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

High-alert medication list for acute care settings updated for 2024

High-alert medications are an essential component of drug therapy. However, while errors with these products are not necessarily more common, the consequences are often quite harmful and can even be fatal. To reaffirm and identify possible additions or deletions to our high-alert medication list, we recently reviewed reports submitted to the ***ISMP National Medication Errors Reporting Program*** *(ISMP MERP)*, clinical and safety literature, and input that we received from US medication safety experts. In addition, between September and October 2023, ISMP conducted a survey on high-alert medications in acute care settings.

The first list of high-alert medications was published in 1989 (Davis NM, Cohen MR. Today's poisons: how to keep them from killing your patients. *Nursing*. 1989;19[1]:49-51). That initial list included six medications that are still on ISMP's list today—intravenous (IV) lidocaine, vin**CRIS**tine, sodium chloride for injection greater than 0.9%, morphine injection, insulin, and potassium chloride for injection concentrate. In this newsletter, we report the results of our recent survey and compare them to a survey we conducted in 2018. We will also discuss changes we made to the list. The updated ***ISMP List of High-Alert Medications in Acute Care Settings*** can be found on the last page of this newsletter and on our website at: www.ismp.org/node/103.

2023 Findings

Respondent profile. ISMP extends our thanks to nearly 100 practitioners who validated our ***ISMP List of High-Alert Medications in Acute Care Settings***. Most practitioners were pharmacists (85%) working in an inpatient pharmacy (63%), although we also heard from others (e.g., nurses, risk/quality/safety managers, pharmacy technicians).

Drugs considered high-alert medications. Table 1, on page 3, shows the drugs on the 2018 ***ISMP List of High-Alert Medications in Acute Care Settings***, and the percent of respondents who considered these to be high-alert medications in 2018 and 2023. Half or more of the 2023 respondents thought that all of the drugs on our list were high-alert medications except IV adrenergic antagonists (49%) as well as oral sulfonylurea hypoglycemics (39%), which was up from 29% in our 2018 survey.

In 2023, more than 80% of respondents thought these medication classes or specific drugs were high-alert medications:

- U-500 insulin (100%)
- potassium chloride for injection concentrate (100%)
- epidural and intrathecal medications (100%)
- sodium chloride for injection, greater than 0.9% (100%)
- chemotherapeutic agents, parenteral and oral (98%)
- insulin, subcutaneous and IV (98%)
- neuromuscular blocking agents (98%)
- antithrombotic agents (96%)

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B. Braun potassium chloride for injection concentrate pharmacy bulk package almost infused into patient. A hospital reported a close call with two high-alert medications when potassium chloride for injection concentrate (500 mEq/250 mL) was found in the heparin injection (25,000 units/250 mL) bin of an automated dispensing cabinet (ADC) on a nursing unit. Both products, made by B. Braun, look similar and come in a 250 mL EXCEL plastic bag with blue and red labeling (**Figure 1**). Fortunately, a nurse caught the error after removing the bag's overwrap and scanning the barcode prior to administration.

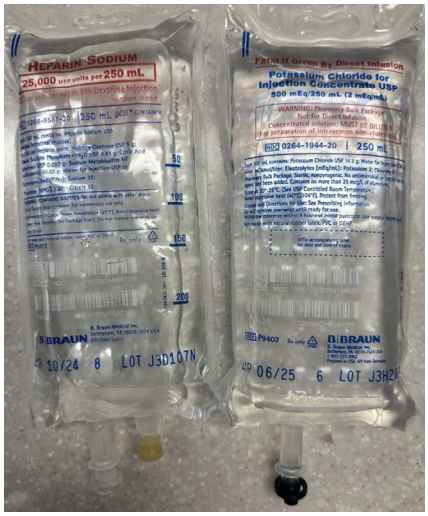

Figure 1. A nurse found B. Braun's heparin (left) and potassium chloride concentrate (right) in 250 mL EXCEL bags in the same ADC bin.

The organization purchased B. Braun's heparin due to a supply shortage from their typical manufacturer. Similar to concerns that we have previously published (www.ismp.org/node/80419), the organization noted that a seam on the overwrap of B. Braun premixed bags obscures the already difficult-to-scan white barcode on the clear bag, resulting in the inability to scan the product in the pharmacy prior to dispensing and when filling the ADC. Since this event, the reporting organization has implemented a process in which, in addition to the manufacturer-supplied auxiliary label,

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- potassium phosphates injection (93%)
- methotrexate, oral, nononcologic use (93%)
- epoprostenol (e.g., Flolan), IV (90%)
- opioids, all routes of administration (e.g., oral, sublingual, parenteral, transdermal) (88%)
- parenteral nutrition preparations (82%)

Possible additions and changes. ISMP asked for feedback about one possible addition, tranexamic acid injection, to the ISMP list, upon which about half (49%) of respondents agreed that it should be added to the list.

