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ISMP

Nurse AdviseERR®

Educating the Healthcare Community About Safe Medication Practices

Problems associated with the use of U-500 insulin syringes

We received two reports of accidental prescribing of the new BD U-500 insulin syringes for outpatients who were using a U-100 insulin product. In one case, an endocrinology clinic called the hospital pharmacy to ask how to order U-500 syringes. During the conversation, it became apparent that there was some confusion about the use of these syringes. The pharmacist emphasized that the patient should not use a U-500 syringe to measure any insulin concentration other than U-500, or the measurement would be incorrect, leading to a 5-fold underdose.

At another organization, some providers have been selecting U-500 insulin syringes in error via the electronic prescribing systems. There have been 8 incidents where U-500 syringes were prescribed in error, although pharmacists intervened each time and prevented patients from receiving the wrong syringes. The computer system at the clinic where this happened listed the "U-500" designation far to the right of the entry, making it easy for both the prescriber and dispensing pharmacist to overlook. The line item read: "SYRINGE INSULIN SYRINGE 0.5ML 31G 6MM (U-500) XA854 100/Box...." Moving the "U-500" designation to the left of the insulin syringe entry can help give it prominence. Also, it is important for practitioners to caution patients about the risk of a mix-up and dosing errors if multiple family members in the home use insulin and both U-500 and U-100 insulin syringes are available.

Another issue with U-500 syringes is they lack a needle guard to protect staff from needlestick injuries. Many hospitals refuse to stock U-500 syringes without the needle guard, so staff are unable to properly train patients who need to use them. We have received multiple complaints about this issue and have communicated with BD, the U-500 syringe manufacturer. Unfortunately, BD has not made us aware of any plans to produce syringes with safety needles. Since U-500 syringes and pens have become available, we no longer recommend using a tuberculin (TB) syringe or U-100 syringe with U-500 insulin vials due to the risk of patients miscommunicating their dose or measuring it incorrectly. If your hospital does not stock U-500 syringes without a safety needle for patient education, consider using the U-500 insulin pen to prevent dosing errors.

A third issue with U-500 syringes is that they only measure up to 250 units, even though patients who use U-500 insulin may need more than 250 units per dose. (U-500 insulin pens only measure up to 300 units.) Although many patients' doses are below this amount, one hospital recently ran a report and found 31 patients in its system who required doses greater than 250 units per single dose. The hospital also reported that some patients received as much as 700 units per dose, requiring multiple subcutaneous injections. Unfortunately, this may cause some hospitals to return to using TB syringes or, even worse, U-100 syringes. We have communicated this concern to BD and Lilly (the manufacturer of U-500 insulin).

Finally, remind staff involved with obtaining drug histories and performing medication reconciliation to be sure to find out what type of insulin syringe (U-100 or U-500) U-500 insulin patients are using when they state their dose. Some patients

continued on page 2—U-500 >

SAFETY wires

"Hanger" from Actavis propofol tears label. A redesigned bottle of Actavis propofol 1,000 mg/100 mL (10 mg/mL) has a label designed to be peeled down to create a hanger to infuse the solution from an IV pole. Previously, Actavis had provided plastic hangers to put around the bottle to hang the infusion. Unfortunately, when peeling down the redesigned label to create the hanger, part of the manufacturer label with the drug name and concentration is cut off (**Figure 1**). Also, as with the plastic hangers, the new design still makes it difficult to attach the patient-specific label. Additionally, along with some other vials of medications intended to be hung on an IV pole, the label will be upside down and not easy to read once the vial is hung. We have contacted the US Food and Drug Administration (FDA) and the manufacturer about the problem. Until the issue is remedied, consider purchasing propofol in 1,000 mg/100 mL bottles from a manufacturer that provides plastic hangers. Although it would add expense, there are also companies that sell plastic bottle hangers in various sizes (e.g., Health Care Logistics, www.ismp.org/sc?id=2913).

Figure 1. New hanger incorporated into product labeling creates problems when used.

ON-Q pump for nerve block attached to IV line. An elastomeric pump (**ON-Q** device) infusing a local anesthetic was purposefully connected to a peripheral intravenous (IV) line by an alert, hospitalized patient. He was receiving a continuous nerve

continued on page 2—SAFETY wires >

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> U-500—continued from page 1

who are still using a U-100 syringe with U-500 insulin vials will state their dose in "syringe units," which is one-fifth of the actual dose they should be receiving with U-500 insulin. Such an error was reported recently. A pharmacy technician obtaining a drug history was confused by a patient who had been drawing up his U-500 insulin with a U-100 syringe. When an order for U-500 insulin was later entered electronically, a 5-fold underdose was accidently prescribed.

