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ISMP An ECRI Affiliate

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

Prevent errors during emergency use of hypertonic sodium chloride solutions

Problem: As early as 1919, hyperosmolar agents administered intravenously (IV) were shown to reduce intracranial pressure (ICP) or reduce cerebral edema in adult and pediatric patients after neurological injury, including traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and hepatic encephalopathy (HE).[1-3] The hyperosmolar therapy reduces ICP by establishing an osmotic gradient between the extracellular and intracellular space, thereby optimizing blood viscosity and cerebral blood flow. Mannitol as a hyperosmolar agent was introduced in 1961 and became the agent of choice to manage ICP.[1,4] In the 1990s, hypertonic sodium chloride (e.g., 3%, 5%, 23.4%) was introduced as a hyperosmolar agent, and its use to manage ICP has increased while mannitol use has decreased.[1,5]

Using hypertonic sodium chloride rather than mannitol has become the standard of care in treating several neurological injuries. For adults, current guidelines suggest the use of hypertonic sodium chloride over mannitol for the management of elevated ICP or cerebral edema in patients with TBI or ICH, and for patients with AIS who do not respond adequately to mannitol.[3] For other neurological injuries, using either mannitol or hypertonic sodium chloride is recommended. For pediatric patients 18 years and younger with a severe TBI, current guidelines suggest using hypertonic sodium chloride.[1] Mannitol has not been subjected to current controlled clinical trials in children—most investigations were carried out in both children and adults in the 1970s.[1,4] For refractory ICP and cerebral herniation syndrome, 23.4% sodium chloride is recommended for both adult and pediatric patients.[1,3]

Hypertonic sodium chloride has several theoretical advantages over mannitol, including 1) less penetration of sodium across the blood-brain barrier, 2) lack of a diuretic effect, 3) restoration of normal cellular resting membrane potential and cell volume, 4) stimulation of arterial natriuretic peptide release, 5) inhibition of inflammation, and 6) enhancement of cardiac output.[1,3] Once administered, hypertonic sodium chloride begins to reduce ICP within minutes; its peak is at 20-30 minutes; and ICP reduction lasts for 6-24 hours.

Recent Errors

Since the beginning of 2020, most errors associated with hypertonic sodium chloride reported to the ***ISMP National Medication Errors Reporting Program*** (ISMP MERP) occurred during preparation in the pharmacy. For example, there were numerous errors in which the wrong concentration of sodium chloride was used to manually compound a solution or was loaded incorrectly onto an auto-compounder, and 23.4% sodium chloride vials were used instead of sterile water to compound parenteral fluids for neonates. These errors were often associated with look-alike labeling and packaging of the products. A few reports were associated with prescribing errors in which physicians ordered the wrong sodium chloride concentration to be added to compounded IV solutions for pediatric patients with an elevated ICP. These errors were often caused by a confusing prescribing process or unfamiliarity with the solutions used to treat elevated ICP.

We received a few reports about stocking/storage errors (e.g., 500 mL bags of 3% sodium chloride stocked instead of 0.9% sodium chloride or look-alike magnesium sulfate 20 g/500 mL bags). In one report, the central supply department distributed 500 mL

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SAFETY briefs

Adult and pediatric COVID-19 vaccine mix-ups are predictable. The US Food and Drug Administration (FDA) authorized emergency use of the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine for children ages 5 through 11 years on October 29, 2021, and as of November 2, 2021, the Centers for Disease Control and Prevention (CDC) now recommends vaccination in children ages 5 through 11 years. This allows for the immediate distribution of the pediatric vaccine to physician offices, pharmacies, and clinics, so vaccinations can begin this week. Based on previous mix-ups at locations where the influenza (flu) vaccine and COVID-19 vaccines are both being administered (www.ismp.org/node/28044), ISMP is concerned about the potential for similar mix-ups between the pediatric and adult formulations of the COVID-19 vaccine since both will be available in most vaccination sites. Unfortunately, age-related errors have been linked to more than 1 in 3 vaccine errors (www.ismp.org/node/208) reported to the ***ISMP National Vaccine Errors Reporting Program*** (VERP).

According to the *Fact Sheet* (www.ismp.org/ext/803) for the 2-dose vaccine series for children ages 5 through 11 years, the pediatric formulation (10 mcg per 0.2 mL after dilution) will be supplied in a multiple-dose vial with an orange border on the label and an orange cap. The pediatric formulation must be diluted with 1.3 mL of 0.9% sodium chloride prior to use, to prepare 10 doses of 0.2 mL (10 mcg). The label states: "Age 5y to < 12y" (**Figure 1**), but this is not as prominent as "**DILUTE PRIOR TO USE**" and could be

Figure 1. The vaccine vial label for ages 5 through 11 years has an orange border, and the vial (not pictured) has an orange cap.

