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ISMP

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

High-alert medication survey results lead to several changes for 2018

Between June and July 2018, ISMP conducted a survey on high-alert medications in acute care settings to learn about possible additions or deletions before updating our longstanding list. High-alert medications are an essential component of drug therapy, but they carry a significant risk of causing serious injuries or death to patients if they are misused. Errors with these products are not necessarily more common, but the consequences of an error are often quite harmful and can even be fatal.

ISMP published its first list of "high-alert" medications 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 6 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. Today, our list is based upon an extensive review of errors submitted to the ISMP National Medication Errors Reporting Program (ISMP MERP), review of clinical and safety literature, input from our clinical advisory board and US safety experts, and periodic newsletter surveys. In this newsletter, we report the results of our most recent survey, compare these results to a previous survey conducted in 2014, and discuss the changes that we have made to the list. We have also included a copy of the updated ***ISMP List of High-Alert Medications in Acute Care Settings*** on **page 5**.

2018 Survey Results

Respondent profile. ISMP extends our thanks to the 296 practitioners who completed our survey on high-alert medications in acute care settings. Most (82%) respondents were pharmacists, although nurses (10%), physicians (3%), pharmacy technicians (3%), and others (2%) also participated. Respondents were evenly split between staff-level and management-level, and nearly all (98%) worked in inpatient settings.

Organizational lists of high-alert medications. Almost all (95%) respondents reported that their organization maintains a list of high-alert medications. However, only 64% reported that special precautions are in place to minimize and prevent errors for all of the high-alert medications on their list. Another 21% of respondents said that special precautions are in place for most of the medications on their list. However, 15% of respondents reported that there are few or no special precautions in place to minimize and prevent errors with the high-alert medications on their list.

Among respondents who reported having special precautions in place to prevent errors, most felt that they are very (20%) or mostly (55%) effective in minimizing and preventing errors with high-alert medications. One in 4 respondents thought the precautions in their organization were only somewhat (23%) or weakly (2%) effective, citing examples of how practitioners often bypass these safety precautions. A few respondents commented that they could not assess the effectiveness of precautions because they only have a voluntary medication error-reporting system in place for measurement.

When respondents were asked which 3 medications or classes of medication on their list caused the most concern with regards to medication errors, the most fre-

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SAFETY briefs

Rabies immune globulin vial sizes look similar. A *Safety Brief* in the June 28, 2018, *ISMP Medication Safety Alert!* noted a change in concentration for rabies immune globulin (human) (**HYPERRAB**) manufactured by Grifols. Since a higher concentration allows for more efficient wound infiltration (i.e., more of the immune globulin can be delivered to the affected area in less volume), the concentration was increased from 150 units per mL to 300 units per mL. When stocking, storing, and dispensing HyperRAB, it is important to recognize that the product is available in both 1 mL and 5 mL vials and cartons that are hard to tell apart (**Figure 1**). The only visual differences are

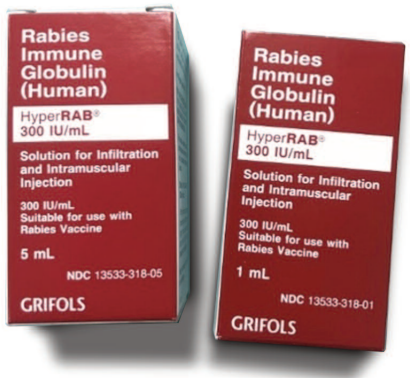

Figure 1. Look-alike 5 mL (left) and 1 mL (right) HyperRAB vial cartons.

the volume noted in the lower left corner of the carton and different NDC numbers. The vials themselves both have a 5 mL capacity although one contains 5 mL while the other contains only 1 mL.

According to the package insert, the 1 mL vial is sufficient for a child weighing 15 kg, while the 5 mL vial is sufficient for an adult weighing 75 kg. Both are single-use vials. While each vial contains 300 units per mL, confusing the vial sizes may lead to costly waste if a 5 mL vial is dispensed and used for a child. The situation could also result in inventory issues. For example, someone

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quent responses were (in descending order): anticoagulants, insulin, neuromuscular blocking agents, chemotherapy, opioids, hypertonic sodium chloride injection (concentrations greater than 0.9%), adrenergic agonists, and other concentrated electrolytes.