FDA Advise-ERR: Concomitant use of Entresto and ACE inhibitors can lead to serious outcomes

ENTRESTO (sacubitril/valsartan) is an angiotensin II receptor-neprilysin inhibitor (ARNI) used to reduce the risk of cardiovascular death and hospitalization in patients with chronic heart failure and reduced ejection fraction. It contains the angiotensin II receptor blocker (ARB) valsartan and the neprilysin inhibitor sacubitril. Entresto is contraindicated with concomitant use of angiotensin converting enzyme (ACE) inhibitors due to the increased risk of angioedema, which is caused by the inhibition of neprilysin from the sacubitril component in Entresto combined with an ACE inhibitor.[1] Also, the dual renin-angiotensin-aldosterone system blockade that occurs when valsartan is combined with ACE inhibitors increases the risk of hypotension, acute kidney injury, and hyperkalemia. Thus, Entresto should not be administered within 36 hours of switching from or to an ACE inhibitor. Still, the US Food and Drug Administration (FDA) has received 55 cases reporting concomitant use of Entresto and an ACE inhibitor, with several cases describing serious outcomes.

The cases submitted to FDA describe patients who were taking an ACE inhibitor and were prescribed Entresto, and patients who started taking Entresto in the hospital and inadvertently restarted their ACE inhibitor after discharge. Several cases described a washout period of less than 36 hours when switching from an ACE inhibitor to Entresto. Eleven patients were hospitalized. The most common adverse events reported due to this drug interaction were angioedema, hyperkalemia, acute kidney injury, and hypotension.

Table 1. ACE inhibitors/ARBs to avoid with Entresto

ACE Inhibitors	ARBs
benazepril (**LOTENSIN**)	azilsartan (**EDARBI**)
captopril	candesartan (**ATACAND**)
enalapril (**VASOTEC**)	
enalaprilat	eprosartan (**TEVETEN**)
fosinopril	
lisinopril (**PRINIVIL**, **ZESTRIL**)	irbesartan (**AVAPRO**)
	losartan (**COZAAR**)
moexipril	olmesartan (**BENICAR**)
perindopril (**ACEON**)	
quinapril (**ACCUPRIL**)	telmisartan (**MICARDIS**)
ramipril (**ALTACE**)	
trandolapril (**MAVIK**)	valsartan (**DIOVAN**)

Entresto is used to lessen morbidity and mortality, and replaces an ACE inhibitor or ARB in patients with chronic symptomatic heart failure (NYHA class II or III) with a reduced ejection fraction (HFrEF) who tolerate an ACE inhibitor or ARB.[2] Due to the previous standard of care, many patients starting Entresto are already taking ACE inhibitors. This could lead to serious adverse events if the ACE inhibitor is not discontinued, or if the patient continues taking the previously prescribed ACE inhibitor at home. These errors may be related to the lack of familiarity with Entresto. But since its approval in 2015, the drug's use has increased. Entresto was added in the updated 2016 heart failure guidelines published by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA). The new guidelines recommend an ACE inhibitor, an ARB, **or** an ARNI (e.g., Entresto) for patients with chronic HFrEF, but **not** in combination (**Table 1**, prepared by ISMP).

continued on page 3—FDA Advise-ERR >

> SAFETY wires continued from page 1

block for pain management of an open fracture of the calcaneus (heel bone). He was in tremendous pain and attempted to help manage his pain by giving himself the drug from the ON-Q device IV. Fortunately, the patient's nurse quickly identified the misconnection and took appropriate action. Anesthesia was notified, the patient was monitored, and the ON-Q pump was discontinued due to concern for compliance.

It is likely that many hospitals are seeing increased use of nerve blocks with local anesthetics to reduce opioid use. Keep in mind that, accidental IV infusion of local anesthetics, including ropivacaine, is concerning due to the potential for significant systemic toxicity, such as cardiotoxicity. Therefore, increased awareness of patient safety concerns with elastomeric devices and regional anesthesia is needed to prevent the likelihood of similar events.

