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ISMP 25 YEARS ADVANCING MEDICATION SAFETY

Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Dangerous wrong-route errors with tranexamic acid—a major cause for concern

Problem: Earlier this month, we were notified about two cases of accidental intraspinal injection of tranexamic acid, occurring in two different states. Unfortunately, the report was sent anonymously, and we were unable to learn additional details about the events, including the outcome of each patient.* In previously reported cases, mix-ups mostly occurred with vials/ampules of tranexamic acid and bupivacaine or ropivacaine when selecting products prior to regional anesthesia. In the US, all three drugs can be found packaged in vials with the same blue color plastic cap (**Figure 1**). While label colors may be different, when the vials are stored upright, in close proximity to one another, and in a bin, drawer, or below eye level, only the caps may be visible. To make matters worse, these drugs are often stored in areas where barcode scanning may not have been implemented or is not routinely utilized (e.g., perioperative areas, labor and delivery, emergency department). So, mix-ups are less likely to be detected.

Tranexamic acid is an antifibrinolytic that is used in a variety of hemorrhagic conditions to control bleeding, including post-partum hemorrhage. It works by preventing the breakdown of fibrin, thus promoting clotting. When given intraspinally instead of a local anesthetic, tranexamic acid injection is a potent neurotoxin with a mortality rate of about 50% and is almost always harmful to the patient. Survivors of intraspinal tranexamic acid often experience seizures, permanent neurological injury, and paraplegia (Palanisamy A, Kinsella SM. Spinal tranexamic acid – a new killer in town. *Anaesthesia*. April 15, 2019 [Epub ahead of print]; www.ismp.org/ext/263). Unfortunately, the literature is replete with reports of serious medication errors due to mix-ups between tranexamic acid and bupivacaine or ropivacaine during regional anesthesia.

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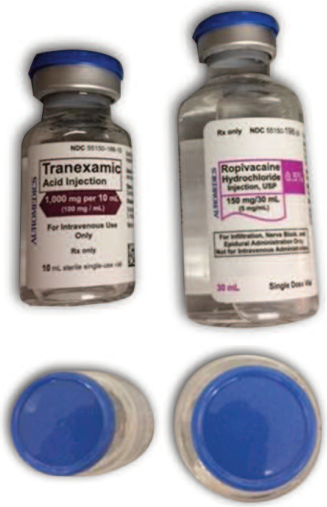

Figure 1. While label colors and vial sizes are different, the caps on ropivacaine and tranexamic acid vials (top), each from AuroMedics, are both blue and could lead staff to select a vial based on cap color, without reading the label, especially if the vials are stored upright with only the caps showing (bottom), not the labels. The company's bupivacaine vial also has a blue cap (to the left).

**ISMP discourages individuals from submitting reports anonymously. When reports are sent anonymously, it makes it impossible to learn additional information that may be key to understanding what took place and the root causes of an event. ISMP always holds report information in strict confidence, as do the US Food and Drug Administration (FDA) and manufacturers, with whom we communicate. We do not share reporter information with the FDA or manufacturers without your permission. Also, as noted in the error reporting section of the ISMP website, upon request, reports can be sent to ISMP as a federally recognized Patient Safety Organization (PSO), which affords further protection from discovery during a plaintiff's lawsuit.*

SAFETY briefs

Potential for mix-ups between Prolia and Udenyca syringes. ISMP has received 8 reports this year about the potential for mix-ups between **PROLIA** (denosumab; Amgen), an osteoporosis drug, and **UDENYCA** (pegfilgrastim-cbqv; Coherus BioSciences), a biosimilar leukocyte growth factor associated with the reference peg-filgrastim product, **NEULASTA**. In one case, Prolia syringes were found stocked in place of Udenyca syringes at an outpatient infusion site. At another center, staff found Udenyca syringes stocked instead of Prolia syringes in an automated dispensing cabinet refrigerator. While we have not received any reports of patients receiving the wrong drug, the similarities between these two medications increases the risk of a mix-up.

While the brand names are listed clearly on the cartons, both medications have

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Additional Fellowship Opportunity at ISMP

We learned last week that we have received additional funding that allows us to provide another opportunity for a nurse, pharmacist, or physician to serve a 1-year Fellowship at ISMP, beginning this summer. This will be the second **ISMP Safe Medication Management Fellowship** offered for 2019-2020. The first Fellowship position has been filled. The Fellowship program is open to US citizens and is based in ISMP's office located in Horsham, PA. For more than 2 decades, ISMP Fellows have gone on to make major contributions to medication safety worldwide. If you or anyone you know might be interested in joining us, please take the first step and access our website description of the program along with application information (www.ismp.org/node/871). Applications will be accepted until **June 30**.

