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 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.

(continued on page 5)
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 products 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 (Randomized OlmesArtan and Diabetes MicroAlbuminuria Prevention) trial and ORIENT (Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial) 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 (continued on page 3)
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.

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Alcohol (ethanol) content (grams) in 200 mg dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel Injection</td>
<td>Pfizer</td>
<td>6.4</td>
</tr>
<tr>
<td>Docetaxel Injection</td>
<td>Sandoz</td>
<td>5.5</td>
</tr>
<tr>
<td>Docetaxel Injection</td>
<td>Accord</td>
<td>4.0</td>
</tr>
<tr>
<td>Docetaxel Injection</td>
<td>Actavis</td>
<td>4.0</td>
</tr>
<tr>
<td>Taxotere one vial formulation</td>
<td>Sanofi</td>
<td>4.0</td>
</tr>
<tr>
<td>Docetaxel Injection</td>
<td>Hospira</td>
<td>3.7</td>
</tr>
<tr>
<td>Docefrez</td>
<td>Sun Pharma</td>
<td>2.9</td>
</tr>
<tr>
<td>Taxotere two vial formulation</td>
<td>Sanofi</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Assumes maximum dose of 100 mg/m², body surface area = 2.0 m²

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.
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 electoretinography changes which may contribute to reduced function. Of note, published literature reporting a case of inadvertent intravitreal injection of unpreserved lidocaine showed no adverse or toxic effects.

REFERENCES:

1. Internal data.

Figure 1. Vial resemblance contributes to a look-alike error at one site.
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**POSACONAZOLE AND POSSIBLE DOSAGE FORM CONFUSION**

(continued from page 1)

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

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>INDICATION</th>
<th>DOSE AND DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole Oral Suspension</td>
<td>Prophylaxis of invasive <em>Aspergillus</em> and <em>Candida</em> infections</td>
<td>Loading dose: 200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days.</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal Candidiasis</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole</td>
<td>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.</td>
</tr>
<tr>
<td>Posaconazole Delayed-Release Tablets</td>
<td>Prophylaxis of invasive <em>Aspergillus</em> and <em>Candida</em> infections</td>
<td>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.</td>
</tr>
<tr>
<td>Posaconazole Injection</td>
<td>Prophylaxis of invasive <em>Aspergillus</em> and <em>Candida</em> infections</td>
<td>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.</td>
</tr>
</tbody>
</table>

**REFERENCES:**