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bags of 3% sodium chloride instead of 0.9% sodium chloride to various patient care units. We also received numerous drug administration error reports. A few involved mix-ups between 500 mL bags of 3% sodium chloride and either 0.9% sodium chloride or 5% dextrose in 0.3% sodium chloride when retrieving IV solutions from an automated dispensing cabinet (ADC). Intravenous administration errors also involved infusing 3% sodium chloride solution longer than prescribed, and administering the solution at 100 mL/hour instead of 25 mL/hour.

We also learned about dosing errors that occur during order entry or when programming smart infusion pumps because pediatric hypertonic sodium chloride may be dosed in mEq/kg, mEq/kg/hour, mL/kg, or mL/kg/hour. In fact, when providers verbally order repeat doses of hypertonic sodium chloride at the child's bedside, the dose is often expressed in mL/kg (as noted in prescribing information and dosing guidelines[1,3]) or mL/kg/hour, but the smart infusion pump libraries may list the solution in mEq/kg (bolus dose) or mEq/kg/hour (infusion).

Delays in Treatment

In a March 25, 2021, Medication Safety Officers Society (MSOS) *Briefing*, we heard from several facilities with a high demand for hypertonic sodium chloride to treat elevated ICP that were struggling with clinical delays in treatment while awaiting pharmacy preparation and dispensing of all doses or infusions. ISMP's 2019 ***Guidelines for the Safe Use of Automated Dispensing Cabinets*** (www.ismp.org/node/1372) recommend to avoid stocking vials/ampules of concentrated electrolytes, including sodium chloride in concentrations greater than 0.9%, in ADCs. A *Frequently Asked Question* (FAQ) associated with this guideline specifically notes that vials of 23.4% sodium chloride should not be stocked in ADCs, suggesting that the pharmacy should prepare, label with appropriate warnings, and hand-deliver any IV push doses of 23.4% sodium chloride used in critical care or emergency/urgent care units.

Our 2017 ***ISMP Medication Safety Self Assessment® for High-Alert Medications*** (www.ismp.org/node/580) provides the same recommendations for vials/ampules of 23.4% sodium chloride, but also suggests that appropriately labeled and sequestered bags of 3% sodium chloride may be stocked in limited quantities in approved critical care or emergency/urgent care units. Nevertheless, since hypertonic sodium chloride, especially 23.4% sodium chloride, is used during a life-threatening emergency when the patient exhibits symptoms of cerebral herniation syndrome, any treatment delay can be significant.

Safe Practice Recommendations: To promote safety and allow for the rapid administration of IV hypertonic sodium chloride solutions in emergencies, implement the following risk-reduction strategies:

Procurement and Storage

- Allow only the pharmacy department to purchase and dispense hypertonic sodium chloride in vials and infusion bags.
- In the pharmacy, physically separate and store containers of hypertonic sodium chloride in a designated area for IV compounding and admixture supplies.
- Restrict bags of 3% sodium chloride to the pharmacy and/or certain approved critical care or emergency/urgent care units.
- When making decisions about stocking hypertonic sodium chloride in patient care units, conduct a robust risk assessment (e.g., failure mode and effects analysis) with an interdisciplinary team (e.g., pharmacists, nurses, physicians). If storage in selected patient care units is allowed, consider the following safeguards:

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missed. Surprisingly, the dose in mcg is not listed on the label, which would have been helpful in differentiating this product from the 30 mcg/0.3 mL formulations for patients 12 years and older. ISMP believes FDA should require this information on the label.

The adult formulation vial has a purple cap, while the pediatric formulation has an orange cap. While different color caps might help prevent some mix-ups, once the cap is removed and discarded, doses may be prepared one at a time rather than all at once, which will render the cap color irrelevant. Also, it is unlikely that the vial will accompany prepared syringes, so the vial label cannot be verified by those administering the vaccine or parents/patients receiving the vaccine.

Previous experience with vials available for pediatric and adult hepatitis A and hepatitis B vaccines has demonstrated that different color caps and labels may not prevent errors. For example, the hepatitis A vaccine, **VAQTA** by Merck (and **HAVRIX** by GlaxoSmithKline, not pictured), are available in single-dose containers in pediatric/adolescent (0.5 mL) and adult (1 mL) formulations. While the adult and pediatric/adolescent Vaqta syringes have different color plungers and the vials have different color caps and bands on the label (**Figure 2**), mix-ups do still occur. The media has also reported that some parents with 5- through 11-year-old children have expressed vaccine hesitancy, especially after hearing about some vaccine errors (www.ismp.org/ext/804). We certainly do not want mix-ups between the pediatric and adult COVID-19 vaccine formula-

Figure 2. Despite color differences, mix-ups between hepatitis A formulations (pediatric/adolescent, top; adult, bottom) are among the most common age-related vaccine errors reported to ISMP.