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In 2015, we wrote about a 68-year-old woman undergoing a total knee replacement who received tranexamic acid intrathecally instead of the intended bupivacaine and morphine (www.ismp.org/node/398). The surgeon planned to irrigate the open knee with tranexamic acid to minimize blood loss, and the anesthesiologist intended to administer bupivacaine and morphine intrathecally for pain control. Pharmacy dispensed 10 mL vials of both the tranexamic acid (1 g or 100 mg/mL) and bupivacaine (2.5 mg/mL) to the surgical suite for staff to prepare in syringes just prior to administration. The vials were similar in size. Despite label dissimilarities, the anesthesiologist picked up a 10 mL vial of tranexamic acid, believing it was bupivacaine.

The anesthesiologist later administered tranexamic acid intraspinally. The barcode on the medication had not been scanned before preparation and administration. The patient immediately developed myoclonus of her lower extremities and seizures. She was intubated and placed on a ventilator while receiving a neuromuscular blocker. She required treatment in the intensive care unit, and after 23 days of hospitalization, the patient was finally discharged to a skilled nursing facility for physical rehabilitation.

A recent review article identified 21 cases of spinal tranexamic acid administration (Patel S, Robertson B, McConachie I. Catastrophic drug errors involving tranexamic acid administered during spinal anesthesia. *Anaesthesia*. April 15, 2019 [Epub ahead of print]; www.ismp.org/ext/264). Other case reports are listed in the references provided in our 2015 newsletter article.

Safe Practice Recommendations: Avoid storing these drug vials in an upright position to prevent reliance on identifying the drug by viewing only the vial caps. Store them in a way that always makes their labels visible. Minimize look-alike vials or ampules by purchasing these products from different manufacturers, and separate or sequester tranexamic acid in storage locations to provide an additional layer of safety to help prevent errors. We also recommend using an auxiliary label to indicate the intended route of administration on all tranexamic acid container labels.

Readers may be aware of a new neuraxial connector that is becoming available, known as NRFit. These connectors may be helpful in preventing wrong-route errors but won't prevent all mix-ups. Since regional anesthesia is generally administered as a one-time event in an operating or delivery room, the local anesthetic is usually drawn into a syringe by anesthesia personnel and injected via the intraspinal catheter (with a NRFit connector, if used). If a vial mix-up occurs and tranexamic acid is drawn into a NRFit syringe that is compatible with the NRFit catheter, it's still possible for the wrong drug to be injected. Of course, barcode scanning and pharmacy preparation of prefilled syringes or infusions would help to alleviate these errors.

Last month, Exela Pharma Sciences received approval to manufacture a premixed bag of tranexamic acid in a sodium chloride solution for injection as 1 g/100 mL (10 mg/mL), as opposed to vials of 1 g per 10 mL (100 mg/mL) (www.ismp.org/ext/251). The product will be distributed by X-Gen Pharmaceuticals. The company is preparing to launch this product within the next quarter. Although approval was granted specifically for patients with hemophilia to reduce the risk of hemorrhage during and following tooth extraction, the premixed product could find use with other forms of bleeding. A 100 mL bag would greatly reduce the potential for mix-ups with bupivacaine or ropivacaine vials; however, use of the infusion product and dosing information for any condition other than the approved indication is not provided in the product labeling. Also, since loading doses may be required prior to infusion, vials/ampules may still be needed (or a smart infusion pump loading dose feature could be used that automatically switches to a continuous infusion once the loading dose has been delivered).

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similar green and white packaging, with the concentration listed in a green circle in the same location (**Figure 1**). Each carton holds one single-dose, prefilled syringe, and both medications are intended for subcutaneous administration. The Prolia 1 mL syringe

Figure 1. Package similarity has led to dispensing and storage errors.

contains 60 mg, and the Udenyca 0.6 mL syringe contains 6 mg. Both concentrations include the numbers 6 and 0, which one reporter thought could add to confusion. Once the carton is opened, the syringes look different. The Prolia syringe has a green plastic needle safety device, and the Udenyca syringe is clear plastic. However, the differences might not be helpful to staff who are unfamiliar with the syringes. Prolia and Udenyca are likely to be dispensed to the same outpatient centers. Both are refrigerated items and may be near one another if stored alphabetically by brand name.

Store these products away from one another in the pharmacy, and verify the medication via barcode scanning before dispensing or administering. Pharmacy staff may also want to circle (with a permanent marker) the drug name on the carton to draw attention to it.