Medications considered high-alert. Table 1 shows the drugs on the ***ISMP List of High-Alert Medications in Acute Care Settings*** at the time of the survey, and the percent of respondents who considered these to be high-alert medications. Half or more of the 2018 respondents thought that all of the drugs on our list were high-alert except:

- IV radiocontrast agents (34%)
- oral hypoglycemics (29%)

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Table 1. Comparison of respondents who believe these are high-alert medications, 2018 and 2014 surveys

Classes/Categories of Medications	High-Alert (%)	
	2018	2014
chemotherapeutic agents, parenteral and oral	99	97
insulin, subcutaneous and IV	98	93
neuromuscular blocking agents	97	96
antithrombotic agents	96	92
epidural and intrathecal medications	93	94
sodium chloride for injection, greater than 0.9%	88	87
opioids, IV, oral, transdermal	83	74
moderate sedation agents, oral for children	73	70
cardioplegic solutions	73	60
dextrose, hypertonic, 20% or greater	72	64
anesthetic agents, general, inhaled and IV	71	85
moderate sedation agents, IV	69	74
adrenergic agonists, IV	69	75
parenteral nutrition	68	61
inotropic medications, IV	65	53
antiarrhythmics, IV	58	58
adrenergic antagonists, IV	57	75
sterile water for injection (inhalation/irrigation) in containers (excluding pour bottles) of 100 mL or more	52	35
liposomal forms of drugs	50	49
dialysis solutions, peritoneal and hemodialysis	50	39
radiocontrast agents, IV	34	42
hypoglycemics, oral	29	29
Specific Medications	**High-Alert (%)**	
	2018	**2014**
insulin U-500 (special emphasis)	96	98
potassium chloride for injection concentrate	95	92
methotrexate, oral, nononcologic use	74	67
potassium phosphates injection	72	79
epoprostenol (e.g., Flolan), IV	70	64
magnesium sulfate injection	64	70
oxytocin, IV	60	61
opium tincture	60	56
nitroprusside sodium for injection	59	65
vasopressin, IV and intraosseous	57	63
promethazine, IV	56	59
EPINEPHrine, subcutaneous	51	66*

*2014 survey included subcutaneous and IM **EPINEPH**rine together

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may visually scan their inventory, not notice the volume differences, and mistakenly believe enough product is on hand when there may be far less than needed to treat patients. To prevent this, one hospital is storing the two sizes apart from one another along with a note to double check the vial volume before using. Auxiliary labels to better differentiate the products and the use of barcode scanning during inventory and product selection are additional risk-reduction strategies. ISMP has also forwarded complaints to the manufacturer and the US Food and Drug Administration (FDA).

HIGH-ALERT

Another imported potassium chloride for injection concentrate. In cooperation with the US Food and Drug Administration (FDA), importation of potassium chloride for injection concentrate, 20 mEq/10 mL (2 mEq/mL), has been initiated by a French company, Laboratoire Aguettant. Reported in a previous newsletter, Athenex Pharmaceutical Division began temporary importation of potassium chloride from the Italian company, Industria Farmaceutica Galenica Senese S.r.l. (Galenica). The French product is packaged in a plastic ampule and is labeled in French. English translation is provided on the carton label (and prescribing information), and a sticker with important information is on the carton. The strength is listed as "0,15 g/mL" but is equivalent to 2 mEq/mL. As with the Italian product, the ampule label does not contain a barcode. Additional information and a side-by-side comparison can be found on the FDA website at: www.ismp.org/ext/79.

HIGH-ALERT

Methotrexate "Call to Action" brings results. In our "Call to Action" to prevent methotrexate medication errors published in our August 9, 2018 newsletter, one of the suggestions we made was to: "Create a daily list of active orders and discharge prescriptions for oral methotrexate generated from the order entry system; and require a pharmacist to review the orders and prescriptions to verify the dose and frequency based on the patient's diagnosis." While testing the implementation of this strategy, one hospital told us that they already picked up an improper oral methotrexate 2.5 mg **daily** discharge prescription that had been sent to the patient's pharmacy. One of the root causes of the error was an erroneous

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More than 80% of respondents thought these medication classes or specific medications were high-alert:

- chemotherapeutic agents, parenteral and oral (99%)
- insulin, subcutaneous and IV (98%)
- neuromuscular blocking agents (97%)
- antithrombotic agents (96%)
- U-500 insulin (96%)
- potassium chloride for injection concentrate (95%)
- epidural and intrathecal medications (93%)
- sodium chloride for injection, greater than 0.9% (88%)
- opioids, IV, oral, transdermal (83%)

Possible additions and changes. In the survey, ISMP asked respondents about one possible addition to the ISMP list, along with two possible changes to the list (**Table 2**). Almost three quarters (74%) of respondents agreed that oral solutions of concentrated sodium chloride should be added to the list, and more than half (54%) of respondents thought that IV promethazine should be changed to promethazine injection. Less than half of respondents thought that ISMP should expand the oral hypoglycemics category to include the newer antidiabetic injectable agents.

Table 2. Respondents' views about potential additions or changes in 2018 to the ***ISMP List of High-Alert Medications in Acute Care Settings***

Potential Additions or Changes	Add or Change?
	Yes (%)
concentrated sodium chloride oral solutions	74
promethazine injection	54
antidiabetic agents, oral and injectable	45

Comparison of 2018 and 2014 Survey Results

Differences between 2018 and 2014 surveys. Prior to 2018, ISMP last conducted a survey on high-alert medications in 2014 (**Table 1**, page 2), after which we updated our list based in part on the survey results. When comparing the results of the two surveys, we found some differences in whether practitioners viewed certain medications as high-alert. These differences were greatest for:

- sterile water for injection (inhalation/irrigation) in containers (excluding pour bottles) of 100 mL or more (35% thought this was a high-alert medication in 2014, 52% in 2018)
- dialysis solutions, peritoneal and hemodialysis (39% in 2014, 50% in 2018)
- IV inotropic medications (53% in 2014, 65% in 2018)
- IV adrenergic antagonists (75% in 2014, 57% in 2018)
- subcutaneous **EPINEPH**rine (66% in 2014, 51% in 2018, although the 2014 survey queried about both intramuscular [IM] and subcutaneous **EPINEPH**rine)
- inhaled and IV general anesthetic agents (85% in 2014, 71% in 2018)

Roughly, the same percent of respondents reported that there were special precautions in place for the high-alert medications on their organizations' lists (85% in 2018, 87% in 2014); however, fewer respondents in 2018 felt these precautions were very or mostly effective (75% vs. 89%, respectively).

2018 Changes to the ISMP List

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

- Examples of antithrombotic agents were expanded to include direct oral anticoagulants currently on the market.

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entry for daily methotrexate on a home medication list that eventually resulted in a discharge prescription with daily dosing. The patient was actually taking 10 mg of methotrexate weekly at home. Fortunately, the patient had enough methotrexate at home so he did not need to immediately fill the incorrect discharge prescription. Once the mistake was discovered, a pharmacist called the patient's community pharmacy to correct the daily methotrexate dosing. The hospital will continue to generate the list daily for a clinical pharmacist to review.

Standardization should result in improvements, not simply conformity. Standardization is a powerful risk-reduction strategy—it reduces variation, which introduces unnecessary risks in a process, and helps maximize important goals, such as interoperability, quality, and safety. As such, many health systems strive for standardization across all facilities. However, keep in mind that standardization is **NOT** the goal—optimized interoperability, quality, and safety are the goals. Standardization is merely a tool to be used to meet these goals. Standardization for the sake of standardization alone is pointless, even dangerous.

In one hospital, pharmacy staff followed the ISMP-recommended practice of drawing up basal insulin doses in the pharmacy and delivering them to nurses shortly before the doses were due. The larger healthcare system wanted to standardize this best practice across all hospitals, but other pharmacy staff in the system were concerned about the workload involved in drawing up doses in the pharmacy. Thus, system leaders initially asked the first hospital to move to a less safe practice used by other sites—dispensing vials and asking nurses to draw up doses as needed—so the system could standardize the process. Fortunately, the first hospital was eventually allowed to maintain the best practice of dispensing basal insulin doses.

Standardization across facilities in a health system should only be implemented if it will produce improvements and enhance interoperability, quality, and safety. Best practices should be created by the experts who carry out the work and then spread to others as able, not abandoned for the sake of conformity within an entire health system.

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- **LOR**azepam was added as an example of an IV moderate sedation agent.

