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ISMP An ECRI Affiliate

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

Analysis identifies multiple common causes of norepinephrine errors

Problem: Norepinephrine is a high-alert medication that is administered intravenously (IV) as a continuous infusion. It is a vasopressor typically titrated to maintain adequate blood pressure and end-organ perfusion in critically ill adult and pediatric patients with severe hypotension or shock that persists after adequate fluid volume replacement. Even minor titration or dose-related errors or delays in therapy may result in harmful adverse events. A multi-site health system recently sent ISMP the results of a common cause analysis (CCA) of 106 norepinephrine errors that occurred in 2020 and 2021. Using CCA to examine multiple events allows an organization to aggregate the shared root causes and system vulnerabilities. Data from the organization's reporting program and smart infusion pumps were used to identify potential errors.

ISMP received a total of 16 reports involving norepinephrine in 2020 and 2021 through the ***ISMP National Medication Errors Reporting Program*** (ISMP MERP). About one-third of these reports were hazards related to look-alike names, labeling, or packaging, for which no actual error occurred. We have published seven of the reported norepinephrine errors that reached patients: four dosing errors (www.ismp.org/node/30420; www.ismp.org/node/30485; www.ismp.org/node/29916); one wrong concentration error (www.ismp.org/node/19990); one wrong drug titration error (www.ismp.org/node/19990); and one accidental discontinuation of a norepinephrine infusion (www.ismp.org/node/30484). All 16 ISMP reports were added to the multi-site health system CCA (n=106), and the combined results (N=122) for each phase of the medication-use process are presented below. A reported error is included to provide an example of certain common causes.

Common Causal Factors

Prescribing. We identified several causal factors associated with prescribing errors, including the unnecessary use of verbal orders, prescribing norepinephrine without using an order set, and unclear or undefined titration goals and/or parameters (especially if an order set was not used). Occasionally, the prescribed titration parameters were too rigid or unrealistic (e.g., ordered in too large of an increment), making it difficult for nurses to follow the order while controlling the patient's blood pressure. In other cases, prescribers were able to order either weight-based or non-weight-based doses, which were occasionally mixed up. This nonstandard prescribing approach made it more likely that practitioners downstream would make errors, including pump programming errors, as both dosing options were available in the pump library. Also, delays from needing to clarify orders were reported when prescribers' orders included both weight-based and non-weight-based dosing instructions.

A physician asked a nurse to enter a norepinephrine order for a patient with an unstable blood pressure. The nurse entered the order exactly as the physician had verbally prescribed it: 0.05 mcg/kg/minute IV to titrate to a goal mean arterial pressure (MAP) above 65 mm Hg. But the physician's administration instructions mixed both a non-weight-based dosing increment and a maximum weight-based dose: titrate by 5 mcg/minute every 5 minutes to a maximum of 1.5 mcg/kg/minute. The organization's smart infusion pumps were unable to titrate doses in mcg/minute to a maximum weight-based dose, mcg/kg/minute. The pharmacist had to clarify the instructions with the physician, resulting in a delay in care.

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SAFETY briefs

Confusion with Fetroja preparation instructions. Prior to dispensing a dose of **FETROJA** (cefiderocol) for the first time, a pharmacist noticed the preparation instructions on the carton did not match the preparation instructions in the package insert. The vial states that there is 1 g per vial. The package insert states to reconstitute a 1 g Fetroja vial with 10 mL of diluent, which will result in a volume of approximately 11.2 mL of reconstituted solution. To provide a 750 mg dose, 8.4 mL should be withdrawn from the reconstituted vial (final concentration of 0.089 g/mL [89 mg/mL], as noted in the package insert), and then further diluted in a 100 mL infusion bag (**Table 1**). However, when the error was reported to ISMP, the Fetroja carton label stated, once the 1 g vial is reconstituted with 10 mL of diluent, the resultant concentration is 0.1 g/mL