Comparison between 2023 and 2018

Differences between 2023 and 2018 findings. Prior to 2023, ISMP last conducted a survey on high-alert medications in acute care settings in 2018 (**Table 1**, on page 3), after which we updated our list based in part on the survey results.

Compared to 2018, the drugs listed below had the largest increase in the percentage of respondents who consider them high-alert medications.

- sterile water for injection, inhalation, and irrigation (excluding pour bottles) in containers of 100 mL or more (52% thought this was a high-alert medication in 2018, 77% in 2023)
- potassium phosphates injection (72% in 2018, 93% in 2023)
- epoprostenol (e.g., Flolan), IV (70% in 2018, 90% in 2023)
- methotrexate, oral, nononcologic use (74% in 2018, 93% in 2023)
- oxytocin, IV (60% in 2018, 79% in 2023)
- **EPINEPH**rine, IM, and subcutaneous (51% in 2018, 68% in 2023)

2023 Change to the ISMP List

Based on practitioner feedback, review of the literature and error reports, and input from our clinical advisory board, ISMP has made the following change to its current ***ISMP List of High-Alert Medications in Acute Care Settings***:

- Tranexamic acid injection was added to our list under "specific medications." Tranexamic acid is an antifibrinolytic agent that is used in a variety of hemorrhagic conditions to control bleeding, including postpartum hemorrhage. It works by preventing the breakdown of fibrin, thus promoting clotting. Respondents shared that errors are often related to storage issues and mix-ups with look-alike medication vials, most often anesthetics that are also commonly stored in surgical and procedural locations. When accidentally administered via a neuraxial route, tranexamic acid injection is a potent neurotoxin with a mortality rate of about 50% and is almost always harmful to the patient. Survivors of neuraxial tranexamic acid often experience seizures, permanent neurological injury, and paraplegia (www.ismp.org/ext/1139). ISMP has repeatedly warned against errors with tranexamic acid, including a feature article in the May 23, 2019, ***ISMP Medication Safety Alert!*** (www.ismp.org/node/8706), and most recently a ***Worth* repeating** in the August 24, 2023 newsletter (www.ismp.org/node/94378). ISMP also published a ***National Alert Network (NAN)*** warning on September 9, 2020 (www.ismp.org/node/20154).

We also received suggestions to consider adding about a dozen other medications to our list, including investigational medications, any controlled drugs, IV immunosuppressive agents, hypotonic sodium chloride, naloxone, alprostadil, and tolvaptan. Of note, about half of the suggested

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the pharmacy applies a pharmacy-generated barcode to the potassium overwrap bags to facilitate scanning. The organization is also storing the potassium in the controlled substance storage vault in the pharmacy. They are planning to purchase heparin from a different manufacturer once the shortage is resolved, which we would also recommend if using these products.

In May 2022, we issued a ***National Alert Network (NAN)*** alert (www.ismp.org/node/31719), with recommendations to prevent an error with the new presentation of B. Braun potassium chloride for injection concentrate pharmacy bulk package. The product was formerly available in glass containers, which looked different than other premixed products, but the company decommissioned its glass manufacturing line in the first quarter of 2022. Organizations that use this product should review the NAN Alert and take immediate steps to prevent a potentially fatal medication error. This includes ensuring that only pharmacy can purchase, store, and use this product; segregating this product from other similar-looking infusion bags in pharmacy storage; affixing auxiliary labels on the case of the product and both sides of the overwrap on bags; and scanning the barcode on the bag (as well as the barcodes on all intravenous [IV] infusion bags to ensure none are potassium chloride for injection concentrate).

Both heparin and concentrated potassium chloride injections are high-alert medications that can lead to serious harm when involved in medication errors. The US Food and Drug Administration (FDA) and the manufacturer need to urgently address these long-standing look-alike issues and scanning difficulties *before* any deaths are reported.

We reached out to B. Braun and they told us they have added a white two-dimensional (2D) barcode to the left of the linear barcode on some bags, which is not obstructed by the overwrap seam and can be easier to scan. We recommended they use dark ink on white backgrounds for all barcodes and consider moving the 2D barcode away from the linear barcode to allow for proper scanning per FDA guidance—*Safety Considerations for Container*

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additions were already on our list (e.g., bivalirudin, heparin, alteplase, tenecteplase, intrathecal medications). We greatly appreciate the suggestions that readers made for additions to the ISMP list of high-alert drugs. Although other changes were not made at this time, we will continue to monitor the suggested items and consider them for further assessment in our next survey.

