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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

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) AND LIMB THROMBOSIS ASSOCIATED WITH HEPARIN-COATED CATHETERS OR DEVICES

A recent Institute for Safe Medication Practices (ISMP) alert describes an adverse event of heparin-induced thrombocytopenia (HIT) resulting from a heparin-coated wire and catheter inserted into a patient's venous access site during a radiology procedure. About a week after the procedure, the patient developed thrombocytopenia and tested positive for HIT. Since a diluted heparin solution was used to coat the wire and catheter to reduce the risk of clotting, no documentation of heparin administration was listed in the patient's records because the radiologist had not "prescribed" the heparin and the patient did not receive a typical measured heparin dose. As such, the patient's physician concluded that the HIT result was a false positive and discharged the patient with an order for follow-up lab testing. The patient subsequently experienced thrombosis in his left arm and required partial amputation.

HIT is associated with significant morbidity and mortality, especially if unrecognized. HIT is a prothrombotic immune-mediated response where early, significant falls in platelet counts in patients receiving large or small heparin doses appear to be associated with the development of thrombotic complications (i.e., deep vein thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and limb occlusion). The mortality rate is 20-30% and approximately the same percentage requires amputations. To reduce patient harm, ISMP recommends that health care professionals should:

- Maintain a current list of medication-coated catheters or devices as well as drug eluting stents that expose patients to heparin or other medications. Identify an "owner" of the list that can be responsible for updates.
- Obtain from patients a history of HIT or

(continued on page 3)

NEWSWORTHY...

from the pbm

- Riomet (Metformin) Recall Due to Microbial Contaminant – 05/05/2017 – National PBM Patient Level Recall Communication (TARGETED TO AFFECTED SITES ONLY)

(continued on page 2)

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.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141; www.pbm.va.gov

from the fda

(continued from page 1)

ENDOCRINOLOGY

FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

5/16/2017

Last year FDA investigated interim safety results from an ongoing clinical trial showing an increase in leg and foot amputations, mostly affecting the toes, in patients treated with canagliflozin for diabetes (see Issue 6; Volume 6; June 2016). New data show an approximately two-fold increased risk of lower limb amputations associated with canagliflozin use in two large clinical trials, CANVAS (Canagliflozin Cardiovascular Assessment Study) [Table 1] and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) [Table 2]. Amputations most commonly occurred with the toe and middle of the foot but also involved the leg, below and above the knee. Some patients had more than one amputation and both limbs may have been affected. Events observed in the trials that preceded the need for amputation included lower limb infections, gangrene, diabetic foot ulcers, and ischemia. Because of these findings, FDA requires new warnings, including a *Boxed Warning*, to be added to the canagliflozin drug labels to describe this risk. FDA also recommends that health care practitioners:

- Consider a patient's risk factors for amputations (such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers) before initiating canagliflozin.
- Monitor patients receiving canagliflozin for signs and symptoms of infection, new pain or tenderness, sores, or ulcers involving the lower limbs.
- Instruct patients taking canaglifozin to notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.
- Discontinue canagliflozin if any of the above complications occur.

It is not known whether the increased risk extends to other SGLT2 inhibitors. Empagliflozin is on the VA national formulary (with criteria for use). While an increase in lower extremity amputations has not been reported for empagliflozin, additional study is needed to assess if amputations are a class effect or limited to canagliflozin.

Table 1. CANVAS Findings

	Placebo N=1,441	Canagliflozin 100 mg N=1,445	Canagliflozin 300 mg N=1,441	Canagliflozin (pooled) N=2,886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations*	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard ratio (95% CI)	—	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

* Some patients had more than one amputation.

Table 2. CANVAS-R Findings

	Placebo N=2,903	Canagliflozin 100 mg (with up-titration to 300 mg) N=2,904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations*	36	59
Amputation incidence rate (per 1,000 patient-years)	4.2	7.5
Hazard ratio (95% CI)	—	1.80 (1.10, 2.93)

* Some patients had more than one amputation.

CENTRAL NERVOUS SYSTEM (CNS) AGENTS

FDA approves label changes for use of general anesthetic and sedation drugs in young children

4/27/2017

In December 2016, FDA required new warnings to the labels of general anesthetic and sedation drugs for use in children younger than 3 years (see Issue 10; Volume 6; November/December 2016). Approved label changes include:

- A new Warning that exposure to anesthetic and sedation medicines for long periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years.
- Addition of information (to the pregnancy and pediatric use sections) describing studies in young animals and pregnant animals that showed exposure to general anesthetic and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the developing brain; and studies in young animals suggested these changes resulted in long-term negative effects on the animals' behavior or learning.

FDA advises:

- Pregnant women should not delay or avoid surgeries or procedures that are medically necessary during pregnancy, as doing so can negatively affect themselves and their infants.
- Surgeries or procedures in children younger than 3 years should not be delayed or avoided when medically necessary. Consider delaying potentially elective surgery in young children where medically appropriate.