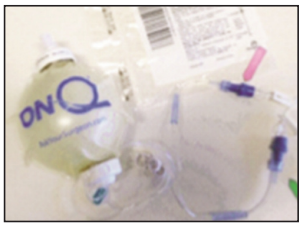

Figure 1. ON-Q PainBuster device should NOT be connected to IV tubing as shown.

ON-Q devices are also used for epidural infusions, but it is unclear whether the requirement for new neuraxial connectors (NRFit) will affect elastomeric pumps used epidurally. The pumps do not currently use the new connector and, if they do in the future, this will require tubing that accepts the new connector.

Patient selection plays an important role in the safe use of elastomeric devices, both in and out of the hospital. Still, it is hard to predict what a patient (or family member) might do. Therefore, warning patients about any manipulation of these devices on their own is warranted. Mix-ups like this can also occur when staff maneuver various tubings. For now, affix identification labels on lines if the patient has more than one port of entry into the body (e.g., IV, arterial, umbilical, enteral, bladder, drainage tubes).

This is not the first time that an ON-Q pump (or other elastomeric pump) was involved in such an error. We have written about

continued on page 3—SAFETY wires >

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> FDA Advise-ERR—continued from page 2

Please consider the recommendations below to help prevent the concomitant use of Entresto and ACE inhibitors.

For Prescribers, Pharmacists, and Nurses:

- Prior to prescribing Entresto, ensure that patients are not already taking an ACE inhibitor. For patients taking an ACE inhibitor, ensure that it is stopped and allow for a 36-hour washout period prior to starting Entresto.
- Work with information technology (IT) staff to create and/or enable order entry system alerts to warn against the concomitant use of Entresto and ACE inhibitors when both of these drugs have been prescribed for the patient. If possible, configure the alert to continue for 36 hours after Entresto or the ACE inhibitor has been discontinued.
- Before dispensing or administering Entresto, review patients' medication regimens. If ACE inhibitors are listed, ensure that patients have discontinued the ACE inhibitor and wait 36 hours before starting Entresto.
- Educate patients about the importance of not taking Entresto and ACE inhibitors together.
- Conduct a thorough medication reconciliation (on admission and at discharge) to ensure that patients who are prescribed Entresto, but were taking an ACE inhibitor or ARB in the past, do not restart the ACE inhibitor or ARB upon discharge from the hospital.

For Insurers:

- Create alerts to warn against the concomitant use of Entresto and ACE inhibitors when claims are submitted for both drugs.

References

1) Entresto [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, NJ; Aug 2015. www.ismp.org/sc?id=2848
2) Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Failure Society of America. *Circulation*. 2016;134(13):e282-93.

ISMP thanks Ashleigh Lowery, PharmD, BCCCP, at the US Food and Drug Administration (FDA) Division of Medication Error Prevention and Analysis, for providing this article.

2017-2018 ISMP *Fellows*

ISMP welcomes two new **2017-2018 ISMP Safe Medication Management Fellows**, Viktoriya Ingram, PharmD, sponsored by Baxter International Inc., and David Valentine, PharmD, supported by the US Air Force (USAF).

Viktoriya was employed previously by Consonus Healthcare in California as a long-term care (LTC) consultant pharmacist, where she conducted medication regimen reviews and medication handling audits. She served on various committees and worked with interdisciplinary teams to improve medication safety in the LTC setting. She received her Doctor of Pharmacy in 2011 from Albany College of Pharmacy and Health Science in NY.

David is an active duty USAF officer who holds the rank of Major. While working in both community and inpatient pharmacy settings, he initiated collaborative practice agreements; helped treat patients diagnosed with hyperlipidemia, hypertension, and diabetes; and managed a tobacco cessation clinic. David received his Doctor of Pharmacy from Midwestern College of Pharmacy in Glendale, AZ in 2011.

> *SAFETY* wires continued from page 2

line mix-ups with ON-Q pumps in our May 2012 newsletter (www.ismp.org/sc?id=138) and added additional safe use suggestions in our September 2013 issue (www.ismp.org/sc?id=2990).