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FETROJA Dose	Number of 1-gram FETROJA Vials to be Reconstituted	Volume to Withdraw from Reconstituted Vial(s)	Total Volume of FETROJA Reconstituted Solution for Dose into a mL (entire content
2 grams	2 vials	11.2 mL (entire contents) of each vial	8.4 mL
1.5 grams	2 vials	11.2 mL (entire contents) of first vial AND 5.6 mL of second vial	
1 gram	1 vial	11.2 mL (entire contents)	11.2 mL
0.75 gram	1 vial	8.4 mL	8.4 mL

Table 1. The Fetroja package insert preparation instructions for a 0.75 g (750 mg) dose state to withdraw 8.4 mL after reconstitution. Although not mentioned in the table, the package insert lists the concentration of the drug as 0.089 g/mL (89 mg/mL).

ISMP Medication Safety Alert! Acute Care readership survey

It has been almost a decade since we last surveyed our newsletter readers regarding how and when you read the newsletter, how you use it, its effectiveness, and your overall satisfaction with the ***ISMP Medication Safety Alert! Acute Care***. Please take about **10 minutes** to complete this important survey and submit your responses by **May 13, 2022**, by visiting: www.ismp.org/ext/863. A copy of the survey questions appears on **pages 5 and 6**. Your participation will help us cover important topics that are of interest to you, as well as improve the newsletter to better serve you and your patients.

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Preparation and Dispensing. Many of the preparation and dispensing errors were related to a demanding pharmacy workload, exacerbated by the need for pharmacy staff to compound maximum concentration (32 mg/250 mL) norepinephrine infusions (which are available from 503B compounding pharmacies but were not purchased at all sites). The demanding workload led to multitasking and fatigue. Other common causes of dispensing errors included hidden norepinephrine labels due to light-protective bags, and the pharmacy staffs' lack of knowledge about the urgency of dispensing norepinephrine.

ⓘ *An error occurred with norepinephrine and ni**CAR**dipine compounded infusions in light-protective amber bags. For light-protected infusions, the dispensing system printed two labels, one to affix to the actual infusion bag, and one for the outside of the amber bag. Prior to dispensing the products, which were intended for different patients, the norepinephrine infusion was accidentally put into the amber bag labeled as ni**CAR**dipine, and vice versa. The error was not noticed prior to dispensing or administration. The patient who was prescribed ni**CAR**dipine was given norepinephrine, but she suffered no long-term harm.*

Administration. Common mistakes included wrong dose or concentration errors, wrong rate errors, and wrong drug errors. Most of these errors were caused by incorrectly programming smart infusion pumps, partly due to having both weight-based and non-weight-based dosing options in the drug library; storage errors; leaving a discontinued or paused infusion connected to the patient and restarting the wrong infusion; or not labeling lines and tracing them when starting or restarting infusions. A few errors occurred in the emergency department and the operating room, where smart pump interoperability with the electronic health record (EHR) was not available. Extravasations that resulted in tissue damage were also reported.

ⓘ *A nurse administered a norepinephrine infusion that was prescribed to run at 0.1 mcg/kg/minute. Instead of programming the pump to deliver 0.1 mcg/kg/minute, the nurse programmed the pump to administer 0.1 mcg/minute. Thus, the patient received 80 times less norepinephrine than prescribed. When the infusion was titrated to effect and reached a rate of 1.5 mcg/minute, the nurse thought she had reached the prescribed maximum limit of 1.5 mcg/kg/minute. Since the patient's MAP was still not within range, a second vasopressor was added.*

Inventory and Storage. Most errors occurred when filling automated dispensing cabinets (ADCs) or when replacing vials of norepinephrine in code carts. The primary causal factor for these stocking errors was look-alike labeling and packaging. However, other common causes were identified, such as low par levels of norepinephrine infusions in ADCs that were insufficient for the patient care unit, which led to delays in therapy if the pharmacy had to compound the infusion due to a backorder. Failing to scan the barcode of each norepinephrine product when stocking an ADC was another common cause of the errors.