Getting the most from our safety surveillance

ETHANOLAMINE OLEATE (ETHAMOLIN) 5% INJECTION, 2ML, AND FENTANYL CITRATE INJECTION, USP 50MCG/ML, 2ML: LOOK-ALIKE PRODUCT CONFUSION

One medical center reported look-alike product confusion that occurred between ethanolamine oleate (Ethamolin®) injection, 5%, 2 milliliters (mL), and fentanyl citrate injection, USP 50 micrograms (mcg)/mL, 2mL, due to similarities in size, shape, and color of product packaging (Figure 1).

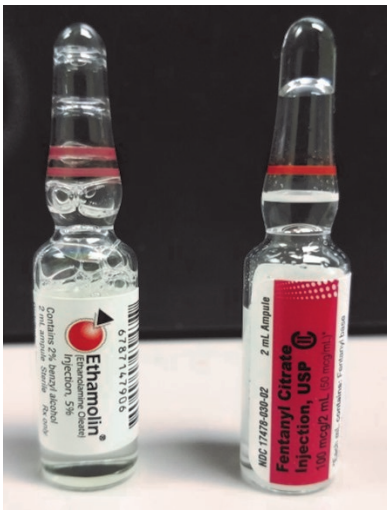

Figure 1. *Similar appearance of the single-dose ampules of ethanolamine oleate (Ethamolin®) injection, 5%, 2mL, (manufactured by QOL Medical , LLC) and fentanyl citrate injection, USP 50 mcg/mL, 2mL, (manufactured by Akorn, Inc.) led to look-alike product confusion at one local site.*

Ethanolamine is a mild sclerosing agent indicated for the treatment of patients with esophageal varices that have bled in order to prevent rebleeding. Fentanyl is a narcotic analgesic. Inadvertent administration of ethanolamine instead of fentanyl may result in inadequate analgesia during a patient's surgical procedure as well as possible tissue irritation or injury.

This mix-up involved five unused vials of ethanolamine 5% injection (2mL) that were returned along with 1 unused vial of fentanyl 50mcg/ml injection (2mL) into the controlled substance return bin of an automated dispensing cabinet, which has the capacity to store multiple medications in order to enable remote dispensing of needed medications at the point of care. Because of similar appearance, all were recorded as fentanyl 50mcg/ml injection (2mL) and placed back into pharmacy inventory. Both the authorized pharmacy staff and witness returning medications back to stock did not catch that 5 vials were actually ethanolamine and not fentanyl. These five ethanolamine vials were filled as fentanyl and set for storage in other automated dispensing cabinets. A pharmacy technician found the discrepancy during the restocking process. Pharmacy recovered all 5 vials of ethanolamine 5% injection (2mL) mistakenly filled as fentanyl and followed appropriate reporting procedures. No harm came to any patient.

Since the ethanolamine 5% injection (2mL) ampules passed several layers of verification as fentanyl 50mcg/ml injection (2mL), the product was sequestered to avoid future issues. This facility reports that they will start placing ethanolamine 5% injection (2mL) into a bag with a name alert and light sensitivity label to prevent errors. Providers were notified of the incident and made aware of the new precautionary measures taken. There was no alternative product available for purchase. Fortunately, no one received the product in error. A report regarding this look-alike confusion will also be sent to the Institute for Safe Medication Practices (ISMP).

REFERENCES:

1. Internal data.
2. ETHAMOLIN® (Ethanolamine Oleate) Injection, 5% [package insert]. Vero Beach, FL: QOL Medical, LLC; Aug 2012.
3. Fentanyl Citrate Injection, USP 50 mcg/mL [package insert]. Lake Forest, IL: Akorn, Inc.; Nov 2012.

Helping to achieve safe medication use

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) AND LIMB THROMBOSIS ASSOCIATED WITH HEPARIN-COATED CATHETERS OR DEVICES

(continued from page 1)

other allergies, and document responses in patients' medical record.

- Work up patients for HIT if they have heparin exposure from heparin-coated or –dipped catheters and also exhibit thrombocytopenia and other risk factors (e.g., decreased platelet count 5-10 days after initiation of heparin or sooner if prior [within 30 days] heparin exposure, thrombosis).
- If HIT is suspected or diagnosed, discontinue all sources of heparin (including heparin-coated catheters and heparin flushes) and initiate appropriate treatment.
- Document adverse responses.
- Evaluate use of medication-coated devices and catheters in order to reduce unnecessary exposure.

REFERENCE

Institute for Safe Medication Practices (ISMP). Unrealized exposure to heparin leads to missed HIT diagnosis and subsequent limb thrombosis. *ISMP Medication Safety Alert! Acute Care* May 2017; 22 (9): 1-3. ■