Concentrated insulin pens and the visually impaired. An endocrinologist prescribed a U-200 **TRESIBA** (insulin degludec) pen for an 88-year-old woman with labile type 1 diabetes and recurrent hypoglycemia. The patient also has severe macular degeneration with visual impairment. Visually impaired patients commonly use touch and sound to assist them. In the past, the patient was taking U-100 **LANTUS** (insulin glargine) using the **SOLOSTAR** pen. With this pen, you can hear and feel a faint click for each unit as you turn the dial to set the dose. For Tresiba, the doctor had prescribed 18 units daily, unaware that the patient had been setting her previous Lantus dose by listening to the number of clicks. (It is uncertain why the physician prescribed U-200 Tresiba for such a small dose.) The patient prepared the dose by counting 18 clicks. Later, she mentioned to her daughter that the clicks seemed different than with other pens. Her daughter looked at the pen and realized that, for Tresiba U-200 (which is also available in a U-100 concentration), each click represents 2 units rather than 1. The patient had taken twice (18 clicks = 36 units) the prescribed dose of Tresiba!

In the US, the approved package insert provides no warning about using the Tresiba U-200 pen with visually impaired patients. In Europe, the approved package insert does provide a warning: "Patients who are blind or have poor vision must get assistance from another person with good vision who is trained in using the insulin device." This is good advice. Both the prescriber and the pharmacist instructed the patient how to use the pen but did not pick up any potential problem, and certified diabetes educators (CDEs) working with the doctor were also unaware of this potential problem. Any time you change a device with a visually impaired patient, or any patient, you need to reeducate the patient and require a return demonstration to confirm his or her ability to use the device properly.

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what's in a Name?

The "-olol" drug name stem

In our June 2017 issue, we began a regular series highlighting common drug name stems. This month we focus on drugs that have the suffix "-olol." These drugs are considered beta blockers, which block beta adrenergic receptors from responding to stress hormones such as **EPINEPH**rine and norepinephrine. Their antagonist action slows down the heart rate, eases the force of contraction, and subsequently lowers blood pressure. They are commonly used to manage hypertension, angina, arrhythmia, heart failure, and other cardiovascular conditions.

There are dozens of beta blockers that are routinely used in clinical practice. Most of these drug names end with the stem "-olol."[1] Some of the commonly used beta blockers are listed in **Table 1**.

There are a few things to note about this rule. Carve**dilol** ends with the stem "-**dil**ol" because of its vaso**dil**ator property. Labet**alol** and sot**alol** end with the stem "-**a**lol" due to a different molecular structure. In the past, there was one notable exception to the "-olol" naming convention: stanozolol (**WINSTROL**), which is no longer available, was not a beta blocker but rather an anabolic steroid.

The side effects of beta blockers can be more severe than for many other drugs used in cardiology. The biggest safety risk is the potential for beta blocker rebound. This can happen when the beta blocker is abruptly stopped in patients who have taken this class of drugs for a long time. The patient may experience tachycardia, hypertension, angina, and worsening heart failure symptoms.[2] Surgical patients and heart failure patients who have their beta blockers discontinued inappropriately have a higher mortality risk.[3,4] If your patients are on beta blockers at home, they should continue taking them postoperatively or during their inpatient stay unless contraindicated (e.g., severe hypotension).

Table 1. Examples of beta blockers

Generic Name	Common Brand Name(s)
aten**olol**	TENORMIN
bisopr**olol**	(generic only)
esm**olol**	BREVIBLOC
metopr**olol**	LOPRESSOR, TOPROL XL
nad**olol**	CORGARD
nebiv**olol**	BYSTOLIC
propran**olol**	INDERAL LA and others
carve**dilol**	COREG, COREG CR
labet**alol**	(generic only)
sot**alol**	BETAPACE and others

ISMP plans to bring you this feature on drug stem names every other month. We are borrowing this idea from an outstanding effort that is already underway in the French publication, *Prescrire International*, a journal that provides reliable, independent information about medications (www.ismp.org/sc?id=2877).

References

1) World Health Organization. The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances. 2013. www.who.int/medicines/services/inn/stembook Accessed August 14, 2017.
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3) Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker withdrawal in acute decompensated heart failure: a systematic review and meta-analysis. *JACC Heart Fail.* 2015;3(8):647-53.
4) Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J.* 2001;141(1):148-53.

Special Announcements

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October 5: *Medication Safety Practitioners: Leading, Innovating, and Improving Healthcare*

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2017 MSI dates
September 14-15: Hackensack, NJ
December 1-2: Orlando, FL

Cheers Awards nominations

Nominations for this year's **Cheers Awards** will be accepted through **September 9**. Outside and self-nominations are accepted. The prestigious awards spotlight efforts to improve medication safety from all healthcare disciplines. To submit a nomination, please visit: www.ismp.org/sc?id=1777.

To subscribe: www.ismp.org/sc?id=384

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