Alaris pump infusion set recall. BD recently sent a recall notice involving certain Alaris pump model 8100 infusion sets that permit incomplete occlusion on the pumping segment when the set is still in place and the pump is not running (www.ismp.org/ext/265). This is caused by a variation in the tubing wall thickness. The issue has the potential to allow unintended free flow when the pump is not running, or faster than expected drug/solution delivery when the pump is infusing. While the recall notice listed the infusion set model numbers that are being recalled, out of an abundance of

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Dosing confusion with Lenvima labeling

LENVIMA (lenvatinib) is an oral tyrosine kinase inhibitor indicated for patients with a certain kind of thyroid cancer, unresectable hepatocellular carcinoma, or advanced renal cell carcinoma (in combination with everolimus). Lenvima is only available in 4 mg and 10 mg capsules that come in blister packages containing a combination of those two strengths to create the required dose, depending on the patient's diagnosis—24 mg once daily for thyroid cancer; 18 mg once daily for renal cancer; 12 mg once daily for patients with hepatocellular cancer weighing 60 kg or more; and 8 mg once daily for hepatocellular cancer patients weighing less than 60 kg. The dose may be modified for certain patients with impaired hepatic or renal function.

The blister packages hold various capsule configurations that match a wide variety of required daily doses, including 4 mg, 8 mg, 10 mg, 12 mg, 14 mg, 18 mg, 20 mg, or 24 mg. Each carton contains 6 cards of the blister packages. Unfortunately, the daily dose printed on the carton and blister package label within a color band does not mention the specific capsule strength used to make up that daily dose. For example, the 12 mg daily dose blister does not state that three 4 mg capsules are needed for this daily dose. While the exact number of capsules to take is printed in other locations on the carton and blister package, the daily dose expression in the prominent color band may be misleading (**Figure 1**).

Consumers and healthcare providers could also mistakenly believe the daily dose requires all the capsules packaged vertically rather than horizontally. The horizontal borders, designed to help direct users to the daily dose, are overshadowed by the vertical columns, which appear more pronounced.

An error was reported to ISMP in which a patient with hepatocellular cancer received only one-third of his 12 mg daily dose. A dispensing pharmacist had typed "Take one 12 mg capsule daily" on the pharmacy label. These instructions were based on the blister package label that highlights the total daily dose of 12 mg but not the *three* 4 mg capsules needed for each dose. The patient thought each capsule contained 12 mg and took just one capsule daily. Later, when the patient was hospitalized, a nurse recognized the error when the patient refused to take all three 4 mg capsules for the prescribed 12 mg dose.

Figure 1. Daily dose in green colored band (left side of package) misled pharmacist to believe that each capsule contained 12 mg when three 4 mg capsules were needed for the 12 mg daily dose. The vertical orange band containing five 4 mg capsules could also be confused as the daily dose rather than the three 4 mg capsules packaged horizontally.

ISMP supports the use of unit-of-use packages for oral chemotherapy that requires multiple capsules or tablets, particularly when combinations of different strengths are needed to make up each daily dose. We also support the use of unit-of-use packages for medications with tapering or weekly dosing schedules (e.g., methyl**PREDNIS**olone). However, we have informed the manufacturer, Eisai, of the misleading Lenvima label and suggested that revisions to the container labeling are needed to better communicate the exact number of capsules needed for each daily dose.

Pharmacists, nurses, and prescribers should be made aware of the risk of dosing confusion and should provide education and counseling for every patient prescribed this medication to ensure understanding of how to take this medication.

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caution, BD is instructing customers to discard **ALL** model codes and lot numbers with an expiration date between and including 05/2019 and 08/2020. BD said the company will provide replacement sets for all discarded inventory. Until all affected products have been discarded, BD recommends checking the bag of all critical medication infusions more frequently than normal to ensure that the remaining volume corresponds to the expected delivery time. The company and its supplier have implemented corrective actions to prevent recurrence.

HIGH-ALERT **Never underestimate the need for patient education.** As a result of known situations where a single insulin pen was used for multiple patients, the US Food and Drug Administration (FDA) required pen manufacturers to include a statement, "For single patient use only," on all pens and outer cartons. The statement seems cut and dry. However, a patient who was newly started on **NOVOLOG Mix** 70/30 (insulin aspart protamine and insulin aspart) thought "single patient use" meant to administer the entire contents at once. The patient had not received any education about administration technique or dosing. It is unknown if the patient received 60 units (the maximum that can be dialed as a single dose) or the entire 300 units in the pen. The patient became unresponsive and was brought to the hospital with a blood glucose level below 30 mg/dL. The patient was placed on a 10% dextrose infusion and became responsive. When educating patients about the use of insulin pens, be sure to discuss the meaning of "For single patient use only."

