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MEDICATION SAFETY IN SECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

POSACONAZOLE AND POSSIBLE DOSAGE FORM CONFUSION

The Institute of Safe Medication Practices (ISMP) recently reported a dosing error that occurred with posaconazole as a result of product formulation confusion. A patient with acute myelogenous leukemia experiencing neutropenia following chemotherapy induction was prescribed "posaconazole 200 mg PO three times a day with meals" for prophylaxis against Aspergillus and Candida infections. Since no dosage form was specified, the patient received posaconazole 100 mg delayed-release tablets with instructions to take two tablets three times a day instead of posaconazole 200 mg/5 mL oral suspension three times daily as intended. However, posaconazole delayed-release tablets have a higher bioavailability than the oral suspension, and the patient received double the recommended dose specific to the delayed-release tablet formulation for 6 days until discovery of the error. The patient showed no signs of toxicity and was converted back to the originally intended oral suspension.

Posaconazole, an azole anti-fungal, has two new dosage formulations (delayed-release tablets and injection) with different indications for use and dosing regimens than the oral suspension (Table 1, Page 5). Confusion in prescribing one oral formulation over another may lead to dosing errors where toxic events (including QT prolongation and/or hepatotoxicity) may occur in at-risk patients receiving greater than the recommended dose. On the converse, subtherapeutic coverage for treatment of or prophylaxis against certain microorganisms may ensue if patients receive less than the recommended dose, putting them at risk for invasive infections. Sites offering both oral products should consider installing an alert at the point of order-entry that reminds providers of the different product formulations, dosing regimens, and indications in order to avoid any possible mix-ups with these agents.

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NEWSWORTHY...

from the pbm

- Acetaminophen Safety – 06/10/2014 - National PBM Bulletin

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IN THIS ISSUE:

VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

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from the fda

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MISCELLANEOUS

FDA Recommends Not Using Lidocaine to Treat Teething Pain and Requires New Boxed Warning
6/26/2014

As of December 2013, 22 cases of toxicity with the use of prescription oral viscous lidocaine 2 percent solution in infants and young children aged 5 months to 3.5 years were identified in FDA's Adverse Event Reporting System (FAERS) database (15 cases) and the medical literature (7 cases). Symptoms included seizures, severe brain injury, problems with the heart, and death. Of the 22 cases, 6 resulted in death; 3 were considered life-threatening; 11 required hospitalization; and 2 required medical intervention without hospitalization. Causes attributed to the adverse events included: overdose (7 of the 22 cases involved administration technique not according to prescriber directions or additional doses beyond what was prescribed, while 4 cases involved a prescribing error); and accidental ingestion (7 cases). The reported reasons for use of lidocaine in these 22 cases consisted of teething pain (n=5), oral stomatitis (n=6), fever blister (n=1), thrush (n=2), oral ulcer/lesion (n=3), and sore throat due to croup (n=1). In four cases, the reason for use was not reported. Onset of toxicity occurred after multiple doses of lidocaine in 11 of the 22 cases while 6 cases resulted in toxic effects after a single dose. Health care professionals should be aware that prescription viscous lidocaine solution is NOT approved by FDA to treat teething pain. Providers should advise parents and caregivers to follow the American Academy of Pediatrics' recommendations for treating teething pain, including using a chilled teething ring and/or gently rubbing or massaging the affected gum area for symptom relief. FDA requires a new Boxed Warning and revisions to the Warning and Dosage and Administration sections of the drug label to describe the risk of severe adverse events and to include additional instructions for dosing when the drug is prescribed for approved uses.

OVER-THE-COUNTER AGENTS

Rare But Serious Hypersensitivity Reactions with Certain Over-the-Counter Topical Acne Products
6/25/2014

From 1969 through January 28, 2013, FDA's Adverse Event Reporting System (FAERS) database accounted for 131 cases of hypersensitivity reactions resulting in serious outcomes associated with over-the-counter (OTC) topical acne drug products containing benzoyl peroxide or salicylic acid, including various brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveeno, Clean & Clear, and store brands available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs, and other formulations. Adverse reactions ranged from application site reactions (e.g., skin irritation, burning sensation, erythema, and dermatitis) to anaphylactic reactions (e.g., facial swelling, hives, angioedema, pruritus, flushing throat tightness and shortness of breath). While no fatalities occurred, 44 percent (n=58) of the cases resulted in hospitalization. In almost half of the cases, events occurred within minutes to 24 hours of product use. FDA continues to monitor this safety issue and recommends that healthcare providers should educate patients regarding:

- Symptoms of serious hypersensitivity reactions such as skin or mucosal changes as well as respiratory or cardiovascular changes (e.g., dyspnea, hypotension, or syncope) suggestive of anaphylaxis.
- Discontinuation of the product if a hypersensitivity reaction occurs and to seek emergency medical attention immediately if they develop symptoms suggestive of anaphylaxis.
- Sensitivity testing for new users of OTC topical acne drug product that involves applying a small amount to one or two small affected areas for 3 days to ensure against any hypersensitivity symptoms. If no discomfort occurs, patients can use as directed on the Drug Facts label.