Table 1. Comparison of respondents who believe these drugs/categories are high-alert medications, 2023 and 2018

Classes/Categories of Medications	2023 High-Alert (%)	2018 High-Alert (%)
U-500 insulin	100	96
potassium chloride for injection concentrate	100	95
epidural and intrathecal medications	100	93
sodium chloride for injection, greater than 0.9%	100	88
chemotherapeutic agents, parenteral and oral	98	99
insulin, subcutaneous and IV	98	98
neuromuscular blocking agents	98	97
antithrombotic agents	96	96
potassium phosphates injection	93	72
methotrexate, oral, nononcologic use	93	74
epoprostenol (e.g., Flolan), IV	90	70
opioids, all routes (e.g., oral, sublingual, parenteral, transdermal)	88	83
parenteral nutrition preparations	82	68
cardioplegic solutions	80	73
oxytocin, IV	79	60
anesthetic agents, general, inhaled and IV	77	71
sterile water for injection, inhalation, and irrigation (excluding pour bottles) in containers of 100 mL or more	77	52
nitroprusside sodium for injection	71	59
adrenergic agonists, IV	71	69
antiarrhythmics, IV	71	58
inotropic medications, IV	69	65
moderate sedation agents, IV	68	69
EPINEPHrine, IM, and subcutaneous	68	51
magnesium sulfate injection	68	64
promethazine injection*	67	56
opium tincture	65	60
vasopressin, IV and intraosseous	64	57
dextrose, hypertonic, 20% or greater	62	72
moderate and minimal sedation agents, oral, for children†	59	73
dialysis solutions, peritoneal and hemodialysis	56	50
liposomal forms of drugs and conventional counterparts	55	50
adrenergic antagonists, IV	49	57
sulfonylurea hypoglycemics, oral‡	39	29

*2023 survey specified IV only

†2023 expanded to include minimal sedation agents

‡2023 changed oral hypoglycemics to oral sulfonylurea hypoglycemics

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Labels and Carton Labeling Design to Minimize Medication Errors (www.ismp.org/ext/930).

Fluorouracil cream—ensure formulation corresponds to indication. In a large health system, staff recently uncovered several prescribing errors related to confusion between the 0.5% and 5% strengths of fluorouracil cream. A pharmacist was reviewing a patient's prescription for fluorouracil cream 0.5% and saw that the prescriber added a note stating, "ordering 5%." The pharmacist clarified with the prescriber, who confirmed, that the patient required fluorouracil cream 5%.

There are several factors that increase the risk of confusing these products. Aside from the 10-fold difference in strength, fluorouracil is sometimes referred to as "5-FU," which is an error-prone abbreviation and, in this case, can add to the confusion by highlighting the number five. Both medications have the same dosage form and share one of the indications which can all contribute to mix-ups. Fluorouracil cream 0.5% is indicated for the treatment of actinic or solar keratoses. This strength utilizes a porous microsphere delivery system with sustained-release characteristics, so it is administered once daily. Fluorouracil cream 5% is approved for actinic keratoses and basal cell carcinoma, and is administered twice daily.

The event prompted this organization to review hundreds of previously dispensed fluorouracil cream prescriptions. In more than 20 cases, they found the 0.5% cream was ordered and dispensed for patients with cancer instead of the indicated 5% cream. A lower than intended dose for a cancer indication may result in suboptimal control of symptoms and disease progression. In the reverse scenario, an overdose may result in the possibility of increased absorption if the patient has ulcerated or inflamed skin.

Organizations should consult with oncology and dermatology specialists and evaluate which strength(s) to carry on the formulary based on their patient population. If both formulations are required, store them in separate locations and consider adding

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Conclusion

Again, ISMP thanks all who took the time to provide us with feedback about additions or deletions to our high-alert medication list. Our updated list can be found on our website at: www.ismp.org/node/103. We hope you will use this list to determine which medications require special safeguards to reduce the risk of errors in your organization. Safeguards may include strategies such as limiting access to high-alert medications; employing clinical decision support and automated alerts; standardizing the ordering, storage, preparation, and administration of these products; using redundancies such as automated or independent double checks when necessary; using auxiliary labels; and improving access to information about these drugs.

Your *Reports* at *Work*

FDA requires updates to promethazine labeling

Due to the risk of severe chemical irritation and tissue injuries related to intravenous (IV) administration of promethazine injection, the US Food and Drug Administration (FDA) is requiring manufacturers to add administration recommendations to prescribing information as well as carton and container labels (www.ismp.org/ext/1288). The FDA recommends injection via deep intramuscular administration instead of IV administration. If it must be administered IV, it should first be diluted and infused through an IV catheter inserted into a large vein, preferably through a central venous catheter. FDA specifically mentions that the drug should not be given via veins in the hand or wrist.