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- ☐ Stock only the 3% sodium chloride bags in patient care units, not the 23.4% sodium chloride vials (do not stock 23.4% sodium chloride vials outside of the pharmacy)
  - For hospitals without 24-hour pharmacy services, stock 23.4% sodium chloride vials, if needed, in a single, secure critical care location that only a few trained professionals (e.g., house/critical care supervisor, intensivist) can access after pharmacy hours for emergencies
- ☐ Stock only in approved critical care or emergency/urgent care units
- ☐ Stock in limited quantities
- ☐ Label with a customized high-alert medication label and bold warnings (**Figure 1**)
- ☐ Store in a separate locked/lidded compartment, segregated from other medications; avoid storage in matrix drawer configurations
- ☐ If stocked in an ADC, do not allow access via override (override access for a few trained professionals may be necessary but only in facilities without 24-hour pharmacy review of orders)

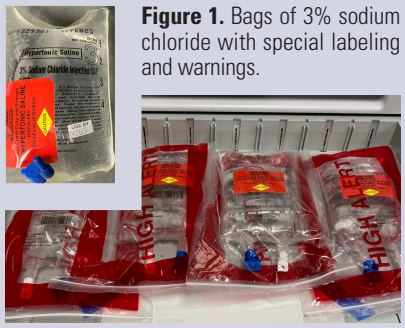

Figure 1. Bags of 3% sodium chloride with special labeling and warnings.

Figure 2. Patient-specific syringe of 23.4% sodium chloride with special labeling and warnings prior to dispensing from the pharmacy.

- To prevent mix-ups with 5% dextrose solutions, do not procure, order, or stock IV containers of 5% sodium chloride anywhere in the facility (even the pharmacy).

Prescribing

- Create standardized protocols and order sets for each indication of IV hypertonic sodium chloride (e.g., ICP, hyponatremia) that allow for different dosing units as necessary (e.g., ICP: mL/kg [bolus] and mL/kg/hour [infusion]; hyponatremia: mEq/kg [bolus] and mEq/kg/hour [infusion]), and match how the practitioner must program a smart infusion pump, when needed.

- Update the nomenclature in order entry systems (and ADC screens as applicable) to include "**HYPERTONIC**" for any sodium chloride product greater than 0.9% concentration. Consider using "**HYPERTONIC**" for 3% sodium chloride injection and "**CONCENTRATED**" for 23.4% sodium chloride injection for further differentiation. Never refer to "**HYPERTONIC**" or "**CONCENTRATED**" sodium chloride as "saline."

- Build alerts in the provider order entry system to warn staff about high serum sodium levels in patients receiving hypertonic sodium chloride, reaching/exceeding maximum or critical doses, and hypertonic sodium chloride orders for patients located outside of a critical care or an emergency/urgent care unit.

- Require all orders from non-physician prescribers, residents, and fellows for IV hypertonic sodium chloride to be approved by an attending physician or intensivist with proper credentials.

- Default all hypertonic sodium chloride orders to "stat," giving them higher priority and moving them to the top of the queue for pharmacy verification to avoid delays.

- Restrict the prescribing of 23.4% sodium chloride to patients with refractory intracranial hypertension and/or cerebral herniation syndrome.

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tions to raise these concerns even more.

If clinics, physician practices, and/or pharmacies in your health system will be administering adult and pediatric COVID-19 vaccines, develop a plan for segregating and storing these in refrigerators and freezers that are organized and properly labeled. Store the adult (12 years and older) and pediatric COVID-19 vaccines apart from one another, such as in separate labeled plastic bins. During the production and/or verification phase of the dispensing process, use barcode scanning whenever possible to verify that the correct product has been retrieved. Make it a policy to clearly label all individual syringes containing vaccines. To facilitate proper labeling, print labels for each patient or provide vaccine preparers with strips of preprinted labels that differentiate adult and pediatric doses. Ideally, prior to administration, barcode scanning should again confirm the correct vaccine.

