August 2022 ▪ Volume 20 Issue 8

ISMP An ECRI Affiliate

Nurse AdviseERR®

Educating the Healthcare Community About Safe Medication Practices

Prevent errors during emergency use of hypertonic sodium chloride solutions

Problem: As early as 1919, hyperosmolar (concentrated) 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 was introduced in 1961 as a hyperosmolar agent 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, 6) enhancement of cardiac output, 7) quicker onset, and 8) a more robust and durable ICP reduction.(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.

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The gab- or -gab- stem names

Medications with the stem **gab-** or **-gab-** in their name belong to a class of antiseizure agents. Two of the medications, gabapentin and pregabalin, are considered gamma-aminobutyric acid (GABA) analogs, which inhibit neurotransmitters from firing, calming the nervous system down. Therefore, these medications are also indicated for use with other neurologic conditions such as postherpetic neuralgia; neuropathic pain and fibromyalgia; restless leg syndrome; and infantile spasms.

Due to the pharmacokinetics of these medications, they have a very wide therapeutic window, which means dosing is highly vari-

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Welcome to **Shannon**, our newest ISMP staff member!

We are pleased to announce that **Shannon Bertagnoli**, PharmD, BCPPS, has joined ISMP as a Medication Safety Specialist, Publications, earlier this year. She develops the content for the acute care newsletter and serves as an editor for our other newsletters and publications. Prior to joining ISMP, Shannon worked at the Children's Hospital of Orange County (CHOC Children's) in California as a pediatric clinical pharmacist for 12 years, and more recently as a Medication Safety & Quality Specialist, where she managed the Medication Safety Committee, the Smart Pump Oversight Committee, the Medication Error Reduction Plan, and a CHOC Children's medication safety blog read by consumers. She received her Doctor of Pharmacy degree from the University of Connecticut and completed her residency at CHOC Children's. Shannon is a Board Certified Pediatric Pharmacy Specialist.

Supported by an educational grant from Fresenius Kabi

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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 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

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able for each patient and indication. Dosing regimens may have low initial doses followed by incremental dose increases over time until the desired effect or maximum dose is reached. The versatility of these medications is found in the various dosage forms, strengths, and indications. These medications may be dosed daily, twice daily, or even up to three times a day.

The US Food and Drug Administration (FDA) approved five gab-/-gab- medications for use in the United States (**Table 1**). Pregabalin is listed as a schedule V drug by the Controlled Substance Act (CSA) which means abuse of the drug may lead to physical and psychological dependence. Some states and organizations restrict or manage gabapentin as a controlled substance as well, even though FDA does not label it as such.

Table 1. Antiseizure/GABA medications available in the United States.

Generic Name	Brand Name	Dose Forms/ Strengths
gabapentin	**GRALISE**	extended release tablet
	NEURONTIN	capsule, tablet, oral solution
gabapentin enacarbil	**HORIZANT**	extended release tablet
pregabalin	**LYRICA**	capsule, oral solution
	LYRICA CR	extended release tablet
tia**GAB**ine	**GABITRIL**	tablet
vigabatrin	**SABRIL**	tablet, oral powder for solution (packet)
	VIGADRONE	oral powder for solution (packet)

Clinical expertise and product labeling should be utilized when prescribing gabapentin and pregabalin for pediatric patients. Tia**GAB**ine is restricted to patients 12 years and older, while vigabatrin is indicated for infantile spasms and has specific dosing regimens for pediatric and adult patients. Gabapentin, pregabalin, tia**GAB**ine, and vigabatrin require dose adjustments for renal dysfunction.

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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:

- ☐ Stock only 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 open 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 is in place 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. **Never** accept verbal orders for hypertonic sodium chloride.

- 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.

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Adverse reactions common to all agents in this class include central nervous system (CNS) side effects such as dizziness, drowsiness, and fatigue, as well as some endocrine effects such as edema and/or weight gain. Visual disturbances have been noted with gabapentin, pregabalin, and tia**GAB**ine. Vigabatrin can cause permanent vision loss and is managed under a Risk Evaluation and Mitigation Strategy (REMS) program to assess for this risk.

SAFETY wire

Paxlovid drug interaction. A physician prescribed **PAXLOVID** (nirmatrelvir and ritonavir) for a 34-year-old patient with flu-like symptoms who tested positive for coronavirus disease 2019 (COVID-19). On day 3 of treatment, the patient presented with signs and symptoms of fatigue and bradycardia, with a heart rate below 40 beats per minute. The physician referred the patient to the emergency department (ED) for further evaluation, where it was discovered that the patient had been taking ivabradine for premature ventricular contractions. Ivabradine is metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme, and the ritonavir component of Paxlovid is a strong CYP3A4 inhibitor. Thus, concomitant use of Paxlovid and ivabradine is contraindicated due to the risk of ivabradine accumulation and toxicity, which could lead to bradycardia, hypotension, and heart failure. Increased plasma concentrations of ivabradine may also exacerbate bradycardia and conduction disturbances. The patient was monitored for 24 hours in the ED and then discharged home.

Educate prescribers and patients, about the potential for Paxlovid drug interactions. Also, organizations should test their electronic health records and/or pharmacy computer systems to ensure they provide alerts for this and other drug-drug interactions. The practitioner who reported this event to ISMP mentioned that the prescriber was not familiar with the patient's medical history. Paxlovid is not a drug that should be prescribed without reviewing the patient's current medication list for potential drug-drug interactions. The ***Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers*** (www.ismp.org/ext/921) from the US Food and Drug

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

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 independent double checks (both stock and patient-specific doses) before dispensing hypertonic sodium chloride to a patient care unit.

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 setting, 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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Administration (FDA) can be used for screening.

Other resources that practitioners can use include the following:

- *Management of Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid): Resource for Clinicians* (www.ismp.org/ext/915), from the Infectious Diseases Society of America (IDSA)
- *COVID-19 Drug Interactions* (www.ismp.org/ext/916), from the University of Liverpool
- *Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications* (www.ismp.org/ext/917), from the National Institutes of Health (NIH)

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ISMP Nurse AdviseERR (ISSN 1550-6304)

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.

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