CARDIOLOGY

Cardiovascular Risks for Diabetics Taking Olmesartan Not Conclusive; Label Updates Required
6/24/2014

The ROADMAP (**R**andomized **O**lmes**A**rtan and **D**iabetes **M**icro**A**lbuminuria **P**revention) trial and ORIENT (**O**lmesartan **R**educing **I**ncidence of **E**nd Stage Renal Disease in Diabetic **N**ephropathy **T**rial) suggested that high-dose olmesartan may increase cardiovascular (CV) risk in diabetic patients. These findings led FDA to examine other studies such as observational studies involving data from Medicare as well as the Clinical

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from the fda

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Practice Research Datalink (CPRD), a manufacturer-conducted patient-level meta-analysis, and an observational study conducted by the manufacturer. FDA's safety review did not show clear evidence of increased CV risks associated with the use of olmesartan in patients with diabetes. As such, recommendations for use of olmesartan (Benicar, Benicar HCT, Azor, Tribenzor, and generics) will remain the same, but FDA will require that the drug labels include information reflecting the findings of some of these studies.

ONCOLOGY

Docetaxel May Cause Symptoms of Alcohol Intoxication after Treatment

6/20/2014

FDA is revising product labels to reflect cases of alcohol intoxication reported with some formulations of the chemotherapeutic agent docetaxel (Taxotere, Docefrez, and Docetaxel Injection) due to the alcohol (ethanol) content. FDA's Adverse Event Reporting System (FAERS) database and evidence in the medical literature documents three cases of alcohol intoxication temporally associated with docetaxel. According to FDA review, alcohol intoxication occurred during infusion in two cases and within 24 hours of drug administration in the other case. Symptoms of alcohol intoxication appeared transient in one patient while another experienced symptoms that resolved in time to complete his treatment using a slower infusion rate.

FDA provides a list of docetaxel formulations and respective alcohol (ethanol) content. The products contain various amounts of alcohol in order to dissolve the active ingredients to allow for intravenous administration.

Product	Manufacturer	Alcohol (ethanol) content (grams) in 200 mg dose*
Docetaxel Injection	Pfizer	6.4
Docetaxel Injection	Sandoz	5.5
Docetaxel Injection	Accord	4.0
Docetaxel Injection	Actavis	4.0
Taxotere one vial formulation	Sanofi	4.0
Docetaxel Injection	Hospira	3.7
Docefrez	Sun Pharma	2.9
Taxotere two vial formulation	Sanofi	2.0

**Assumes maximum dose of 100 mg/m^2, body surface area = 2.0 m^2*

According to the FDA, providers should:

- Consider the alcohol content of docetaxel when prescribing or administering the drug to patients, particularly in those with:
  - alcohol use.
  - concomitant use of other medications that can affect the central nervous system.
  - hepatic impairment.
- Choose a docetaxel formulation with the least amount of alcohol for patients who experience adverse reactions.
- Reduce the infusion rate during administration to help resolve symptoms of alcohol intoxication.
- Monitor patients for signs of alcohol intoxication during and after treatment.
- Counsel patients about the possible effects of intoxication due to the alcohol content in docetaxel, and caution to avoid driving, operating machinery, or performing other dangerous activities for one to two hours after the infusion of docetaxel.

Getting the most from our safety surveillance

LOOK-ALIKE CONFUSION: LIDOCAINE AND RANIBIZUMAB

In one facility, look-alike confusion occurred between a vial of preservative-free lidocaine (Xylocaine) 2% and a vial of ranibizumab (Lucentis) due to likeness in product casing. In this instance, a provider inadvertently administered 0.05 milliliters (mL) of preservative-free lidocaine (Xylocaine) 2% via intravitreal injection instead of the intended ranibizumab (Lucentis) for treatment of a patient's age-related macular degeneration (AMD). The patient experienced no adverse outcomes as a result of this error.

Two factors contributed to this look-alike error. These include:

- Similarity in packaging – Both product vials share the same size and blue lid color although the labels bear a different design (see Figure 1). Ranibizumab (Lucentis) 0.5 mg (NDC 50242-080-01) comes in a single-use, 2-mL glass vial with a blue cap designed to deliver 0.05 mL of 10 mg/mL ranibizumab. Lidocaine hydrochloride injection, solution (Xylocaine) – MPF (NDC 63323-495 -27) also is available as a single-use, 2-mL glass vial with a blue cap containing 2% (20 mg/mL) lidocaine for infiltration and nerve block including caudal and epidural use.
- Preparation process – A technician lays out all instruments and medications needed for the ocular procedure in a side-by-side manner on a table adjacent to the exam chair. The provider then performs the procedure (selecting from the medications and other materials in close arrangement) injecting subconjunctival lidocaine followed by eyelid speculum placement and administration of the intravitreal anti-vascular endothelial growth factor (VEGF) agent.

Since the error entailed selection of the wrong vial, the medical center implemented a new procedure to reduce the potential for future mix-up of these agents. This process improvement involves the technician setting up the instruments and lidocaine only, leaving the ranibizumab vial to remain in the manufacturer's box. The provider will then inject lidocaine subconjunctivally and discard the vial of anesthetic immediately in a sharps container. Afterwards, the provider will remove the anti-VEGF agent from the box and administer the intravitreal injection.