Also, as we recommended for preventing errors between the flu vaccine and COVID-19 vaccines (www.ismp.org/node/28044), only bring the intended and labeled vaccine syringe(s) for one patient into the vaccination area at a time. Involve the parent or patient in verifying the vaccine by reading the label to confirm the correct vaccine. Document the lot number and date of manufacture prior to vaccine administration, and document administration afterwards in the patient's profile, on vaccination records, and via state or other immunization registries. Report all vaccine errors internally as well as to the FDA/CDC Vaccine Adverse Event Reporting System (VAERS, https://vaers.hhs.gov/), which is mandatory for COVID-19 vaccine errors under an Emergency Use Authorization (EUA). ISMP also asks providers to report vaccine errors to the ISMP VERP (www.ismp.org/VERP). Additional vaccine information can be found at: www.cvdvaccine-us.com.

Work continues to improve investigational drug labeling. The US Food and Drug Administration (FDA) has released draft guidance (www.ismp.org/ext/796) for investigator safety reporting responsibilities that includes medication error reporting for any unanticipated problem to Institutional Review Boards (IRBs), which, in the past,

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Dispensing

- Do not manually compound base solutions requiring concentrations of sodium chloride that are available in commercially premixed solutions (e.g., 0.45%, 0.9%, 3%); instead use the commercially available premixed solutions.
- When possible, prepare and dispense IV push doses of 23.4% sodium chloride used in critical care or emergency/urgent care units from the pharmacy, labeled with appropriate warnings (**Figure 2**, page 3), and hand-deliver the patient-specific dose to the healthcare professional administering the drug.
- Require barcode scanning and an independent double check before dispensing hypertonic sodium chloride to a patient care unit, both for stock and patient-specific use.

Administration

- In indication-based protocols for IV hypertonic sodium chloride, include directions for administration (e.g., rate of administration, the concentration at which administration through a central IV access line is required) and the type and frequency of patient monitoring required during administration.
- If hypertonic sodium chloride is available in an ADC, do not allow staff to access it via override. Require verification by a pharmacist prior to removing the drug within the patient's profile for administration (see bullet under **Procurement and Storage** if facilities do not have 24-hour pharmacy services).
- Build a clinical advisory or alert in the smart infusion pump to enter the dose appropriately (e.g., mL, mEq) based on the indication or use.
- Provide pump programming guidance in the protocols or on the patient's medication administration record.
- Require barcode scanning of the patient for identification and of the product as well as an independent double check of the product, concentration, dose, patient, pump programming, and access line prior to administering IV hypertonic sodium chloride.
- Consider building a smart infusion pump drug library entry with maximum dose limits and using a syringe pump to deliver doses of 23.4% sodium chloride.
- Allow only trained, licensed, independent practitioners and registered nurses in critical care units and the emergency department to administer IV hypertonic sodium chloride. Consider requiring the attending physician or an intensivist to be at the bedside during administration.
- Administer hypertonic sodium chloride via a central line if possible (23.4% sodium chloride must be administered via a central line).

Monitoring

- For patients receiving hypertonic sodium chloride, monitor serum sodium levels at baseline and at least every 6 hours, as well as renal function studies as needed for signs of acute kidney injury and unwanted acidosis.
- Monitor the patient for possible side effects of hypertonic sodium chloride (e.g., rebound elevated ICP, renal impairment, subarachnoid hemorrhage, natriuresis, high urinary water losses, hyperchloremic acidosis, masking of diabetes insipidus[1,6]).

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may not have been made aware of medication errors involving investigational drug products. Since a 2-day public meeting, held in May 2021, FDA has been continuing its efforts to mitigate medication errors associated with investigational drug product container labels. Slides and transcripts from the meeting, which was coordinated for FDA by the Reagan-Udall Foundation, are available at: www.ismp.org/ext/666. FDA is soliciting input for the draft guidance from stakeholders (e.g., sponsors, investigators, clinical sites, entities that supply or label investigational drugs, study participants). Please do not hesitate to send ISMP and FDA reports and pictures of investigational drug labels/labeling that have or may contribute to errors as well as any actual medication errors involving investigational drugs.

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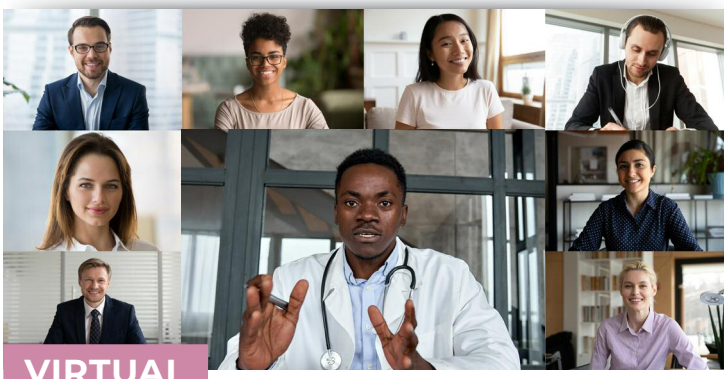

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