ⓘ *A pharmacy technician mistakenly restocked an ADC with a 32 mg/250 mL concentration of a pharmacy-prepared norepinephrine infusion in a drawer intended for 4 mg/250 mL manufacturer premixed infusions. A nurse discovered the error when attempting to retrieve a 4 mg/250 mL norepinephrine infusion from the ADC. The barcode on each individual infusion was not scanned prior to placement in the ADC. When the nurse realized there were only 32 mg/250 mL bags in the ADC (which should have been in the refrigerated section of the ADC), she requested the correct concentration. Due to a backorder of the manufacturer premixed 4 mg/250 mL bags, the pharmacy did not have any norepinephrine infusions in a 4 mg/250 mL concentration, resulting in a delay in care while compounding the infusion.*

Monitoring. Incorrectly monitoring the patient, titrating the norepinephrine infusion outside of the order parameters, and not anticipating when the next infusion bag was needed were the most common causes of errors related to monitoring.

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(100 mg/mL) (**Figure 1**, top). If the volume withdrawn from the reconstituted vial is based on the concentration specified on the carton, this could result in an underdose. So, if referring to the 0.1 g/mL (100 mg/mL) concentration specified on the carton for a 750 mg desired dose, 7.5 mL would be withdrawn, which would only provide 670 mg or about 10% less than intended dose. Underdosing antimicrobials such as Fetroja could potentially lead to treatment failures.

ISMP reached out to the manufacturer, Shionogi, who confirmed that the concentration on the carton was incorrect and that the package insert contains the correct preparation instructions. ISMP also notified the US Food and Drug Administration (FDA) of this discrepancy and our recommendation to revise the carton's labeling. We are happy

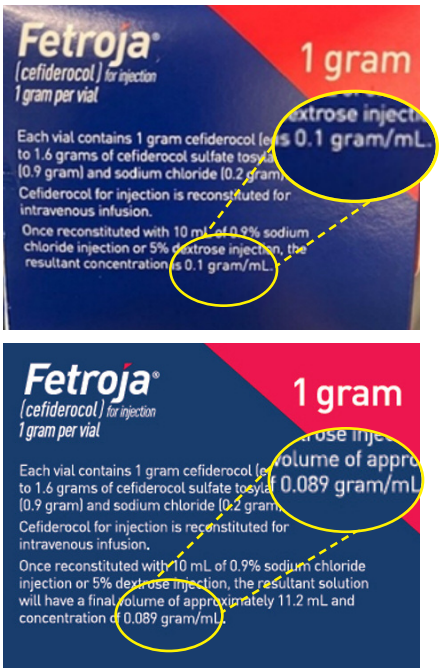

Figure 1. Fetroja carton preparation instructions listed a resultant concentration of 0.1 g/mL (100 mg/mL) (top), which was incorrect. The new, revised carton label (bottom) now lists the correct 0.089 g/mL concentration.

to report that the correct concentration, rounded to 0.089 g/mL (89 mg/mL), following reconstitution of the vial now appears on the current carton (**Figure 1**, bottom).

Please inform pharmacy staff of the potential for error if the older cartons are available in your pharmacy. Until you have the revised cartons in stock, ISMP recommends discarding the outer carton at the time of

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A patient who was at the end of her life and had a "do not resuscitate" order was receiving a norepinephrine infusion to keep her alive long enough for her family to say goodbye. The norepinephrine infusion ran out and there were no back-up bags in the ADC. A nurse called the pharmacy to request a new bag right away. The pharmacy did not have enough time to compound the medication before the patient passed away and before her family could say goodbye.

Hazards. All of the hazards that had not yet resulted in errors were reported to ISMP and involved look-alike labels or drug names. Most of the reports noted that the packaging and labeling on various concentrations of norepinephrine infusions compounded by 503B outsourcers looked nearly identical.

Safe Practice Recommendations: Consider the following recommendations when establishing or reviewing your facility's error-reduction strategies for the safe use of norepinephrine (and other vasopressor) infusions:

Prescribing

Limit the concentrations. Standardize to a limited number of concentrations to treat pediatric and/or adult patients. Designate weight-based limits for the most concentrated infusions, which should be reserved for patients who are fluid restricted or require larger doses of norepinephrine (to minimize bag changes).

