

Therapeutic Interchange Policy Update

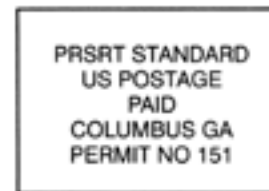
The formulations of liquid combination cough and cold products change frequently. Many manufacturers have replaced the pseudoephedrine decongestant with phenylephrine due to publicity regarding substance abuse and diversion. Many clinicians agree that at doses typically used, phenylephrine is less efficacious for congestion versus pseudoephedrine. Thus, after careful review of the various cough and cold

preparations, the P & T Committee approved the dispensing of equivalent pseudoephedrine containing combination cough and cold products. Please review the

Cough and Cold Preparation Interchange Chart provided (Table 2).

TABLE 2: THERAPEUTIC INTERCHANGE OF COUGH AND COLD LIQUID COMBINATION PRODUCTS

Ordered Medication	Pharmacy Will Dispense
pseudoephedrine 60mg, dextromethorphan 30mg, and brompheniramine 4mg (Anaplex DM® syrup)	dextromethorphan 15mg, pseudoephedrine 45mg, brompheniramine 4mg (Carbofed DM® syrup)
dextromethorphan 15mg, phenylephrine 6mg, and chlorpheniramine 2mg (Atuss DR® syrup)	dextromethorphan 15mg, pseudoephedrine 45mg, brompheniramine 4mg (Carbofed DM® syrup)
guaifenesin 200mg and dextromethorphan 20mg (Duratuss DM® syrup)	guaifenesin 100mg and dextromethorphan 10mg (HT-Tuss DM® syrup)
phenylephrine 12.5mg and chlorpheniramine 4mg (Rondec® syrup)	pseudoephedrine 45mg and brompheniramine 4mg (Bromaxefed RF® syrup)
dextromethorphan 15mg, phenylephrine 12.5mg, and brompheniramine 4mg (Rondec DM® syrup)	dextromethorphan 15mg, pseudoephedrine 45mg, and brompheniramine 4mg (Carbofed DM® syrup)
phenylephrine 3.5mg and chlorpheniramine 1mg (Rondec® drops)	pseudoephedrine 15mg and carbinoxamine 2mg (Andehist® drops)
dextromethorphan 3mg, phenylephrine 3.5mg, and chlorpheniramine 1mg (Rondec DM® drops)	dextromethorphan 4mg, pseudoephedrine 15mg, and carbinoxamine 1mg (Carbofed DM® drops)
dextromethorphan 25mg, pseudoephedrine 75mg, and dexchlorpheniramine 2.5mg (Tanafed DMX® syrup)	dextromethorphan 15mg, pseudoephedrine 45mg, and brompheniramine 4mg (Carbofed DM® syrup)
guaifenesin 150mg and codeine 5mg (Brontex® liquid)	guaifenesin 150mg and codeine 5mg (Guaifen-C® liquid)
phenylephrine 15mg, guaifenesin 100mg, and hydrocodone 3 mg (Pancof XP® syrup)	phenylephrine 7.5mg, hydrocodone 2mg, and diphenhydramine 12.5mg (Hydro DP® syrup)
phenylephrine 7.5mg, hydrocodone 2mg, and diphenhydramine 12.5mg (Endal HD® syrup)	phenylephrine 7.5mg, hydrocodone 2mg, and diphenhydramine 12.5mg (Hydro DP® syrup)



Drug Information Center
Columbus Regional Healthcare System
710 Center Street
Columbus, Georgia 31902

Phone: (706) 571-1934
Fax: (706) 571-1625

Editor, Pharmacy Bulletin
Coordinator, Drug Information
Lisa Boothby, PharmD, BCPS

Director, Department of Pharmacy Services
Burnis D. Breland, M.S., PharmD, FASHP

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GADOLINIUM BASED CONTRAST AGENTS

continued from page 1

chronic severe renal dysfunction (GFR < 30 mL/min/1.73m²), acute renal dysfunction due to hepato-renal syndrome, or following liver transplantation. NSF is a highly debilitating disease involving the skin, muscles, and internal organs. Patients may develop burning, itching sensations, reddened or darkened patches, hardening, tightening or swelling of the skin. Other organs affected include the eyes, which may exhibit yellow raised lesions associated with the sclera. When support structures are involved, patients may exhibit deep pain in hips and ribs, stiffness, or limited range of motion in articulated joints. Fibrosis may even spread beyond connective tissues to affect other organs. The time of onset following administration of GBCAs may vary from days to months. Confirmation of diagnosis is obtained via skin biopsy.

Development of NSF following administration of GBCAs can occur at any time following a single dose or multiple doses. The most common agent identified was gadodiamide (Omniscan[®]) followed by gadopentetate dimeglumine (Magnevist[®])

and gadoversetamide (OptiMARK[®]). Gadodiamide has also been implicated in combination with gadobenate dimeglumine (MultiHance[®]) and gadoteridol (ProHance[®]). The number of cases reported by agent may be associated with a greater emphasis on reporting by some companies. The FDA feels that information regarding adverse effects associated with GBCA use may be incomplete at this time.

In response to FDA suggestions, Imaging Services at The Medical Center has limited the use of gadolinium based agents. Any patient with stage 3, 4, or 5 chronic kidney disease (GFR < 59 mL/min/1.73m²) must obtain a radiologist's approval before receiving contrast media. If approved, stage 3 patients may receive a half-dose of gadopentetate dimeglumine (Magnevist[®]); however, patients with stage 4 or 5 chronic kidney disease will require hemodialysis following a magnetic resonance procedure. Patients with no renal impairment or with stage 1 or 2 chronic renal disease are not dose restricted do not require a radiologist's approval to receive

gadodiamide (Omniscan[®]). Current practice will be re-evaluated based upon the FDA's final analysis.

Christina Creech, PharmD
Candidate
Harrison School of Pharmacy

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