Ranibizumab is an angiogenesis inhibitor, while lidocaine is a local anesthetic and class 1b antiarrhythmic drug. As a monoclonal antibody against proliferation of abnormal blood vessels in the retina stimulated by vascular endothelial growth factor, ranibizumab may prevent and reverse vision loss caused by macular degeneration. If a patient does not receive their regular scheduled dose of ranibizumab, loss of visual acuity benefit may occur. Furthermore, adverse events associated with intraocular injection of lidocaine include increase of intraocular pressure, corneal haze, and transient electroretinography changes which may contribute to reduced function. Of note, published literature reporting a case of inadvertant intravitreal injection of unpreserved lidocaine showed no adverse or toxic effects.

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1. *Internal data.*
2. LUCENTIS (ranibizumab) product package insert. South San Francisco, CA: Genentech, Inc.; February 2014.
3. XYLOCAINE MPF (lidocaine hydrochloride injection, solution) product package insert. Schaumberg, IL: APP Pharmaceuticals LLC; May 2011.
4. Massaoutis P, Niskopoulou M, Tufail A. Inadvertent Intravitreal Injection of 0.1mls of Unpreserved Lidocaine 2%. *The Internet Journal of Ophthalmology and Visual Science*. 2007; 6 (1). http://ispub.com/IJOVS/6/1/8509 . (Accessed July 28, 2014).
5. Doat M, Pierre-Khan V, Bejjani RA, Bourges JL, Renard G, Chauvaud D. Inadvertent intravitreal lidocaine injection following subcutaneous palpebral anesthesia: retinal toxicity of lidocaine? *Journal Francais D'ophtalmologie* . 2006; 29(2):176-180.
6. Schechter RJ. Management of inadvertent intraocular injections. *Ann Ophthalmol.* 1985 Dec; 17(12):771-5.

PROVIDER RECOMMENDATIONS

- **Providers should be aware of the potential for look-alike confusion between 2% (20 mg/mL) lidocaine hydrochloride (Xylocaine) injection (2 mL single dose vial) and 0.5 mg ranibizumab (Lucentis) injection (2 mL single-use vial) due to similar vial size and lid color.**
- **Providers should carefully check the name on the vial when either 2% (20 mg/mL) lidocaine hydrochloride (Xylocaine) injection (2 mL single dose vial) and 0.5 mg ranibizumab (Lucentis) injection (2 mL single-use vial) is ordered and/or administered.**
- **Pharmacy should review their stock for 2% (20 mg/mL) lidocaine hydrochloride (Xylocaine) injection (2 mL single dose vial) and 0.5 mg ranibizumab (Lucentis) injection (2 mL single-use vial), and ensure that a method is in place to distinguish between the two agents in order to avoid future look-alike confusion (i.e., warning stickers/labels, separate product placement on shelves).**
- **Pharmacy should ensure that a system is in place to notify providers regarding the potential for look-alike confusion between 2% (20 mg/mL) lidocaine hydrochloride (Xylocaine) injection (2 mL single dose vial) and 0.5 mg ranibizumab (Lucentis) injection (2 mL single-use vial) to reduce the potential for medication error.**

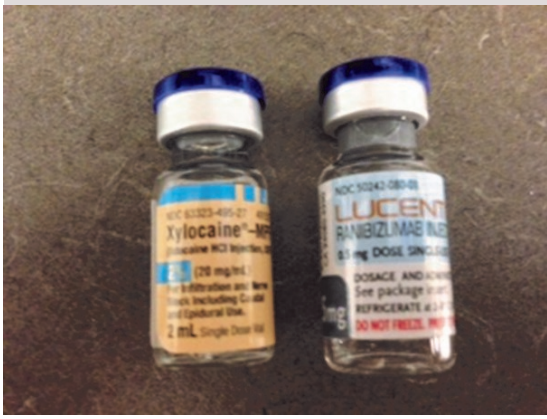

Figure 1. Vial resemblance contributes to a look-alike error at one site.

POSACONAZOLE AND POSSIBLE DOSAGE FORM CONFUSION

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Table 1. Indication, Dosage, and Administration of Posaconazole Based on Formulation

FORMULATION	INDICATION	DOSE AND DURATION OF THERAPY
Posaconazole Oral Suspension	Prophylaxis of invasive *Aspergillus* and *Candida* infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.
	Oropharyngeal Candidiasis	Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days.
	Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.
Posaconazole Delayed-Release Tablets	Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.
Posaconazole Injection	Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg Posaconazole injection intravenously twice a day on the first day. Maintenance dose: 300 mg Posaconazole injection intravenously once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

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1. Noxafil® (posaconazole) product package insert. Whitehouse Station, NJ: Merck & Co., Inc.; March 2014.
2. Institute for Safe Medication Practices. Posaconazole dose depends on doage form. *ISMP Medication Safety Alert! Acute Care*. 2014; 19(10): 3-4. ■