Choose a single dosing method. Standardize the prescribing of norepinephrine infusions to either weight-based (mcg/kg/minute) or non-weight-based (mcg/minute) to reduce the risk of errors. The American Society of Health-System Pharmacists (ASHP) *Standardize 4 Safety* initiative recommends using mcg/kg/minute dosing units for norepinephrine (www.ismp.org/ext/446). Some hospitals may standardize to mcg/minute dosing due to prescriber preference—either is acceptable, but do not allow both dosing options.

Require prescribing via a standard order template. Require norepinephrine infusions to be prescribed using a standard order template with required fields for the desired concentration, a measurable titration goal (e.g., MAP, systolic blood pressure), titration parameters (e.g., starting dose, dose range, incremental units and frequency of dosing changes either up or down), route of administration, and a maximum dose that should not be exceeded and/or the dose at which the prescriber should be called. The processing time should default to "stat" to prioritize these orders in the pharmacy queue.

Limit verbal orders. Limit verbal orders to true emergencies or circumstances in which the prescriber is physically unable to electronically enter or write orders. Prescribers should enter their own orders, except during extenuating circumstances.

Dispensing

Purchase available premixed solutions. Use concentrations of manufacturer premixed norepinephrine solutions and/or solutions prepared by an outsourcer (e.g., 503B company) to decrease pharmacy preparation time, reduce delays in therapy, and avoid pharmacy compounding errors.

Differentiate the concentrations. Prior to dispensing, differentiate various concentrations by making them visually distinctive.

Ensure adequate ADC par levels. Stock ADCs with an adequate supply of norepinephrine infusions to match patient needs. Monitor usage and adjust par levels as needed.

Establish a process for batching and/or on-demand compounding. Since time may be needed to compound maximum concentrations that are not purchased, pharmacies can use various strategies to prioritize timely preparation and delivery,

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preparation (carton provides protection from light) and referring to the package insert for preparation instructions. If applicable, please review your intravenous (IV) workflow systems and formula references to ensure the reconstitution instructions reflect the appropriate 89 mg/mL (0.089 g/mL) concentration. The volume to be withdrawn for various Fetroja doses after reconstitution is listed correctly in the package insert.

HIGH-ALERT

Cometriq listed on discharge form instead of CoQ10. While completing a discharge medication form, a **COMETRIQ** (cabozantinib) 100 mg oral daily dose was incorrectly selected and added to the discharge medication list instead of a coenzyme Q10 (often abbreviated CoQ10) 100 mg oral daily dose. Cometriq is a tyrosine kinase inhibitor indicated to treat patients with progressive, metastatic medullary thyroid cancer. While hospitalized, the patient's own supply of coenzyme Q10, an over-the-counter supplement, was correctly administered. After discharge, the patient's primary care physician noticed the error during medication reconciliation while reviewing medications listed on the discharge form. Thankfully, a prescription was not sent to the pharmacy, so the patient never received the wrong drug and likely would not qualify for insurance coverage given the lack of an appropriate diagnosis.

The two products share overlapping characteristics. Both names start with the letters "c-o" and contain a "q." Also, both products are prescribed in similar 100 mg dosages. For example, Cometriq is available in a 100 mg daily-dose carton containing a combination of 80 mg and 20 mg capsules, while coenzyme Q10 is available as 100 mg capsules. These overlapping letter and dosage strength characteristics can increase the risk of mix-ups. It should be noted that Cometriq is also available in 60 mg and 140 mg daily-dose cartons. Mix-ups may even be more likely when coenzyme Q10 is abbreviated as CoQ10.

Pharmacy staff were notified about the mix-up. After the medication error was brought to the hospital's attention, the Cometriq order was removed from the patient's electronic health record. ISMP will notify the manufacturer, Exelixis, and the US Food and Drug Administration (FDA) about the confusion.

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including batching and/or on-demand preparation triggered by nursing or electronic notification when containers are within several hours of being empty.

Scan each bag/vial. To avoid errors during preparation, dispensing, or stocking, scan the barcode on each individual norepinephrine infusion bag or vial for verification prior to preparation, dispensing, or stocking it in the ADC. A barcode should only be available on the label placed directly on the bag.