- The category of oral moderate sedation agents for children was revised to include minimal sedation agents, and additional examples were provided, including midazolam and ketamine (using the parenteral form). This also matches the high-alert medication category as stated in our recent ***ISMP Medication Safety Self Assessment® for High-Alert Medications***.

- The category of oral hypoglycemics was changed to oral sulfonylurea hypoglycemics, and examples were provided, including chlorpro**PAMIDE**, glimepiride, gly**BURIDE**, glipi**ZIDE**, and **TOLBUT**amide. This narrows the category to agents that may result in significant hypoglycemia and patient harm if administered in error, as reported to the ISMP MERP. Numerous comments suggesting this change were also submitted through the 2018 survey.

- IV radiocontrast media was removed from the list given low support for its continued inclusion and a lack of reported adverse events in our database associated with errors (as opposed to adverse reactions due to allergies or renal impairment).

- IV promethazine was changed to promethazine injection to expand the high-alert medication status of this drug to administration by any parenteral route, including intramuscular (IM). Although Best Practice #13 in the ***ISMP Targeted Medication Safety Best Practices*** (www.ismp.org/node/160) calls for the elimination of injectable promethazine in hospitals, evidence suggests that the drug is still available in some hospitals. Thus, for now, we are keeping promethazine injection on our high-alert medication list.

ISMP decided not to add oral solutions of concentrated sodium chloride (e.g., 23.4%) to our list, despite substantial support for its addition in the 2018 survey. We could not find any error reports or literature regarding errors with this formulation of the medication. More to the point, numerous survey comments suggest that practitioners who supported its inclusion on our list confused this oral formulation with parenteral 23.4% sodium chloride for injection, which is already on our list. However, if you are aware of potentially harmful errors with the oral product, or if you use the product orally and have concerns about harmful errors, please let us know and we will reconsider.

We also received suggestions to consider adding about a dozen medications to our list, such as monoclonal antibodies, tranexamic acid, antiseizure medications, antiretrovirals, glacial acetic acid, and dofetilide. We appreciate all the thought that went into making these suggestions. We have carefully evaluated the suggested additions but will not be adding any of them to our list at this time. We understand the importance of keeping the list manageable. However, we will continue to monitor these medications and include them in our next survey if we believe they may need to be added to our list later.

Conclusion

Again, ISMP thanks all who took the time to complete our survey on high-alert medications. Our updated list can be found on **page 5** and 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. 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.

Special Announcements

Accepting Cheers Awards nominations

Nominations for this year's **Cheers Awards** will be accepted through **September 7**. The awards spotlight efforts to improve medication safety from all healthcare disciplines. For details, visit: www.ismp.org/node/1036.

Free webinar: Global medication safety

Join ISMP on **September 26** for a **FREE** webinar, ***Working Together to Address Global Drug Safety Issues with Packaging and Labeling***. Speakers will discuss drug product issues that contribute to medication errors around the world, and successful changes countries have made to reduce the risk of errors. For details, visit: www.ismp.org/node/1113.

ISMP programs on drug shortages

Attend one of ISMP's educational sessions on ***Balancing Unpredictable Intravenous Medication Supply with the Demand for Safe Injection Practices:***

- **October 5** - California Society of Health-System Pharmacists Seminar in **San Diego**
- **October 7** - American Society for Health Care Risk Management Conference in **Nashville**
- **October 24** - American Nurses Credentialing Center National Magnet Conference in **Denver**

For details, visit: www.ismp.org/node/23.

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

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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., dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban, 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 desoxycholate)
- moderate sedation agents, IV (e.g., dexmedetomidine, midazolam, **LOR**azepam)
- moderate and minimal sedation agents, oral, for children (e.g., chloral hydrate, midazolam, ketamine [using the parenteral form])
- opioids, including:
  - IV
  - oral (including liquid concentrates, immediate- and sustained-release formulations)
  - transdermal
- neuromuscular blocking agents (e.g., succinylcholine, rocuronium, vecuronium)
- 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., chlorpro**PAMIDE**, glimepiride, gly**BURIDE**, glipi**ZIDE**, **TOLBUT**amide)

Specific Medications

- **EPINEPH**rine, 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
- 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 June and July 2018, practitioners responded to an ISMP survey designed to identify which medications were most frequently considered high-alert medications. Further, to assure 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.

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