ISMP first brought attention to this serious issue in a 2006 article, *Action needed to prevent serious tissue injury with IV promethazine* (www.ismp.org/node/934). This topic received a lot of attention and included more stories about this serious issue (**Figure 1**).

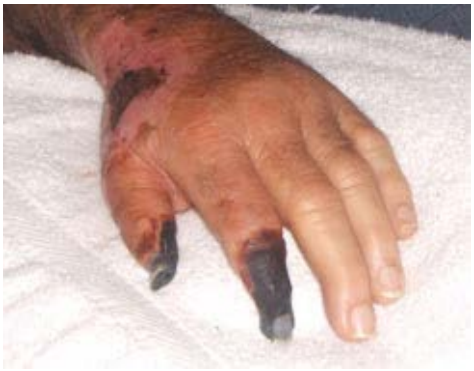

Figure 1. A patient accidentally received promethazine via an arterial line in his wrist, leading to pain that he described as "squeezing my thumb and index finger with pliers." The arterial line was quickly removed. Redness, pain, and swelling extended from his fingers to his forearm. Believing the patient had developed a thrombus, his physician performed an embolectomy, but no clot was found. About a month after the event, the patient's gangrenous thumb and finger were amputated.

Then, in 2007, the drug was added to ***ISMP List of High-Alert Medications in Acute Care Settings*** (www.ismp.org/node/103). Promethazine injection is a vesicant that is highly caustic to the intima of blood vessels and surrounding tissue. Parenteral administration can result in severe tissue damage, regardless of the route of administration. However, inadvertent intra-arterial injection associated with IV use has resulted in significant complications, including burning pain, erythema, swelling, severe spasm of vessels, thrombophlebitis, venous thrombosis, phlebitis, nerve damage, paralysis, abscess, tissue necrosis, and gangrene.

Although the labeling changes are a step in the right direction, we believe stronger action is needed. For this reason, the ISMP ***Targeted Medication Safety Best Practices for Hospitals***, *Best Practice #13* (www.ismp.org/node/160) recommends organizations eliminate injectable promethazine from the formulary.

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warning signs on storage bins to create awareness about the differences. Ensure order sentences include the appropriate dosing frequency (e.g., once-daily, twice-daily) based on indication and automatically link the corresponding product (e.g., 0.5%, 5%) for pharmacy to dispense. Avoid abbreviating drug names and use the full drug name in computer systems. Use barcode scanning prior to stocking, dispensing, and administration. Coach prescribers to avoid using notes or comments to modify orders (i.e., do not select the 0.5% strength with a note to dispense the 5% strength). If a prescriber cannot find the desired formulation/product, they should reach out to pharmacy for guidance. Educate staff and patients about the differences between fluorouracil 0.5% and 5% creams and to confirm the indication prior to dispensing/administration. Warn patients to keep these products away from pets who may develop severe toxicity if they lick their owner's skin (www.ismp.org/node/1493).

Special *Announcement*

IV medication webinar

Join us on **February 6, 2024** for a **FREE** webinar entitled ***Improving Safety, Efficiencies, and Reducing Waste with Ready-to-Administer IV Medications: A Roadmap to Success.*** Please visit: www.ismp.org/node/108857.

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Report medication and vaccine errors to ISMP: Please call 1-800-FAIL-SAF(E), or visit 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.

Special thanks to our 2023 MSOS Member Briefings Presenters

The Medication Safety Officers Society (MSOS) holds Member Briefings every other month on various medication safety topics. The MSOS Member Briefings are webinars that feature three 10-minute presentations from volunteer MSOS members who highlight a project, initiative, or relevant medication safety topic. The goal is for participants to take the information presented and use it to implement similar medication safety initiatives within their organization. At each Briefing, ISMP President **Rita Jew** or President Emeritus **Michael Cohen** provided an update on ISMP activities. Please let us know (ismpinfo@ismp.org) if there is a medication safety topic you would like to present (or see presented) in 2024. We hope others will volunteer to present their work! To join the MSOS and attend the Member Briefings, please visit: www.medsafetyofficer.org/user/register. MSOS membership and the 2024 Member Briefings are **FREE**.

Production of the MSOS Member Briefings would not be possible without the assistance of voluntary MSOS member presenters. ISMP sincerely thanks all of the 2023 presenters and longtime ISMP volunteer, **Bob Feroli**, PharmD, FASHP, for moderating the sessions.