Verify the label on the bag. During routine dispensing checks, if light-protective bags are used, temporarily take the norepinephrine infusion out of the bag for verification. Or, the light-protective bag should be left on top of the infusion until it is verified and then placed inside the bag immediately after verification.

Administration

Establish guidelines. Establish guidelines (or a protocol) for the titration of norepinephrine (or other titratable) infusions that include standardized concentrations, safe dosage ranges, typical titration dose increment(s), frequency of titration (minutes), maximum dose/rate, administration via a primary line, and monitoring requirements. If possible, link the guidelines to the titration order on the medication administration record (MAR).

Use smart pumps. Use smart infusion pumps with an engaged dose error-reduction system (DERS) to infuse and titrate all norepinephrine infusions so the DERS can alert healthcare providers about potential prescribing, calculation, or programming errors.

Implement interoperability. When possible, implement bidirectional smart infusion pump interoperability with the EHR. Interoperability enables the verified prescriber's ordered infusion parameters to prepopulate the pump (at least at the start of titration), and can also improve pharmacy awareness of the amount left in titratable infusions.

Label the lines and trace the tubing. Label each infusion line above the pump and near the patient's access site. Also, trace the tubing by hand from the solution container to the pump, and then to the patient, for verification of the proper pump/channel and route of administration immediately before starting or changing the bag or rate of a norepinephrine infusion.

Employ technology checks. When hanging a new infusion, require technology checks (e.g., barcoding) to verify the drug/solution, drug concentration, and patient.

Discontinue infusions. If the patient is stable for 2 hours after stopping a norepinephrine infusion, consider obtaining a discontinuation order from the prescriber. Once the infusion has been discontinued, immediately disconnect the infusion from the patient, remove it from the pump, and discard it to prevent inadvertent administration. Infusions paused for more than 2 hours should also be disconnected from the patient.

Establish an extravasation protocol. Establish an extravasation protocol for the vesicant norepinephrine. Nurses should receive education about the protocol, including treatment with phentolamine mesylate and avoidance of applying cold compresses to the site, which may worsen the tissue damage.

General

Assess titration practices. Monitor staff compliance with the guidelines, protocols, and specific orders for norepinephrine infusions, as well as patient outcomes. Examples of measures include compliance with ordering the required titration parameters; delays in therapy; use of a smart pump with an enabled DERS (and interoperability); starting the infusion at the ordered rate; titrating according to the prescribed frequency and dosing parameters; frequency and type of smart pump alerts; documentation of the titration parameter (which should coincide with dose changes); and patient harm during therapy.

Special Announcements

FREE webinars on drug diversion

Drug diversion in healthcare can significantly impact both patient and staff safety, but the full extent of the problem is rarely known because it may go unreported or undetected. Join us in April for three **FREE** webinars, each sponsored by Fresenius Kabi, as we explore how to manage drug diversion, quantify the costs of controlled substance waste, and mitigate the risk of diversion in the operating room (OR) and other procedural areas. For information and to register, click on the links below.

April 6: ***Diversion is a Threat to Patient Safety: Adopting Best Practices for Safe Management of Controlled Substances*** (www.ismp.org/node/29575)

April 13: ***Quantifying the Holistic Costs of Controlled Substance Medication Waste*** (www.ismp.org/node/29576)

April 28: ***Engaging the OR and Procedural Areas to Mitigate Risks with Controlled Substance Medications*** (www.ismp.org/node/29577)

Virtual MSI workshops

Don't miss the opportunity to register for one of our unique 2-day, virtual ***ISMP Medication Safety Intensive (MSI)*** workshops in 2022. Our next workshop is being held on **March 31 & April 1, 2022**. For details, visit: www.ismp.org/node/127.