Your *Reports* at *Work*

New penicillin G benzathine warning. Newly labeled penicillin G benzathine injectable suspension prefilled syringes (**BICILLIN L-A**) have reached the market, largely thanks to your reporting to the ISMP National Medication Errors Reporting Program (ISMP MERP)! Before the changes, the syringes were labeled in a way that made reading the name of the drug and a route warning difficult because the label

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Tenfold overdose with levothyroxine

A patient who was taking levothyroxine 25 mcg at home experienced two inpatient admissions in which two different providers, including an endocrinologist, attempted to double the patient's dose to 50 mcg. However, instead of ordering 50 mcg, both providers ordered 0.5 mg of the drug (500 mcg), a tenfold dosing error. A medication reconciliation process had not been completed during either admission; thus, the patient's home medications were never discussed with the patient. While default order sentences in the hospital's computer system displayed mcg strengths for levothyroxine, the prescriber was able to choose the 25 mcg product and modify the dose to 0.5 and the dosing unit to mg. So, the drug was ordered in mg, although mcg is the primary way the strength is expressed on drug containers. The final order read, "levothyroxine 0.5 mg" (500 mcg, not 50 mcg).

ISMP has written previously about prescriber confusion regarding decimal point placement with levothyroxine doses expressed in mg and has recommended using mcg strengths only. Similar errors between levothyroxine 0.25 mg and 0.025 mg have also been reported. We've even received a report about an order for oral "levothyroxine 0.75 mg daily." However, upon checking the patient's drug history from a prior admission, a pharmacist noticed that the patient had been taking 75 mcg (0.075 mg). While most practitioners with experience may realize that 0.5 mg or 0.75 mg doses are most likely excessive, orders for 0.25 mg doses could easily slip by.

Although a 300 mcg strength tablet of levothyroxine is available, doses greater than 200 mcg per day are seldom required, and doses greater than 300 mcg are even more rare. Therefore, consider building a warning with a hard stop whenever a dose above 200 mcg is initially ordered for a new patient. Experience has shown that when such a warning appears, the correct dose has almost always been 25 mcg or 50 mcg, not 250 mcg or 500 mcg. The need for doses above 200 mcg should be documented.

Avoid decimal points by making sure that drug strengths less than 1 mg are listed in mcg amounts, not mg. Additionally, except in emergencies or in unusual circumstances, a medication history should be obtained, and medication reconciliation should be performed before prescribing medications. In the hospital where the two recent errors occurred, pharmacy informatics personnel are working to lock levothyroxine dosage units and order sentences, so they are no longer modifiable.

It should be noted that there are a few manufacturers that label levothyroxine in mcg only, and many that label in both mcg and mg. Expression of dosage units should be standardized so label strengths are only displayed in mcg.

Special *Announcements*

FREE ISMP webinar

On **June 20, 2019**, ISMP will present a **FREE** webinar on ***Back to the Basics: Preventing Administration of Neuromuscular Blocking Agents to Unventilated Patients***. Join our ISMP speakers as they describe key vulnerabilities with neuromuscular blockers that have led to errors and patient harm, and best practices for safeguarding their use. For details, visit: www.ismp.org/node/1523.

IV push webinar available on demand

ISMP's recent webinar, ***Designing Reliable Practices for IV Push Medication Use: A Focus on Safe Administration***, is now accessible on demand. The webinar helps practitioners identify and manage risks associated with IV push medication use, reviews ISMP safe practice recommendations, and describes our gap analysis tool that can be used to assess and improve safety. For details, visit: www.ismp.org/node/1377.

Your *Reports*

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was upside down for right-handed practitioners (**Figure 1**). Also, one of the warning statements on the syringe was stated negatively, "**NOT FOR INTRAVENOUS USE**." The concern was that the plunger blocked the "**NOT**" part of the warning, possibly leading staff to read "**FOR INTRAVENOUS USE**." This statement has now been replaced with a very visible, "**WARNING: FATAL IF GIVEN BY OTHER ROUTES**," and the label is now oriented for readability when held in the right hand (**Figure 2**). We appreciate this label revision by Pfizer. ISMP is aware of at least one fatal incident involving an infant who received the drug intravenously, in part because a route warning wasn't seen (www.ismp.org/node/1527). Other cases have happened with penicillin G procaine, which is also an injectable suspension.

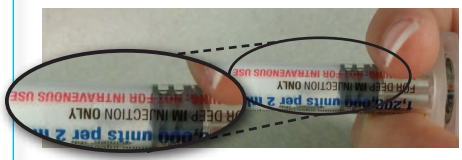

Figure 1. Previous prefilled syringe label was upside down when held in right hand. Also, "NOT" portion of warning statement is not easily visible.

Figure 2. Penicillin G benzathine label now oriented for right-handed readability. Route warning is clearly visible and stated affirmatively.

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