Thank You!

- **Rachelle Albay**, PharmD, CPPS; Kaiser Permanente, Los Angeles, CA
- **Stephen Andrews**, PharmD, BCPS, CPPS; University of Utah Health, Salt Lake City, UT
- **Silvana Balliu**, PharmD; Cleveland Clinic, Cleveland, OH
- **Stacy Carson**, PharmD, BCPS, FISMP; AdventHealth, Altamonte Springs, FL
- **Joel Daniel**, PharmD, MS, CPPS; CoxHealth, Springfield, MO
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MSOS
MEDICATION SAFETY OFFICERS SOCIETY

ISMP List of High-Alert Medications in Acute Care Settings

High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients. We hope you will use this list to determine which medications require special safeguards to reduce the risk of errors. This may include strategies such as standardizing the ordering, storage, preparation, and administration of these products; improving access to information about these drugs; limiting access to high-alert medications; using auxiliary labels; employing clinical decision support and automated alerts; and using redundancies such as automated or independent double checks when necessary. (Note: manual independent double checks are not always the optimal error-reduction strategy and may not be practical for all of the medications on the list.)

Classes/Categories of Medications
adrenergic agonists, IV (e.g., **EPINEPH**rine, phenylephrine, norepinephrine)
adrenergic antagonists, IV (e.g., propranolol, metoprolol, labetalol)
anesthetic agents, general, inhaled and IV (e.g., propofol, ketamine)
antiarrhythmics, IV (e.g., lidocaine, amiodarone)
antithrombotic agents, including: — anticoagulants (e.g., warfarin, low molecular weight heparin, unfractionated heparin) — direct oral anticoagulants and factor Xa inhibitors (e.g., rivaroxaban, fondaparinux) — direct thrombin inhibitors (e.g., argatroban, bivalirudin, dabigatran) — glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide) — thrombolytics (e.g., alteplase, reteplase, tenecteplase)
cardioplegic solutions
chemotherapeutic agents, parenteral and oral
dextrose, hypertonic, 20% or greater
dialysis solutions, peritoneal and hemodialysis
epidural and intrathecal medications
inotropic medications, IV (e.g., digoxin, milrinone)
insulin, subcutaneous and IV
liposomal forms of drugs (e.g., liposomal amphotericin B) and conventional counterparts (e.g., amphotericin B deoxycholate)
moderate and minimal sedation agents, oral, for children (e.g., chloral hydrate, midazolam, ketamine)
moderate sedation agents, IV (e.g., dexmede**TOMID**ine, midazolam, **LOR**azepam)
neuromuscular blocking agents (e.g., succinylcholine, rocuronium, vecuronium)
opioids, all routes of administration (e.g., oral, sublingual, parenteral, transdermal)
parenteral nutrition preparations
sodium chloride for injection, hypertonic, greater than 0.9% concentration
sterile water for injection, inhalation and irrigation (excluding pour bottles) in containers of 100 mL or more
sulfonylurea hypoglycemics, oral (e.g., glimepiride, glipi**ZIDE**, gly**BURIDE**, **TOLBUT**amide)

Abbreviation definitions: IV—intravenous, IM—intramuscular

Specific Medications
EPINEPHrine, IM, and subcutaneous
epoprostenol (e.g., Flolan), IV
insulin U-500 (special emphasis*)
magnesium sulfate injection
methotrexate, oral, nononcologic use
nitroprusside sodium for injection
opium tincture
oxytocin, IV
potassium chloride for injection concentrate
potassium phosphates injection
promethazine injection
tranexamic acid injection
vasopressin, IV and intraosseous

** All forms of insulin, subcutaneous and IV, are considered a class of high-alert medications. Insulin U-500 has been singled out for special emphasis to bring attention to the need for distinct strategies to prevent the types of errors that occur with this concentrated form of insulin.*

Background

Based on error reports submitted to the ***ISMP National Medication Errors Reporting Program*** *(ISMP MERP)*, reports of harmful errors in the literature, studies that identify the drugs most often involved in harmful errors, and input from practitioners and safety experts, ISMP created and periodically updates a list of potential high-alert medications. During September and October 2023, practitioners responded to an ISMP survey designed to identify which medications were most frequently considered high-alert medications. Further, to ensure relevance and completeness, the clinical staff at ISMP and members of the ISMP advisory board were asked to review the potential list. This list of medications and medication categories reflects the collective thinking of all who provided input.

Report medication errors to the ***ISMP National Medication Errors Reporting Program*** *(ISMP MERP) at: www.ismp.org/MERP.*

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