To subscribe: www.ismp.org/node/10

ISMP Medication *Safety Alert!* Acute Care (ISSN 1550-6312)

Report medication and vaccine errors to ISMP: Call 1-800-FAIL-SAF(E) or visit our website at: www.ismp.org/report-medication-error. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

ISMP Medication Safety Alert! Acute Care Readership Survey

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1 When do you usually read the newsletter? (select one)
☐ Immediately when received ☐ Within a week of publication ☐ Within a month of publication
☐ I don't read it at all (please skip to question #9) ☐ Other (please specify): _____

2 Which newsletter format or version do you typically read? (select all that apply)
☐ PDF version ☐ Text version ☐ Online version (on the ISMP website) ☐ Other format (please specify): _____

3 How do you read the newsletter? (select all that apply)
☐ From a computer screen ☐ From a tablet screen ☐ From a phone screen ☐ From a printed copy ☐ Other (please specify): _____

4 How is the newsletter provided to you and/or shared with others in your organization? (select all that apply)
☐ PDF ☐ Text ☐ Link to the online version ☐ Other (please specify): _____

5 Please share your thoughts about the *ISMP Medication Safety Alert! Acute Care* by selecting the answer that best describes your opinion using the following Key.

KEY 1 = strongly disagree; 2 = disagree; 3 = neutral; 4 = agree; 5 = strongly agree; NA/DK = not applicable/don't know

Statements	Disagree ..... Agree					NA/ DK
	1	2	3	4	5	
The newsletter increases my understanding of the causes of medication errors.						
The newsletter increases my understanding of how to prevent medication errors.						
The recommendations for medication error prevention or reduction are practical and helpful.						
Many of the newsletter recommendations *could* be implemented in my organization.						
The information is relevant to my practice.						
The information is presented in an easy-to-read, organized manner.						
The content is presented at an appropriate academic level.						
The content stimulates productive discussion among my colleagues.						
My organization uses the ISMP **Action Agenda** to assess risk and reduce the frequency of medication errors.						
I have used the newsletter to educate staff, other healthcare providers, and/or students.						
The newsletter serves as a credible, respected, and reliable source of information on medication safety.						
The newsletter has led to positive changes in medication safety practices.						
The newsletter has led to positive changes in medical product safety.						
The newsletter has helped reduce or prevent harmful medication events in my organization.						
I use past newsletters as a resource when planning error-reduction strategies in my organization.						
I have visited the ISMP website for additional information.						
The newsletter has increased my awareness and/or understanding of additional ISMP services or tools (e.g., consulting, education and mentorship, error reporting, self assessments, guidelines, best practices).						

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> Survey — continued from page 5

6 **I find the number of newsletter pages/length of the newsletter to be:**

- ☐ Just right
- ☐ Too many pages/Too long
- ☐ Too few pages/Too short

7 **Select the best response to the statements about the *ISMP Medication Safety Alert! Acute Care* (NA/DK = not applicable/don't know).**

Statements	Yes	No	NA/DK	Comments
I have used information from the newsletter to:				
a. Make specific improvements in my unit/department				
b. Make specific improvements in my personal practice habits				
c. Collaborate with others to implement specific system-wide improvements in my organization				
I would prefer to read the newsletter in another format than currently available (PDF, text, website).				

8 **Who do you share the newsletter with in your organization?** (select all that apply)

- ☐ No one
- ☐ All physicians ☐ Select physicians
- ☐ All nurses ☐ Select nurses
- ☐ All pharmacists ☐ Select pharmacists
- ☐ All pharmacy staff ☐ Select pharmacy staff
- ☐ All administrators ☐ Select administrators
- ☐ Others involved in the medication-use process (please specify): _____

9 **What topics would you like to see covered in future newsletters?** _____

10 **Please select the categories that best describe your profession, position, and practice setting.**

Profession: ☐ Physician/Prescriber ☐ Pharmacist ☐ Pharmacy Technician ☐ Nurse ☐ Quality/Risk/Safety ☐ Other
Position: ☐ Staff ☐ Manager/Director ☐ Administrator ☐ Educator ☐ Medication Safety Specialist/Officer ☐ Other
Setting: ☐ Inpatient Acute Care ☐ LTC/Rehab ☐ Ambulatory Surgery Center ☐ Outpatient Pharmacy ☐ Clinic ☐ Other